ACADEMIC BOOK 2023-24

Semester VII

Better Science, Better Health

PRAVARA RURAL EDUCATION SOCIETY'S

COLLEGE OF PHARMACY (FOR WOMEN)

NASHIK

College Code PH - 5201

Approved by A.I.C.T.E., New Delhi & Pharmacy Council of India, New Delhi
Affiliated to Savitribai Phule Pune University, Pune
Recognized by Govt. of Maharashtra

PHARMACIST'S OATH

I swear by the code of ethics of Pharmacy Council of India, in relation to the community and shall act as an integral part of health care team.

I shall uphold the laws and standards governing my profession.

I shall strive to perfect and enlarge my knowledge to contribute to the advancement of pharmacy and public health.

I shall follow the system which I consider best for Pharmaceutical care and counseling of patients.

I shall endeavor to discover and manufacture drugs of quality to alleviate sufferings of humanity.

I shall hold in confidence the knowledge gained about the patients in connection with my professional practice and never divulge unless compelled to do so by the law.

I shall associate with organizations having their objectives for betterment of the profession of Pharmacy and make contribution to carry out the work of those organizations.

While I continue to keep this oath unviolated, may it be granted to me to enjoy life and the practice of pharmacy respected by all, at all times!

Should I trespass and violate this oath, may the reverse be my lot!

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Vision

To emerge as the most preferred pharmacy educational institute with global recognition and developing competent and socially sensitive pharmacists committed to healthcare needs of society.

Mission

To develop students as global citizen with conscience,
commitment and dedication.

To create world class facilities and ambience for advanced level of
teaching, research and practical training.

To recruit and retain highly motivated and qualified faculty to promote the cause of teaching and learning.

Program Objectives (POs)

The Program Outcomes of Bachelor in Pharmacy course are:

1. **Pharmacy Knowledge:** An ability to acquire, demonstrate, core and basic knowledge of Pharmaceutical and Life Sciences
2. **Planning Abilities:** An ability to develop, implement, effectively plan and organize work using time management, resource management, delegation skills and organizational skills to achieve goals in specified timeline.
3. **Problem Analysis:** An ability to identify, analyze, interpret data and take appropriate decision to solve problems related to routine Pharmacy Practices by applying acquired knowledge.
4. **Modern Tool Usage:** An ability to understand, choose and utilize Modern techniques and computing tools for Pharmacy practices by considering constraints.
5. **Leadership Skills:** An understanding of pharmaceutical management principles and apply these to one's own work, as a member and leader in a team, to manage projects to facilitate improvement in social health and well being.
6. **Professional Identity:** An ability to recognize, analyze and communicate Pharmacy professional values as a healthcare promoter.
7. **Pharmaceutical Ethics:** An ability to understand and use professional, ethical, legal, social issues and responsibilities for well being of the society.
8. **Communication:** An ability to comprehend, write reports, present and document to communicate effectively for exchange of professional information to Pharmacy community and society.
9. **The Pharmacist and Society:** An ability to overcome the societal, health and legal problems by providing better pharmaceutical care relevant to the Pharmacy profession.
10. **Environment and Sustainability**: An ability to recognize the impact of the professional Pharmaceutical solutions in social and environmental circumstances for sustainable development.
11. **Life-Long Learning:** An ability to recognize the need to engage in continuous Professional development by taking in consideration timely feedback and technological changes for life long learning process.

Program Specific Outcomes (PSO)

Pharmacy Students are able to:

PSO 1: To build graduate to excel in technical or professional careers in various pharmaceutical industry and/ or institute and /or Health care system through rigorous education. Also analyze and communicate the skills, values of their professional roles in society.

PSO 2: To learn, select, apply appropriate methods, procedures, resources and modern pharmacy-related computing tools with an understanding of the limitations.

PSO 3: To operate, control, analyze and evaluate chemical substances and finished products also processes within permissible limits.

PSO 4: To design a system, component or process to meet desired needs within realistic constraints such as economic, environmental, sustainability social, ethical, health, safety and manufacturability for humans.

ACADEMIC CALENDAR

(July 2023 - December 2024)

Semester: **All Semesters of B. Pharm** Academic Year: **2023-2024**

Week No.	Month	Week Days						Working days	Events
		Mon	Tue	Wed	Thu	Fri	Sat		
1	July 23						1	0	
2		3	4	5	6	7	8	6	03-Subject Choice for AY 2023-24 6-Subject Allotment for AY 2023-24
3		10	11	12	13	14	15	5	12- Commencement of Sem. V, VII
4		17	18	19	20	21	22	6	21-Tree Plantation
5		24	25	26	27	28	29	5	24-28-First yr. IInd sem Sessional exam 25-28- Soft skill training
5		31						1	31-Student Council Election 31-Academic Staff & Research Meeting
6	Aug 23		1	2	3	4	5	4	1-4-M.Pharm IInd Sem sessional exam
7		7	8	9	10	11	12	6	07-GB & CDC Meeting 11-Dr. Vitthalrao Vikhe Patil Jayanti 13-Sports & Cultural Meeting
8		14	15	16	17	18	19	3	15-Independance Day 16-Parsi New Year 17-M. Pharm. Sem IV Viva-Voce
9		21	22	23	24	25	26	6	21-30-First year IInd sem semsester exam 25-Mentoring Meeting Regular Lectures of V & VII sem
10		28	29	30	31			4	29-Industrial Visit of Sem. VII 30- Academic Staff & Research Meeting
11	Sep 23					1	2	1	01-Soft Skill Training for Sem. V & VII
12		4	5	6	7	8	9	6	4sept-Commencement of IIrd em and Ist sem,M.Pharm Ist sem 05-Teacher's Day 9-Parent's Meet
		11	12	13	14	15	16	5	11-First Sessional Exam of Sem. V, VII sem
		18	19	20	21	22	23	5	19-Ganesh Chaturthi 20--IV of Vth sem
13		25	26	27	28	29	30	5	26-Industrial Visit of Sem. V 30- Academic Staff & Research Meeting
14	Oct 23	2	3	4	5	6	7	4	2-Mahatma Gandhi Jayanti 3-IV of VIIth sem
15		9	10	11	12	13	14	5	08- Swach Bharat Abhiyaan (NSS Activity)

16		16	17	18	19	20	21	5	16-Mid Semester Feedback (Google form) 18-Soft Skill Training for Sem. IIIrd sem 20- Alumni Overview meeting
17		23	24	25	26	27	28	6	24-Dusshera Regular Lectures of Sem.I, III, V & VII M. PharmI, III
18		30	31					2	31- Academic Staff & Research Meeting
19	**Nov 23**			1	2	3	4	3	03-Industrial Visit of Sem. III
20		6	7	8	9	10	11	3	9-15 Diwali vacation
21		13	14	15	16	17	17	2	18-Mock Interview for Sem. VII
22		20	21	22	23	24	25	6	20-24-Sessional exam of Ist ,IIrd sem,V,VIIth sem and M.PharmI, IIIrd sem
23		27	28	29	30			3	28- Industrial Visit of Sem. I 30- Academic Staff & Research Meeting
24	**Dec 23**					1	2	1	Regular Lectures of Sem. III, V & VII M. Pharm III
25		4	5	6	7	8	9	6	7-Synopsis Submission of M. Pharm. Sem. III 08- Practice School Presentation 4-11 Semester Practical Exam for V & VII
26		11	12	13	14	15	16	5	12- End Semester Feedback of Students (Google Form) 15- Mock Interview for Sem. VII
27		18	19	20	21	22	23	6	19-Research Proposal Presentation of M. Pharm Sem. III 18-28 -V,VII sem and M. Pharm Sem.I, III Semester Exam
28		25	26	27	28	29	30	5	26-30-Sessional exam of I,III and M.Pharm IIIrd sem 30- Internal Academic Audit 31- Academic Staff & Research Meeting
END OF SEMESTER		**Total Working Days**						**130**	

Occasional holiday	**University Exams**	**Teaching Working Days**	**Holidays(Saturday/ Sunday)**
14	**25**	**130**	**40**

Course Structure

Course of study for semester VII

Course Code	Name of the course	No. of hours	Tutorial	Credit points
BP701T	Instrumental Methods of Analysis – Theory	3	1	4
BP702T	Industrial PharmacyII – Theory	3	1	4
BP703T	Pharmacy Practice- Theroy	3	1	4
BP704T	Novel Drug Delivery System– Theory	3	1	4
BP705P	Instrumental Methods of Analysis – Practical	4	0	2
BP706PS	Practice School*	12	0	6
	Total	**28**	**4**	**24**

* Non University Examination (NUE)

Schemes for internal assessments and end semester examinations semester wise

Course Code	Name of the course	Internal Assessment				End Semester Exams		Total Marks
		Continuous Mode	Marks	Duration	Total	Marks	Duration	
BP701T	Instrumental Methods of Analysis – Theory	10	15	1 Hr	25	75	3 Hrs	100
BP702T	Industrial PharmacyII – Theory	10	15	1 Hr	25	75	3 Hrs	100
BP703T	Pharmacy Practice - Theroy	10	15	1 Hr	25	75	3 Hrs	100
BP704T	Novel Drug Delivery System– Theory	10	15	1 Hr	25	75	3 Hrs	100
BP705P	Instrumental Methods of Analysis – Practical	5	10	4 Hr	15	35	4 Hrs	50
BP706PS	Practice School*	25	-	-	25	125	5 Hrs	150
Total		**70**	**70**	**18 Hrs**	**140**	**460**	**21 Hrs**	**600**

EVALUATION GUIDELINES

Scheme for Continuous mode (Theory): [Total: 10 Marks]

Criteria	Maximum Marks	
Attendance	4	2
Academic activities (Average of any 2 activities e.g. class test, quiz, assignment, open book test, field work, group discussion and seminar)	4	3
Student -Teacher interaction	2	
Total	10	05

Guidelines for the allotment of marks for attendance

Percentage of Attendance	Theory
95 – 100	4
90 – 94	3
85 – 89	2
80 – 84	1
Less than 80	0

In-Semester Examination (Sessional): [Total: 15 Marks]

Two Sessional exams shall be conducted for each theory / practical course as per the schedule fixed by the college. The scheme of question paper is given below. The average marks of two Sessional exams shall be computed for internal assessment.

Paper pattern and marks distribution for In Semester Exam: As per university guideline

I. Objective Type Questions (Answer 5 out of 7) = 05 x 2 = 10
II. Long Answers (Answer 1 out of 2) = 1 x 10 = 10
II. Short Answers (Answer 2 out of 3) = 2 x 5 = 10

Total = 30 marks (1.5 Hrs)

Sessional exam shall be conducted for 30 marks for theory and shall be computed for 15 marks.

End Semester Examination [Total: 75 Marks]:

Paper pattern and marks distribution for End Semester Exam: As per university guideline

I. Objective Type Questions (Answer 5 out of 7) = 5 x 3 = 15
II. Long Answers (Answer 2 out of 4) = 2 x 10 = 20
II. Short Answers (Answer 8 out of 10) = 8 x 5 = 40

Total = 75 marks (3 hrs)

SUBJECT I

BP701T INSTRUMENTAL METHODS OF ANALYSIS

THEORY

SCHEME

BP701T Instrumental Methods of Analysis–Theory

SCHEME FOR TEACHING

Course of study for semester VII

Course Code	Course Name	No. of Hours per week			Credit Points
		Theory	Practical	Tutorial	
BP701T	Instrumental Methods of Analysis	03	0	01	04
BP705P	Instrumental Methods of Analysis	-	04	-	02

SCHEME FOR INTERNAL AND END SEMESTER EXAMINATIONS

Course code	Name of the course	Internal Assessment				End Semester Exams		Total Marks
		Continuous Assessment	Sessional Exams		Total	Marks	Duration	
			Marks	Duration				
BP701T	Instrumental Methods of Analysis	10	15	01 hrs	25	75	03 hrs	100
BP705P	Instrumental Methods of Analysis	05	10	04 hrs	15	35	04 hrs	50

SYLLABUS

BP701T Instrumental Methods of Analysis–Theory

Sr. No	Name of Topic	Hrs	CO mapping
	Unit-I		
01	**UV Visible spectroscopy** Electronic transitions, chromophores, auxochromes, spectral shifts, solvent effect on absorption spectra, Beer and Lambert's law, Derivation and deviations.Instrumentation - Sources of radiation, wavelength selectors, sample cells, detectors- Phototube, Photomultiplier tube, Photo voltaic cell, Silicon Photodiode.Applications - Spectrophotometric titrations, Single component and multi componentanalysis	10	CO1
02	**Fluorimetry** Theory, Concepts of singlet, doublet and triplet electronic states, internal and external conversions, factors affecting fluorescence, quenching, instrumentation and applications.		CO2
	UNIT-II		
03	**IR spectroscopy** Introduction, fundamental modes of vibrations in poly atomic molecules, samplehandling, factors affecting vibrations Instrumentation - Sources of radiation, wavelength selectors, detectors - Golay cell, Bolometer, Thermocouple, Thermister, Pyroelectric detector and applications	10	CO1,CO3
04	**Flame Photometry**-Principle, interferences, instrumentation and applications		CO1,CO3
05	**Atomic absorption spectroscopy**- Principle, interferences, instrumentation andapplications		CO1,CO3
06	**Nepheloturbidometry**- Principle, instrumentation and applications		CO1,CO3
	UNIT –III		
07	**Introduction to chromatography** **Adsorption and partition column chromatography**-Methodology, advantages,disadvantages and applications	10	CO1
08	**Thin layer chromatography-** Introduction, Principle, Methodology, Rf values, advantages, disadvantages and applications		CO2
09	**Paper chromatography-**		CO1,C

	Introduction, methodology, development techniques, advantages, disadvantages and applications		O2
10	Thin layer chromatography: Introduction, Principle, Methodology, Rf values, advantages, disadvantages and applications		CO2
11	HPTLC: Introduction, Instrumentation and applications		CO2
	UNIT-IV		
11	**Theory of Chromatography** Plate theory, Rate theory, System suitability parameters	8	CO1
12	**Gas chromatography -** Introduction,theory,instrumentation,derivatization,temperature programming, advantages, disadvantages and applications		CO2
13	**High performance liquid chromatography (HPLC)-** Introduction, theory,instrumentation, advantages and applications		CO1,CO2
	UNIT-V		
14	**Ion exchange chromatography** Introduction, classification, ion exchange resins, properties, mechanism of ion exchange process, factors affecting ion exchange, methodology and applications	7	CO1
15	**Gel chromatography** Introduction, theory, instrumentation and applications Affinity chromatography- Introduction		CO1

Recommended Books (Latest Editions)

1. Instrumental Methods of Chemical Analysis by B.K Sharma
2. Organic spectroscopy by Y.R Sharma
3. Text book of Pharmaceutical Analysis by Kenneth A. Connors
4. Vogel's Text book of Quantitative Chemical Analysis by A.I. Vogel
5. Practical Pharmaceutical Chemistry by A.H. Beckett and J.B. Stenlake
6. Organic Chemistry by I. L. Finar
7. Organic spectroscopy by William Kemp
8. Quantitative Analysis of Drugs by D. C. Garrett
9. Quantitative Analysis of Drugs in Pharmaceutical Formulations by P. D. Sethi
10. Spectrophotometric identification of Organic Compounds by Silverstein

LESSION PLAN

BP701T Instrumental Methods of Analysis–Theory

Name of the faculty: Dr. Charushila J. Bhangale/ Mr. Balu T. Jagtap

Lecture Number	Description	Teaching Methodology	References	COs	POs
1	**UV spectroscopy** Electronic transitions, chromophores	Chalk and talk	Fundamentals of Analytical Chemistry by Skoog, Chatwal and Anand,	1	1
2	Auxochromes, spectral shifts, solvent effect on absorption spectra,	Chalk and talk		1	1
3	Beer and Lambert's law, Derivation and deviations	Chalk and talk		1	1
4	Tutorial				
5	Instrumentation - Sources of radiation, wavelength selectors,	Chalk and talk		1	1
6	sample cells, detectors- Photo tube, Photomultiplier tube, Photo voltaic cell, Silicon Photodiode	Chalk and talk		2	2
7	Applications - Spectrophotometric titrations, Single component and multi componentanalysis	Chalk and talk		2	2
8	Tutorial				
9	**Fluorimetry** Theory, Concepts of singlet, doublet and triplet electronic states	Chalk and talk	Fundamentals of Analytical Chemistry by Skoog,Instrumental method of Analysis by Supriya Mahajan	2	2
10	internal and external conversions, factors affecting fluorescence,	Power point		1,2	2
11	Quenching, instrumentation and applications	Chalk and talk		1,3	1

12	Tutorial				
13	**IR spectroscopy** Introduction, fundamental modes of vibrations in poly atomic molecules	Youtube demonstration and power point	Fundamentals of Analytical Chemistry by Skoog,Chatwal and Anand	1	3
14	Sample handling, factors affecting vibrations	Power point	Nazma Inamdar	3	3
15	Instrumentation - Sources of radiation, wavelength selectors, detectors	Chalk and talk	Nazma Inamdar	3	3
16	Tutorial				
17	Golay cell, Bolometer, Thermocouple, Thermister, Pyroelectric detector and applications	Power point	Fundamentals of Analytical Chemistry by Skoog	3	4
18	**Flame Photometry-** Principle, interferences	Chalk and talk	Fundamentals of Analytical Chemistry by Skoog	3	4
19	instrumentation and applications	Youtube demonstration and power point	Fundamentals of Analytical Chemistry by Skoog, instrumental analysis by Kasture and Wadodkar	3	4
20	Tutorial				
21	**Atomic absorption spectroscopy-** Principle, interferences,	power point		3	6
22	instrumentation and applications	power point		3	4
23	**Nepheloturbidometry-** Principle,Theory	Power point	Instrumental Methods of Chemical Analysis by BK Sharma	4	4
24	Tutorial				
25	instrumentation and applications	Power point		4	4
26	**Introduction to chromatography**	Power point		4	7,8
27	**Adsorption and partition column chromatography-** Methodology	Power point		1,4	1

28	Tutorial				
29	advantages, disadvantages and applications.	Chalk and talk	Instrumental Methods of Analysis by Willard	1,4	3
30	**Thin layer chromatography-** Introduction, Principle	Power point		1,4	7,8
31	Methodology, Rf values	power point		1,4	1
32	Tutorial				
33	advantages, disadvantages and applications	Power point	Insrumental method of chemical Analysis by Chatwal and Anand, instrumental analysis by Kasture and Wadodkar	1,3	4
34	**Paper chromatography-** Introduction,Theory	power point		1,4	3
35	methodology, development techniques	power point		1,4	3
36	Tutorial				
37	advantages, disadvantages and applications	Power point		1,4	7
38	**TLC Principle, theory**			3	3
39	Methodology, Rf values	Chalk and talk	Instrumental Methods of Chemical Analysis by BK Sharma Instrumental analysis by supriya Mahajan	3	4
40	advantages, disadvantages andapplications.				
41	**HPTLC:** Introduction	power point		4	7,8
42	Instrumentation and applications				
43	**Gaschromatography-** Introduction, theory	power point		3,4	3
44	instrumentation,derivatization ,temperature programming,	power point		3	6
45	advantages, disadvantages and applications				
46	Tutorial	Chalk and talk		3	6
47	**Theory of Chromatography** Plate theory, Rate theory,	power point		3	4
48	System suitability parameters	power point		3	3
49	**High performance liquid**				

	chromatography (HPLC)-Introduction, theory				
50	Tutorial	power point		3	7,8
51	instrumentation	power point		4	7,8
52	advantages and applications	power point		4	3
53	**Ion exchange chromatography-** Introduction, classification, ion exchange resins, properties,				
54	Tutorial	Chalk and talk		3	4
55	mechanism of ion exchange process, factors affecting ion exchange	Chalk and talk	Instrumental analysis by supriya Mahajan	4	7,8
56	methodology and applications	Chalk and talk		3	3
57	**Gel chromatography-** Introduction, theory		Instrumental analysis by supriya Mahajan		
58	Tutorial			3	1,11
59	instrumentation	power point		3	4
60	applications	Chalk and talk		4	7

COURSE DELIVERY, OBJECTIVES, OUTCOMES

BP701T Instrumental Methods of Analysis–Theory

Course Delivery:

The course will be delivered through lectures, class room interaction, and presentations.

Course Objectives:

1. To understand the different types of instrumental analytical techniques available for quality control of APIs & formulations.
2. Understand the interaction of matter with electromagnetic radiations and its applications in drug analysis
3. Understand the chromatographic separation and analysis of drugs.
4. Perform quantitative & qualitative analysis of drugs using various analytical instruments

Course Outcomes (COs):

After successful completion of course student will able to

Upon the completion students are able to **CO-PO**

CO1	Learner will be able to understand [L1: Knowledge] principles, instrumentation and applications of various chromatographic, spectroscopic employed [L4: Analysis] for the analysis of APIs and formulations
CO2	Learner will be able to understand Theoretical [L1: Knowledge] and practical [L3: Application] skills of instruments
CO3	Ability to interpret the analytical data [L4:Analysis] and identify the structure of the compound [L2: Understanding]
CO4	Perform quantitative analysis of drugs form different dosage forms using various analytical tools [L4: Analysis]

Mapping of Course Outcome (CO) with Program Outcome (PO) and Program Specific Outcome (PSO)

1: Slight (Low) 2: Moderate (Medium) 3: Substantial (High)

If there is no correlation, put "-"

CO	PO 1	PO 2	PO 3	PO 4	PO 5	PO 6	PO 7	PO 8	PO 9	PO 10	PO 11	PSO1	PSO2	PSO3	PSO4
CO1	3	2	2	3	3	-	-	-	-	-	-	3	2	3	3
CO2	3	3	2	3	3	-	-	-	-	-	-	2	1	1	2
CO3	3	2	3	2	3	-	-	-	-	-	-	1	2	2	1
CO4	3	3	2	2	3	-	-	-	-	-	-	3	2	2	2
Avg	3	2.5	1.25	2.5	3	-	-	-	-	-	-	1.25	1.75	2	2

Justification of CO-PO Mapping

CO1 with PO1	CO1 is aligned with PO1 because it demonstrate the technical knowledge of analytical technique
CO1 with PO2	CO1 is aligned with PO2 because it deals with planning to develop the new method and organize the work
CO1 with PO3	CO1 is aligned with PO3 because it deals with the design of analytical methods for method development
CO1 with PO4	CO1 is aligned with PO4 because it deals with utilization of modern took for analysis of API and formulation
CO1 with PO5	CO1 is aligned with PO5 because it deals with the improvement of skills of individuals for handling the analytical tools
CO2 with PO1	CO2 is aligned with PO1 because it moderately deals with the basic knowledge of chromatographic technique
CO2 with PO2	CO2 is aligned with PO2 because it moderately deals with the planning method analysis by chromatography
CO2 with PO3	CO2 is aligned with PO3 because analysis of simple process to meet desired need is useful for the design of new process.
CO2 with PO4	CO2 is aligned with PO4 because it deals with consideration different chromatographic techniques for the design of new process for new formulation of drug
CO2 with PO5	CO2 is aligned with PO5 because modern analytical tools can be used to improve practical skill in pharmacy practices
CO3 with PO1	CO3 is aligned with PO1 because for method development the knowledge of techniques needed in pharmaceutical sciences
CO3 with PO2	CO3 is aligned with PO2 because it deals with proper planning to achieve the goals
CO3 with PO3	CO3 is aligned with PO3 because through the analysis one can interpret the data and identify the component of the substances
CO3 with PO4	CO3 is aligned with PO4 because it deals with using modern tools for detection of new compounds

CO3 with PO5	CO3 is aligned with PO5 because it deals with the modern tools used for process validation
CO4 with PO1	CO4 is aligned with PO4 because it deals with the qualitative and quantitative analysis and method validation in pharmaceutical sciences
CO4 with PO2	CO4 is aligned with PO2 because it helps to formulate and solve problems related to Pharmaceutical Industry by method validation
CO4 with PO3	CO4 is aligned with PO3because it deals to design and conduct the experiment to meet desire needs
CO4 with PO4	CO4 is aligned with PO4 because it deals to analyze the method by qualitative and quantitative analysis
CO4 with PO5	CO4 is aligned with PO6 because it deals with validation and detection through analysis
Justification of CO-PSO Mapping	
CO1 with PSO1	CO1 is aligned with PSO1 because it deals with the technical knowledge of subject
CO1 with PSO2	CO1 is aligned with PSO2 because it deals with understanding of the theoretical concept of the techniques and procedures used for analysis
CO1 with PSO3	CO1 is aligned with PSO3 because it defines the method used for the analysis of finished product and also defines the process used for analysis.
CO1 with PSO4	CO1 is aligned with PSO4 because it deals with the knowledge of technique one can define the process to meet desired need
CO2 with PSO1	CO2 is aligned with PSO1because it deal with the theoretical knowledge of the analytical technique
CO2 with PSO2	CO2 is aligned with PSO2 because it deals with understanding of the practical skills
CO2 with PSO3	CO2 is aligned with PSO3 because it defines the analysis of process and finished product in limits
CO2 with PSO4	CO2 is aligned with PSO3 because it deals with the defining the procedure for the analysis which meet the desired standard of safety for humans
CO3 with PSO1	CO3 is aligned with PSO1 because it deals with the development of technical knowledge of safety measures analytical instruments
CO3 with PSO2	CO3 is aligned with PSO2 because it deals with the development of new process and procedure for manufacturing new drug with understanding of its limitation
CO3 with PSO3	CO3 is aligned with PSO3 because it deals with the evaluation of drugs and finished products lies in permissible limit
CO3 with PSO4	CO3 is aligned with PSO4 because it deals with the designing of method for stable formulation which meet desire needs of safety for humans
CO4 with PSO1	CO4 is aligned with PSO1 because it deals with the theoretical knowledge of the analytical technique
CO4 with PSO2	CO4 is aligned with PSO2 because it deals it deal appropriate methods, procedures, resources and modern pharmacy-related computing tools
CO4 with PSO3	CO4 is aligned with PSO3 because it deals analyze and evaluate chemical substances and finished products
CO4 with PSO4	CO4 is aligned with PSO4 because it deals design a system, component or process to meet desired needs within realistic constraints

QUESTION BANK

BP701T Instrumental Methods of Analysis–Theory

Bloom's Taxonomy level: Bloom Levels (BL) : 1. Remembering 2. Understanding 3. Application 4. Analysis

Q. No.	Questions	CO mapped	Bloom level
	Topic- UV spectroscopy		
1	Define- Absorbance, Transmittance,wavelength,wave number	**CO1**	**2**
2	Explain Band and line spectra	**CO1**	**2**
3	Explain Electromagnetic radiation	**CO2**	**2**
4	Write a note on chromophore	**CO2**	**2**
5	With the help of appropriate examples discuss in detail deviations in Beers' law.	**CO3**	**2**
6	Draw a neat diagram of a photomultiplier tube and explain its construction, working and advantages over phototube.	**CO3**	**3**
7	State and derive Beer-Lamberts' law in absorption spectroscopy.	**CO1**	**1,2**
8	Compare gratings vs. prisms as monochromators.	**CO3**	**2**
9	With the help of a neat diagram explain the construction and working of a barrier layer cell.	**CO3**	**3**
10	Applications of UV spectroscopy	**CO4**	**3,4**
11	Short Note: Sources used in UV spectroscopy	**CO2**	**2**
12	Short Note: Bathochromic and hypsochromic shifts	**CO3**	**3**
13	Characteristics of an ideal detector	**CO3**	**2**
14	With the help of a neat diagram explain the construction, working, advantages and disadvantages of a photocell.	**CO4**	
15	With the help of proper examples explain the phenomena of auxochromic effect.	**CO3**	**2**
	FLUORIMETRY		
16	Explain with examples how the inherent structure of a molecule plays a role in deciding intensity of fluorescence?	**CO3**	**2**
17	Explain the term Quenching of fluorescence. Describe in detail the factors affecting intensity of fluorescence.	**CO4**	**2**
18	Short Note Difference between fluorescence and phosphorescence	**CO3**	**2**
19	Discuss various deactivation processes that take place when an excited molecule comes back to a ground state.	**CO3**	**2**
20	Explain the mechanism of fluorescence and phosphorescence. Why is fluorescence used widely as	**CO3**	**2**

	compared to phosphorescence?		
21	Discuss deactivation of an excited molecule by internal conversion and intersystem crossing.	**CO3**	**2**
22	Applications of fluorimetry	**CO4**	**3**
	IR SPECTROMETRY		
23	Describe sample preparation in IR spectroscopy for solid samples.	CO2	3
24	Describe KBr pellet method and mull method in IR spectroscopy.	CO2	3
25	With the help of neat diagrams explain different types of vibrations in IR spectroscopy.		
26	Describe various sources used in IR spectroscopy.	CO1	2
27	With the help of a neat diagram explain the construction and working of a Golay cell	CO2	3
	FLAME PHOTOMETRY		
28	With the help of neat diagrams, describe absorption profiles for various metallic ions in atomic spectroscopy.	CO3	3
29	Compare laminar flow burners with turbulent flow burners	CO1	2
30	With the help of a neat diagram explain the working of a laminar flow burner.	CO2	3
	ATOMIC ABSORPTION and EMISSION SPECTROMETRY		
31	Explain flame absorption profile and its significance.	**CO3**	**3**
32	Explain the effect of temperature variation on flame spectra.	**CO3**	**3**
33	Compare atomization of compounds by flame and non-flame atomizers.	**CO3**	**2**
34	With the help of a neat diagram explain different parts of the flame and also the reactions that can occur in those parts.	**CO3**	**2**
35	Flame ionization detector	**CO3**	**2**
	TURBIDIMETRY		
36	Draw a neat diagram of an Eel's nephelometer. How do you calculate concentration of an unknown sample using it? (Show only calculations).	**CO3**	**3**
37	What is Tyndall effect? Explain important applications of the light scattering phenomena.	**CO3,CO 4**	**2**
38	Differentiate between nephelometry and turbidometry	**CO3**	**2**
39	Draw a neat diagram of Eel's nephelometer and explain its advantages over Duboscq nephelometer.	**CO4**	**2**

40	Applications of nephelometry and turbidometry	**CO4**	**3**
CHROMATOGRAPHY			
41	Sample injection system in HPLC.	CO1	2
42	With the help of neat diagrams describe two dimensional technique used in TLC to develop the plate	CO3	2
43	Note-Paper Chromatography.	CO2	1
44	Describe different methods used to locate position of compounds on the plate in TLC		
45	Describe the following with respect to HPLC. Column efficiency Column selectivity Resolution	CO2	2
46	Explain how principles of chromatography can be applied to the separation of compounds using ion-exchange resins.	CO3	2
47	Explain how principles of chromatography can be applied to the separation of compounds using ion-exchange resins.	CO3	2
48	Explain the theory of HPTLC technique. Discuss the advantages and Detection system in HPTLC	CO1	2
49	Instrumentation of GC	CO1	2

MODEL ANSWERS
BP701T Instrumental Methods of Analysis–Theory

Q.1 Define- Absorbance, Transmittance

Absorbance (A). Absorbance is the amount of light absorbed by a sample. It is calculated from T or %T using the following equations:

$A = - \log_{10} T$ or **$A = \log_{10} (1/T)$**

$A = 2 - \log_{10} \%T$

These equations reveal that transmittance and absorbance are inversely related. That is, the more a particular wavelength of light is absorbed by a substance, the less it is transmitted. Moreover, the inverse relationship between A and T is not linear, it is logarithmic

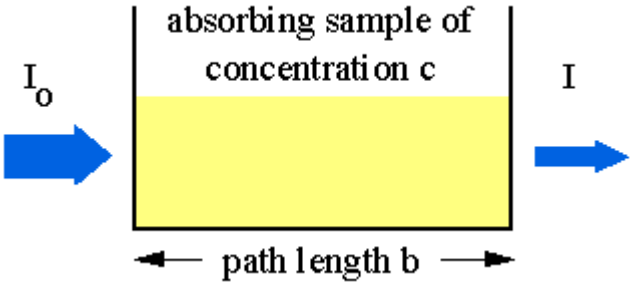
Transmittance (T), which is defined as:

$T = I / I_o$

where I is the **light intensity** after it passes through the sample and I_o is the **initial light intensity**. The relation between A and T is:

$A = -\log T = - \log (I / I_o)$.

Absorption of light by a sample



Modern absorption instruments can usually display the data as either transmittance, %-transmittance, or absorbance. An unknown concentration of an analyte can be determined by measuring the amount of light that a sample absorbs and applying Beer's law. If the absorptivity coefficient is not known, the unknown concentration can be determined using a working curve of absorbance versus concentration derived from standards.

Q.2 Explain Band and line spectra

When white light falls on a prism, placed in a spectrometer, the waves of different wavelengths are deviated to different directions by the prism. The image obtained in the field of view of the telescope consists of a number of coloured images of the slit. Such an image is called a spectrum.

1. Line spectrum

Line spectra are sharp lines of definite wavelengths. It is the characteristic of the emitting substance. It is used to identify the gas.

Fig 5.4 Line spectrum of hydrogen

Atoms in the gaseous state, i.e. free excited atoms emit line spectrum. The substance in atomic state such as sodium in sodium vapour lamp, mercury in mercury vapour lamp and gases in discharge tube give line spectra (Fig. 5.4).

2. Band Spectrum

It consists of a number of bright bands with a sharp edge at one end but fading out at the other end.

Band spectra are obtained from molecules. It is the characteristic of the molecule. Calcium or Barium salts in a bunsen flame and gases like carbon-di-oxide, ammonia and nitrogen in molecular state in the discharge tube give band spectra. When the bands are examined with high resolving power spectrometer, each band is found to be made of a large number of fine lines, very close to each other at the sharp edge but spaced out at the other end. Using band spectra the molecular structure of the substance can be studied.

Q.3 **Electromagnetic radiation**

The electromagnetic spectrum covers a wide range of wavelengths and photon energies. Light used to "see" an object must have a wavelength about the same size as or smaller than the object. Electromagnetic radiation waves, as their names suggest are fluctuations of electric and magnetic fields, which can transport energy from one location to another. Visible light is not inherently different from the other parts of the electromagnetic spectrum with the exception that the human eye can detect visible waves. The visible spectrum constitutes but a small part of the total radiation spectrum. Most of the radiation that surrounds us cannot be seen, but can be detected by dedicated sensing instruments. This electromagnetic spectrum ranges from very short wavelengths (including gamma and x-rays) to very long wavelengths (including microwaves and broadcast radio waves). As light interacts with matter it can be become altered and by studying light that has originated or interacted with matter, many of the properties of that matter can be determined. It is through the study of light that for example we can understand the composition of the stars light years away or watch the processes that occur in the living cell as they happen. The energy associated with a given segment of the spectrum is proportional to its frequency. The bottom equation describes this relationship, which provides the energy carried by a photon of a given wavelength of radiation.

Q.4 Chromophore

The chromophore is a region in the molecule where the **energy difference between two separate molecular orbitals** falls within the range of the visible spectrum. Visible light

that hits the chromophore can thus be absorbed by exciting an electron from its ground state into an excited state.

Chromophore is the part of a molecule or chemical group which is responsible for its colour. The colour arises when a molecule absorbs certain and transmits or reflects others .

The atomic grouping on which the color of a substance depends. Any chemical group or residue (as NO2; N2; or O2) which imparts some decided color to the compound of which it is an ingredient. Visible light that hits the chromophore can thus be absorbed by exciting an electron from its ground state into an excited state . In biology, molecules that serve to capture or detect light energy; the Chromophore is the moiety that causes a conformational

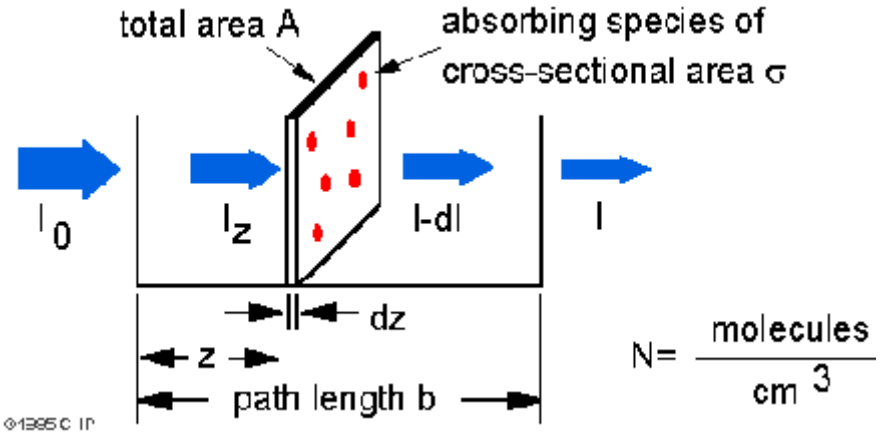
change of the molecule when hit by light. The color ranges are given for visible electromagnetic radiations are given Chemical structure of beta-carotene . The eleven

conjugated double bonds that form the chromophore of the molecule are highlighted in red When white light passes through or is reflected by a colored substance, a characteristic portion of the mixed wavelengths is absorbed. The remaining light will then assume the complementary color to the wavelength(s) absorbed. This relationship is demonstrated by the color wheel shown on the right. Here, complementary colors are diametrically opposite each other. Thus, absorption of 420-430 nm light renders a substance yellow, and absorption of 500-520 nm light makes it red

Q.5 With the help of appropriate examples discuss in detail deviations in Beers' law

Derivation of the Beer-Lambert law

The Beer-Lambert law can be derived from an approximation for the absorption coefficient for a molecule by approximating the molecule by an opaque disk whose cross-sectional area, σ, represents the effective area seen by a photon of frequency w. If the frequency of the light is far from resonance, the area is approximately 0, and if w is close to resonance the area is a maximum. Taking an infinitesimal slab, dz, of sample:



I_o is the intensity entering the sample at z=0, I_z is the intensity entering the infinitesimal slab at z, dI is the intensity absorbed in the slab, and I is the intensity of light leaving the

sample. Then, the total opaque area on the slab due to the absorbers is σ * N * A * dz. Then, the fraction of photons absorbed will be σ * N * A * dz / A so,

$dI / I_z = - \sigma * N * dz$

Integrating this equation from z = 0 to z = b gives:

$\ln(I) - \ln(I_o) = - \sigma * N * b$

or $- \ln(I / I_o) = \sigma * N * b$.

Since N (molecules/cm^3) * (1 mole / 6.023×10^{23} molecules) * 1000 cm^3 / liter = c (moles/liter) and 2.303 * log(x) = ln(x) then

$- \log(I / I_o) = \sigma * (6.023 \times 10^{20} / 2.303) * c * b$

$- \log(I / I_o) = A = \varepsilon * b * c$

where $\varepsilon = \sigma * (6.023 \times 10^{20} / 2.303) = \sigma * 2.61 \times 10^{20}$

Limitations of the Beer-Lambert law

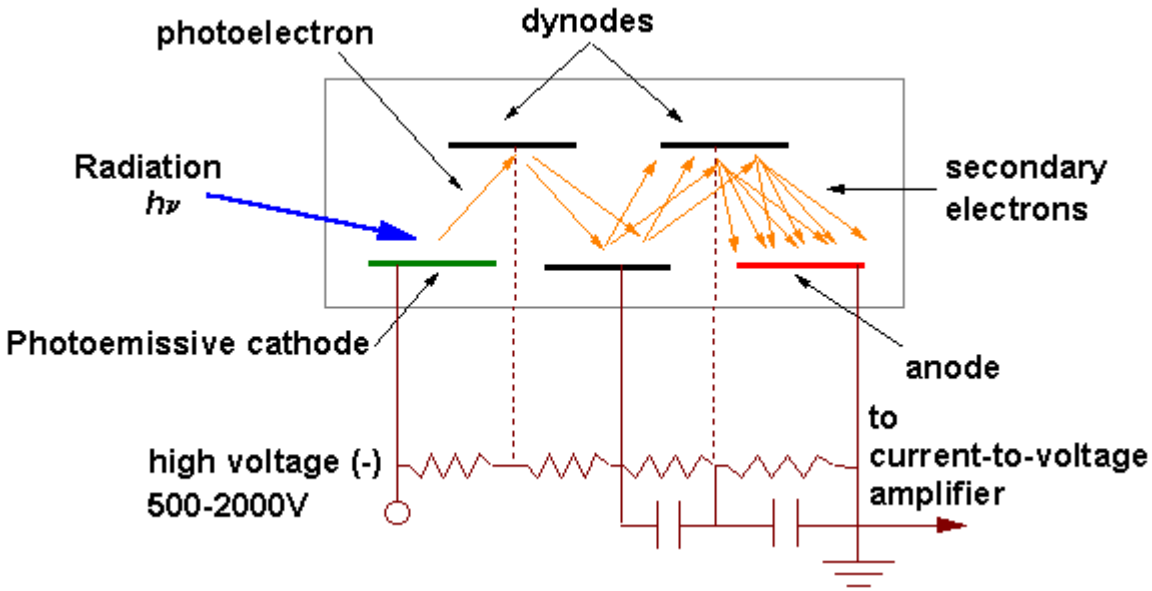
The linearity of the Beer-Lambert law is limited by chemical and instrumental factors. Causes of nonlinearity include:

- deviations in absorptivity coefficients at **high concentrations (>0.01M)** due to electrostatic interactions between molecules in close proximity
- **scattering of light due to particulates** in the sample
- **fluoresecence or phosphorescence** of the sample
- changes in refractive index at high analyte concentration
- shifts in chemical equilibria as a function of concentration
- non-monochromatic radiation, deviations can be minimized by using a relatively flat part of the absorption spectrum such as the maximum of an absorption band
- stray light

Q.6 Draw a neat diagram of a photomultiplier tube and explain its construction, working and advantages over phototube.

They consist of a photocathode and a series of dynodes in an evacuated glass enclosure. Photons that strikes the photoemissive cathode emits electrons due to the photoelectric effect. Instead of collecting these few electrons (there should not be a lot, since the primarily use for PMT is for verly low signal) at an anode like in the phototubes, the electrons are accelerated towards a series of additional electrodes called dynodes. These electrodes are each maintained at a more positive potential. Additional electrons are generated at each dynode. This cascading effect creates 10^5 to 10^7electrons for each photon hitting the first cathode depending on the number of dynodes and the accelerating voltage. This amplified signal is finally collected at the anode where it can be measured.

Schematic of a PMT



Advantages of Photomultiplier tube (PMT)

Following are the **advantages of Photomultiplier tube (PMT)**:

➨Higher responsivity in A/W

➨Lower dark current

➨High output S/N ratio

➨Low transport delay

➨Wide spectral response

➨High stability

Disadvantages of Photomultiplier tube (PMT)

Following are the **disadvantages of Photomultiplier tube (PMT)**:

➨Mechanically fragile (made of glass envelope).

➨Shapes and sizes are limited and are physically large.

➨Need stable high voltage power supplies.

➨Expensive, available in hundreds of dollars.

➨Responsivity affected by magnetic fields, hence it requires magnetic shielding in critical applications.

➨It requires cooling to LN_2 temperatures for noise reduction in critical applications.

Q.7 State and derive Beer-Lamberts' law in absorption spectroscopy

The **Beer-Lambert law (or Beer's law)** is the linear relationship between absorbance and concentration of an absorbing species. The general Beer-Lambert law is usually written as:

$$A = a(\lambda) * b * c$$

where A is the measured absorbance, $a(\lambda)$ is a wavelength-dependent absorptivity coefficient, **b** is the path length, and **c** is the analyte concentration. When working in concentration units of molarity, the *Beer-Lambert law* is written as:

$$A = \varepsilon * b * c$$

where ε is the wavelength-dependent molar absorptivity coefficient with units of M^{-1} cm^{-1}. Data are frequently reported in percent transmission ($I/I_0 * 100$) or in absorbannce [$A = \log (I/I_0)$]. The latter is particularly convenient. [common coefficients of near-ultraviolet absorption bands of some amino acids and nucleotides]

Sometimes the extinction coefficient is given in other units; for example,

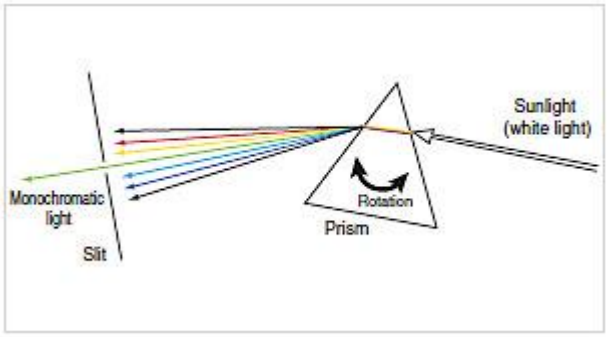
$A = E^{1\%} * b * c$

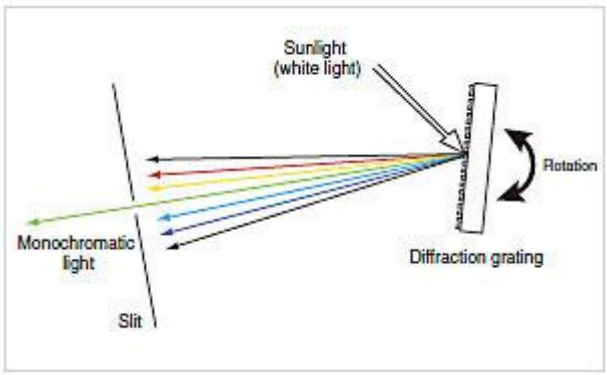
where the concentration C is in gram per 100 ml of solution. This useful when the molecular weight of the solute is unknown or uncertain.

Applications

Beer-Lamberts law is applied to the analysis of a mixture by spectrophotometry, without the need for extensive pre-processing of the sample. Examples include the determination of bilirubin in blood plasma samples. The spectrum of pure bilirubin is known thus the molar absorbance is known. Measurements are made at one specific wavelength almost unique for bilirubin and another measurement at a second wavelength so interferences or deviations can be eliminated or corrected. Generally, it can be used to determine concentrations of a particular substance, or determine the molar absorptivity of a substance.

Q.8 Compare gratings vs. prisms as monochromators





The prism and diffraction grating are typical dispersive elements. Due to their superior dispersion properties, diffraction gratings are often used in modern spectrophotometers. The prism achieves dispersion due to the difference in the material refractive index according to the wavelength. However, the diffraction grating uses the difference in diffraction direction for each

wavelength due to interference. The reflective blazed diffraction grating that is commonly used in spectrophotometers is described below.

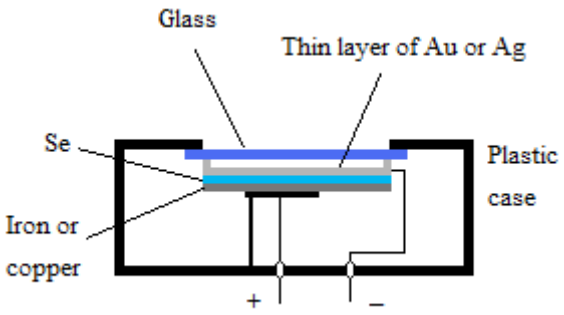
Prism	Grating
The isolation of wavelength is because of the difference in the velocities of the wavelength inside the prism	The isolation of wavelength is because of the diffraction of wavelength
Prism are less efficient than grating because of lower degree of dispersion of radiation	Grating are more efficient than prism because of higher degree of dispersion of radiation
Dispersion by prism is non linear. Hence the fabrication of instrument is difficult	Dispersion by grating is liner. Hence fabrication of instrument is easy
Manufacturing of prism is simple, hence prism are cheaper compared to grating	Manufacturing of gratings is tedious and involves a great skill. Hence gratings are costlier compared to prism
Prism are used mainly in Visible region	Grating are used in UV,Visible and IR region
Prism do not produce higher order spectra	Grating produce higher order spectra

Q.9 With the help of a neat diagram explain the construction and working of a barrier layer cell.

A device that detects or measures electromagnetic radiation by generating a potential at a junction (**barrier layer**) between two types of material, upon absorption of radiant energy. Also known as **barrier-layer cell**; **barrier-layer**photocell; boundary-**layer** photocell; photronic photocell..

The detector has a thin film metallic layer coated with silver or gold and acts as an electrode. ¬ It also has a metal base plate which acts as another electrode. ¬ These two layers are separated by a semiconductor layer of selenium. 39

When light radiation falls on selenium layer, electrons become mobile and are taken up by transparent metal layer. ¬ This creates a potential difference between two electrodes & causes the flow of current. ¬ When it is connected to galvanometer, a flow of current observed which is proportional to the intensity and wavelength of light falling on it



Q. 10 Applications of UV spectroscopy

1. Detection of Impurities

UV absorption spectroscopy is one of the best methods for determination of impurities in organic molecules. Additional peaks can be observed due to impurities in the sample and it can be compared with that of standard raw material. By also measuring the absorbance at specific wavelength, the impurities can be detected.

Benzene appears as a common impurity in cyclohexane. Its presence can be easily detected by its absorption at 255 nm.

2. Structure elucidation of organic compounds.

UV spectroscopy is useful in the structure elucidation of organic molecules, the presence or absence of unsaturation, the presence of hetero atoms.

From the location of peaks and combination of peaks, it can be concluded that whether the compound is saturated or unsaturated, hetero atoms are present or not etc.

3. Quantitative analysis

UV absorption spectroscopy can be used for the quantitative determination of compounds that absorb UV radiation. This determination is based on Beer's law which is as follows.

$A = \log I_0 / I_t = \log 1/ T = - \log T = abc = \varepsilon bc$

Where ε is extinction co-efficient, c is concentration, and b is the length of the cell that is used in UV spectrophotometer.

Other methods for quantitative analysis are as follows.

a. calibration curve method

b. simultaneous multicomponent method

c. difference spectrophotometric method

d. derivative spectrophotometric method

4. Qualitative analysis

UVabsorption spectroscopy can characterize those types of compounds which absorbs UV radiation. Identification is done by comparing the absorption spectrum with the spectra of known compounds.

UV absorption spectroscopy is generally used for characterizing aromatic compounds and aromatic olefins.

5. Dissociation constants of acids and bases.

$PH = PKa + \log [A^-] / [HA]$

From the above equation, the PKa value can be calculated if the ratio of $[A^-] / [HA]$ is known at a particular PH. and the ratio of $[A^-] / [HA]$ can be determined spectrophotometrically from the graph plotted between absorbance and wavelength at different PH values.

6. Chemical kinetics

Kinetics of reaction can also be studied using UV spectroscopy. The UV radiation is passed through the reaction cell and the absorbance changes can be observed.

7. Quantitative analysis of pharmaceutical substances

Many drugs are either in the form of raw material or in the form of formulation. They can be assayed by making a suitable solution of the drug in a solvent and measuring the absorbance at specific wavelength.

Diazepam tablet can be analyzed by 0.5% H2SO4 in methanol at the wavelength 284 nm.

8. Molecular weight determination

Molecular weights of compounds can be measured spectrophotometrically by preparing the suitable derivatives of these compounds.

For example, if we want to determine the molecular weight of amine then it is converted in to amine picrate. Then known concentration of amine picrate is dissolved in a litre of solution and its optical density is measured at λmax 380 nm. After this the concentration of the solution in gm moles per litre can be calculated by using the following formula.

"**c**" can be calculated using above equation, the weight "**w**" of amine picrate is known. From "**c**" and "**w**", molecular weight of amine picrate can be calculated. And the molecular weight of picrate can be calculated using the molecular weight of amine picrate.

9. As HPLC detector

A UV/Vis spectrophotometer may be used as a detector for HPLC. The presence of an analyte gives a response which can be assumed to be proportional to the concentration. For more accurate results, the instrument's response to the analyte in the unknown should be compared with the response to a standard; as in the case of calibration curve.

Q.11 Sources used in UV spectroscopy

Properties :

• A source must generate a beam with sufficient radiant power for easy detection and measurement. • Its output power should be stable for reasonable periods.

• Intensity should not fluctuate over long and short time intervals.

Types of radiation sources.

• Two types of radiation sources

• Continuum Sources and

• Line Sources

1.Continuum Sources

• Emit radiation over a wide range of wavelengths

•Intensity of emission varies slowly as a function of wavelength

• Used for most molecular absorption and fluorescence spectrometric instruments • Examples • Tungsten filament lamp (visible radiation)

• Deuterium lamp (UV radiation)

• High pressure Hg lamp (UV radiation)

• Xenon arc lamp (UV-VIS region)

• Heated solid ceramics (IR region)

• Heated wires (IR region)

Examples. Tungsten filament lamp Xenon arc lamp Deuterium lamp

2.Line Sources

• - Emit only a few discrete wavelengths of light

• - Intensity is a function of wavelength

• - Used for molecular, atomic, and Raman spectroscopy

• Examples • Hollow cathode lamp (UV-VIS region)

• Electrodeless discharge lamp (UV-VIS region)
• Sodium vapor lamp (UV-VIS region)
• Mercury vapor lamp (UV-VIS region)
• Lasers (UV-VIS and IR regions)

Deuterium Lamp

Also known as D2 lamp, its wavelength range is from of 190nm - 370nm. Because of its high temperature behavior, the normal glass housing is not suitable, but requires quartz, MgF_2, or other materials. Life time of a typical deuterium lamp is about 1000 hours. An UV / Vis spectrophotometer, will design a deuterium lamp with a halogen lamps, in order to cover the entire UV and visible light wavelength.

Halogen Lamp

Also known as tungsten or quartz lamp, and the wavelength range of halogen lamp is in the visible light region, which is in the range of 320nm to 1100 nm. If the instrument is equipped with a halogen lamp only, it means the instrument can only measure visible light. General halogen lamp life is about 2000 hours, or more.

Xenon Lamp

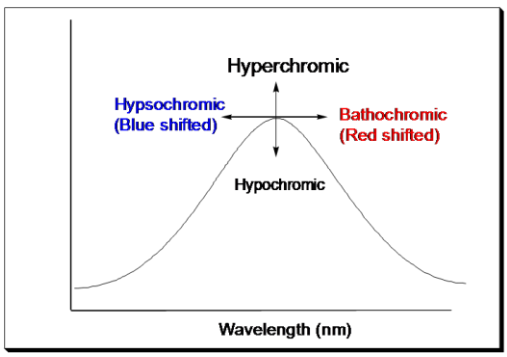
Xenon lamp provides high energy light source, and it can reach a steady state in a short time period. Its light covers the entire UV and visible wavelength range, from 190nm to 1100nm. An xenon lamp flashes in a frequency of 80Hz, so that the life time is longer than deuterium lamp or halogen lamp. However, the cost of a xenon lamp is higher.

LED Lamp

Produce a single wavelength of light, thus, LED lamp does not require a monochromator. Its life is very long. LED light source has little variation in bandwidth, and it's stable. LED lamp is a low-cost light source.

Q.12 Bathochromic and hypsochromic shifts

Bathochromic: a **shift** of a band to lower energy or longer wavelength (often called a red **shift**).**Hypsochromic**: a **shift** of a band to higher energy or shorter wavelength (often called a blue **shift**).



Changes in chemical structure or the environment lead to changes in the absorption spectrum of molecules and materials. There are several terms that are commonly used to

describe these shifts, that you will see in the literature, and with which you should be familiar.

Bathochromic: a shift of a band to lower energy or longer wavelength (often called a red shift).

Hypsochromic: a shift of a band to higher energy or shorter wavelength (often called a blue shift).

Hyperchromic: an increase in the molar absorptivity.

Hypochromic: an decrease in the molar absorptivity.

Q.13 Characteristics of an ideal detector

A sensitive **detector** is one which provides rapid response to changes in mass of analyte reaching it. Slow response can have adverse effect on peak shape so an **ideal detector** should produce instantaneous response to mass changes.

Several features of HPLC Detectors:

(1) it should response to all compounds in the mixture (a general detector) or it should response with known sensitivity (a specific detector).

(2) It should not response to mobile phase.

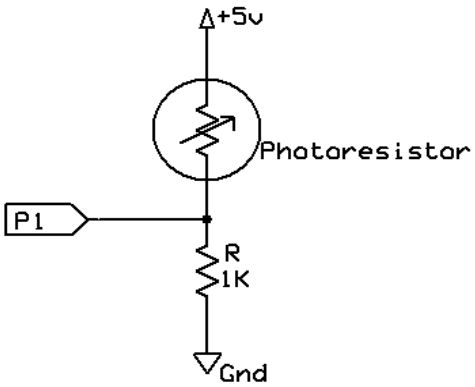
(3) It should give linear response to solute concentration.

(4) It should be unaffected by variation in temperature and flow rate.

(5) It should not contribute to zone spreading. [5]

Q.14 With the help of a neat diagram explain the construction, working, advantages and disadvantages of a photocell

Photocell is a device that is used to detect and measure light. The dusk to dawn **photocell** sensor switch will switch items such as lights and fans on during the night and off during the day. A **photocell** sensor can be regarded as a transducer that is used to detect the light intensity.



Phototubes are also known as photoemissive cells. A phototube consists of an evacuated glass bulb. There is light sensitive cathode inside it. The inner surface of cathode is coated with light sensitive layer such as potassium oxide and silver oxide.

When radiation is incident upon a cathode, photoelectrons are emitted. These are collected by an anode. Then these are returned via external circuit. And by this process current is amplified and recorded.

Q.15 With the help of proper examples explain the phenomena of auxochromic effect

An auxochrome is a functional group of atoms with one or more lone pairs of electrons when attached to a chromophore, alters both the wavelength and intensity of absorption. If these groups are in direct conjugation with the pi-system of the chromophore, they may increase the wavelength at which the light is absorbed and as a result intensify the absorption. A feature of these auxochromes is the presence of at least one lone pair of electrons which can be viewed as extending the conjugated system by resonance. An auxochrome is known as a compound that produces a bathochromic shift, also known as red shift because it increases the wavelength of absorption, therefore moving closer to infrared light.

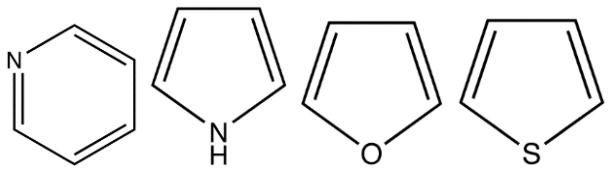
It is a group which itself does not act as a chromophore but when attached to a chromophore, it shifts the adsorption towards longer wavelength along with an increase in the intensity of absorption. Some commonly known auxochromic groups are: -OH, -NH2, -OR, -NHR, and –NR2. For example: When the auxochrome –NH2 group is attached to benzene ring. Its absorption change from λ max 225 (εmax 203) to λmax 280 (εmax1430) All auxochromes have one or more non-bonding pairs of electrons. If an auxochromes is attached to a chromophore, it helps is extending the conjugation by sharing of non-bonding pair of electrons as shown below.

CH2 = CH – NR2 ---------- > CH2-CH-NH2

The extended conjugation has been responsible for bathochromic effect of auxochromes.

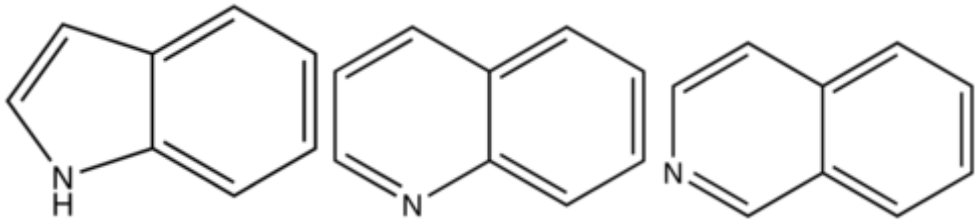
Q.16 Explain with examples how the inherent structure of a molecule plays a role in deciding intensity of fluorescence.

The most intense fluorescence is found in compounds containing aromatic group with low-energy π→π∗π→π∗ transitions. A few aliphatic, alicyclic carbonyl, and highly conjugated double-bond structures also exhibit fluorescence as well. Most unsubstituted aromatic hydrocarbons fluoresce in solution too. The quantum efficiency increases as the number of rings and the degree of condensation increases. Simple heterocycles such as the structures listed below do not exhibit fluorescence.



Pyridine Pyrrole Furan Thiophene

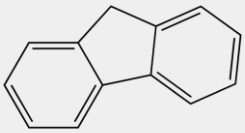
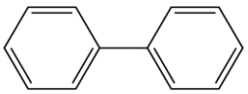
With nitrogen heterocyclics, the lowest energy transitions is involved in n→π∗n→π∗ system that rapidly converts to the triplet state and prevents fluorescence. Although simple heterocyclics do not fluoresce, fused-ring structures do. For instance, a fusion of a benzene ring to a hetercyclic structure results in an increase in molar absorptivity of the absorption band. The lifetime of the excited state in fused structure and fluorescence is observed. Examples of fluorescent compounds is shown below.



quinoline

Benzene ring substitution causes a shift in the absorption maxima of the wavelength and changes in fluorescence emission. The table below is used to demonstrate and visually show that as benzene is substituted with increasing methyl addition, the relative intensity of fluorescence increases. Fluorescence is particularly favored in molecules with rigid structures. The table below compares the quantum efficiencies of fluorine and biphenyl which are both similar in structure that there is a bond between the two benzene group. The difference is that fluorene is more rigid from the addition methylene bridging group. By looking at the table below, rigid fluorene has a higher quantum efficiency than unrigid biphenyl which indicates that fluorescence is favored in rigid molecules.

Quantum Efficiencies in Rigid vs. Nonrigid structures

Compound	**Structure**	**Quantum Efficiency**
Fluorene	 Fluorene	1.0
Biphenyl	 biphenyl	0.2

This concept of rigidity was used to explain the increase in fluorescence of organic chelating agent when the compound is complexed with a metal ion. The fluorescence intensity of 8-hydroxyquinoline is much less than its zinc complex.

Q.17 Explain the term Quenching of fluorescence. Describe in detail the factors affecting intensity of fluorescence.

Quenching refers to any process which decreases the fluorescence intensity of a given substance. A variety of processes can result in quenching, such as excited state reactions, energy transfer, complex-formation and collisional quenching. As a consequence, quenching is often heavily dependent on pressure and temperature.

Molecular oxygen, iodide ions and acrylamide are common chemical quenchers. The chloride ion is a well known quencher for quinine fluorescence

 This may occur due to various factors like pH, concentration, temperature, viscosity, presence of oxygen, heavy metals or, specific chemical substances etc.

Fig: Quenching of quinine fluorescence in presence of chloride ions

Types of quenching

- process Quenching
- Collisional quenching
- Static quenching
- Concentration quenching
- Chemical quenching

1. Collisional quenching Collisional quenching occurs by the interaction of a quencher molecule (Q) with an excited molecule of the fluorescing substance (F*). A simplified mechanism can be written to describe this process: F + hv F* F* F + hv F* + Q F + Q* Here, the interaction results in the dissipation of excitation energy by a non radiative energy transfer from F* to Q without or, less fluorescence.

Fig : Simple mechanism of collisional quenching Halides ions such as chlorides or, iodides are well known collisional quenchers. For example, quenching of quinine drug by chloride ion or, quenching of tryptophan by iodide ion follow collisional quenching process. Weak coupling Light Energy transfer Quenching of light F* Q Distance

2. Static quenching Static quenching occurs at the ground state of fluorescing molecule. It can be simplified by following mechanism: F + Q F : Q F:Q + hv Q* + F Q* Q + energy Here, a complex formation occurs between the fluorescing molecule at the ground state (F) and the quencher molecule (Q) through a strong coupling. Such complex may not undergo excitation or, may be excited to a little extent reducing the fluorescence intensity of the molecule.

Strong coupling Fig: Static quenching Caffeine and related xanthines and purines reduce intensity of riboflavin by static mechanism. Quenching that occurs due to oxygen also follows this mechanism. Light Energy transfer F Q Quenching of light

4 Concentration quenching Concentration quenching is a kind of self quenching. It occurs when the concentration of the fluorescing molecule increases in a sample solution. The fluorescence intensity is reduced in highly concentrated solution (>50 µg/ml). 100 200 300 concentration (µg/ml) Fig: Influence of concentration on the fluorescence of phenol solutions. 80 60 40 20 0 fluorescenceintensity

5. Chemical quenching Chemical quenching is due to various factors like change in pH, presence of oxygen, halides and electron withdrawing groups, heavy metals etc. ¬ Change in pH : Aniline at pH (5-13) gives fluorescence when excited at 290 nm. But pH <5 or, pH >13 it does not show any fluorescence. ¬ Oxygen : Oxygen leads to the oxidation of fluorescent substance to non fluorescent substance and thus, causes quenching.

Q.18 Difference between fluorescence and phosphorescence

Fluorescence : When the absorbed light radiation is re-emitted instantaneously in one or more steps, we call it fluoroscence. This ceases with removal of light source.

This involves the transition of the activated molecule from Singlet state (S1) to ground state (S0).

The transition occurs in about 10^(-8) sec

Phosphorescence : The absorbed light may be given out slowly and even long after the removal of source light. This is known as phosphorescence.

This involves the transition of the activated molecule from triplet state (T1) to ground state (S0)

The life time of phosphorescence is of order 10^(-5) to 10^(-3) sec, as this phenomenon involves the spin inversion.

Both fluorescence and phosphorescence are spontaneous emissions of electromagnetic radiation. The difference is that the glow of fluorescence stops right after the source of excitatory radiation is switched off, whereas for phosphorescence, an afterglow with durations of fractions of a second up to hours can occur .

To compare the photo-physical processes behind both phenomena, there are some facts about electrons that are helpful for understanding: Electrons are particles that have a so-called spin and a spin quantum number. This can have two different values, namely either +1/2 or –1/2 .This number is a property that we actually cannot imagine or describe easily. It is often compared with a spinning top, either spinning in a clockwise or anti-clockwise direction. However, this description is neither mathematically nor physically quite correct. Two electrons in a single orbital of an atom have antiparallel spin, which is noted as (↑↓)

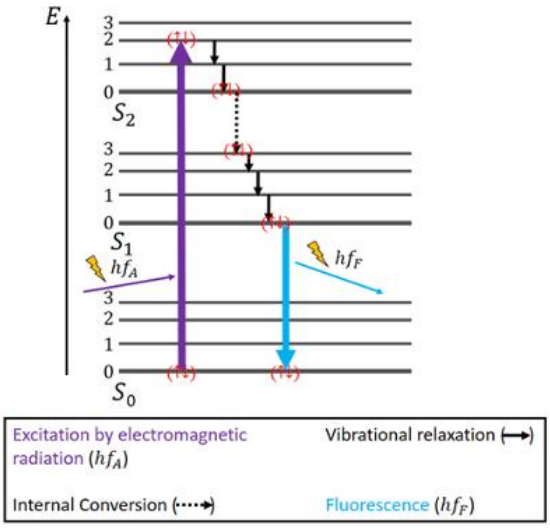
Q.19 Discuss various deactivation processes that take place when an excited molecule comes back to a ground state

A molecule that is excited can return to the ground state by several combinations of mechanical steps that will be described below and shown in Figure 22.The deactivation process of fluorescence and phosphorescence involve an emission of a photon radiation as shown by the straight arrow in Figure 22. The wiggly arrows in Figure 22 are deactivation processes without the use of radiation. The favored deactivation process is the route that is most rapid and spends less time in the excited state.If the rate constant for fluorescence is more favorable in the radiationless path, the fluorescence will be less intense or absent.

- **Vibrational Relaxation:** A molecule maybe to promoted to several vibrational levels during the electronic excitation process.Collision of molecules with the excited species and solvent leads to rapid energy transfer and a slight increase in temperature of the solvent. Vibrational relaxation is so rapid that the lifetime of a vibrational excited molecule ($<10^{-12}$) is less than the lifetime of the electronically excited state. For this reason, fluorescence from a solution always involves the transition of the lowest vibrational level of the excited state.Since the space of the

emission lines are so close together, the transition of the vibrational relaxation can terminate in any vibrational level of the ground state.

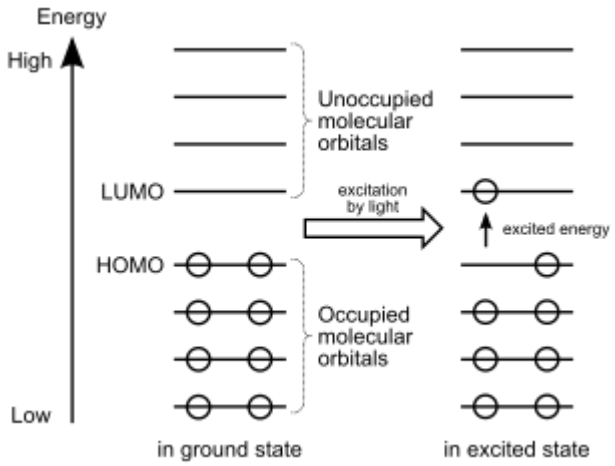
- **Internal Conversion:** Internal conversion is an intermolecular process of molecule that passes to a lower electronic state without the emission of radiation.It is a crossover of two states with the same multiplicity meaning singlet-to-singlet or triplet-to-triplet states.The internal conversion is more efficient when two electronic energy levels are close enough that two vibrational energy levels can overlap as shown in between S_1 and S_2. Internal conversion can also occur between S_0 and S_1 from a loss of energy by fluorescence from a higher excited state, but it is less probable. The mechanism of internal conversion from S_1 to S_0 is poorly understood. For some molecules, the vibrational levels of the ground state overlaps with the first excited electronic state, which leads to fast deactivation.These usually occur with aliphatic compounds (compound that do not contain ring structure), which would account for the compound is seldom fluorescing. Deactivation by energy transfer of these molecules occurs so rapidly that the molecule does not have time to fluoresce.
- **External Conversion**: Deactivation of the excited electronic state may also involve the interaction and energy transfer between the excited state and the solvent or solute in a process called **external conversion.** Low temperature and high viscosity leads to enhanced fluorescence because they reduce the number of collision between molecules, thus slowing down the deactivation process.
- **Intersystem Crossing:** Intersystem crossing is a process where there is a crossover between electronic states of different multiplicity as demonstrated in the singlet state to a triplet state (S_1 to T_1) on Figure 11. The probability of intersystem crossing is enhanced if the vibration levels of the two states overlap. Intersystem crossing is most commonly observed with molecules that contain heavy atom such as iodine or bromine. The spin and orbital interaction increase and the spin become more favorable.Paramagnetic species also enhances intersystem crossing, which consequently decreases fluorescence.
- **Phosphorescence**: Deactivation of the electronic excited state is also involved in phosphorescence. After the molecule transitions through intersystem crossing to the triplet state, further deactivation occurs through internal or external fluorescence or phosphorescence. A triplet-to-singlet transition is more probable than a singlet-to-singlet internal crossing.In phosphorescence, the excited state lifetime is inversely proportional to the probability that the molecule will transition back to the ground state. Since the lifetime of the molecule in the triplet state is large (10^{-4} to 10 second or more), transition is less probable which suggest that it will persist for some time even after irradiation has stopped. Since the external and internal conversion compete so effectively with phosphorescence, the molecule has to be observed at lower temperature in highly viscous media to protect the triplet state.



Q.20 Explain the mechanism of fluorescence and phosphorescence. Why is fluorescence used widely as compared to phosphorescence

Fluorescence occurs when electrons move from their ground state to an excited state. These electrons keep the same spin as in the ground state, but when they return to the ground state they emit energy. This energy has a longer wavelength than the originally absorbed energy. If this longer wavelength is within the visible spectrum, then we can see a glowing light.

Recall that electrons fill up orbitals around the molecule (such as the s, p, d, and f orbitals). They will first fill up the lowest energy orbitals, and then move out from there. But excited electrons will jump up an orbital, even if the one below it isn't filled.



Excited electrons move from the highest occupied molecular orbital (HOMO) to the lowest unoccupied molecular orbital (LUMO)

Phosphorescence is very similar to fluorescence, except when the electron moves into the excited state, the spin changes.

Electrons spin in specific direction based on the magnetic momentum. But when a compound shows phosphorescence, that electron has been given enough additional

energy to change the direction of this spin. This change in spin causes the emission to last longer because it takes longer for the electron to release all of the energy.

Fluorescence has many practical applications, including mineralogy, gemology, chemical sensors (fluorescence spectroscopy), fluorescent labelling, dyes, biological detectors, and, most commonly, fluorescent lamps.

Phosphorescence is a specific type of photoluminescence related to fluorescence. Unlike fluorescence, a phosphorescent material does not immediately re-emit the radiation it absorbs. The slower time scales of the re-emission are associated with "forbidden"energy state transitions in quantum mechanics. As these transitions occur very slowly in certain materials, absorbed radiation may be re-emitted at a lower intensity for up to several hours after the original excitation.

In simple terms, phosphorescence is a process in which energy absorbed by a substance is released relatively slowly in the form of light. This is in some cases the mechanism used for "glow-in-the-dark" materials which are "charged" by exposure to light. Unlike the relatively swift reactions in a common fluorescent tube, phosphorescent materials used for these materials absorb the energy and "store" it for a longer time as the processes required to re-emit the light occur less often.

Q.21 Discuss deactivation of an excited molecule by internal conversion and intersystem crossing.

The processes of internal conversion and vibrational relaxation leave the electronically excited molecule in the lowest vibrational sublevels of the first singlet excited state. If subsequent relaxation to the ground electronic state is accompanied by the emission of a photon, the process is formally known as fluorescence. An excited molecule capable of fluorescence typically stays in the lowest excited singlet state S_1 for a period of several nanoseconds before finally relaxing to the ground state. Internal conversion and vibrational relaxation are responsible for the emitted photon having lower energy than the incident photon. This shift to a longer wavelength is a phenomenon known as the Stokes shift. The Stokes shift is essential for the sensitivity of fluorescence detection because it allows effective separation of the fluorescence emission signal from Rayleigh-scattered excitation light. As emission occurs from the lowest vibrational sublevel of first excited singlet state, the emission spectraare, in general, independent of excitation wavelength.

Emission spectra are usually mirror symmetric to the lowest energy absorption band. This symmetry is a result of relaxation to the vibrationally excited states of the electronic ground state S_0, and the similarities of the vibrational energy levels of S_0 and S_1. According to the Franck–Condon principle, all electronic transitions are vertical (Figure 2) that is, they occur without change in the position of the nuclei. Thus, the various transition probabilities (Franck–Condon factors) are similar and lead to the symmetric nature of the absorption and emission spectra.

Q.22 Applications of fluorimetry

1)Determination of inorganic substances. Al3+,Li+,ZN2+

2)Determination of thiamine Hcl.

3)Detemination of phenytoin.
4)Determination of indoles, phenols, & phenothiazines
5) Determination of napthols, proteins, plant pigments and steroids.
6) Fluorimetry ,nowadays can be used in detection of impurities in nanogram level better than absorbance spectrophotometer with special emphasis in determining components of sample at the end of chromatographic or capillary column.
7)Determination of ruthenium ions in presence of other platinum metals
8) Determination of boron in steel, aluminum in alloys, manganese in steel. ′ Determination of boron in steel by complex formed with benzoin
9) Estimation of cadmium with 2-(2 hydroxyphenyl) benzoxazole in presence of tartarate . ′ Respiratory tract infections.
Fluorometry is a relatively simple analytical technique. Fluorometry is chosen for its extraordinary sensitivity, high specificity, simplicity, and low cost as compared to other analytical techniques. It is ordinarily more sensitive than absorbance measurements. It is a widely accepted and powerful technique that is used for a variety of environmental, industrial, medical diagnostics, DNA sequencing, forensics, genetic analysis, and biotechnology applications. It is a valuable analytical tool for both quantitative and qualitative analysis.

Q.23 Describe sample preparation in IR spectroscopy for solid samples.
SAMPLING OF SOLIDS:
Generally 4 techniques are employed for preparing solid samples:
1. Solids run in solution.
2. Solid Films.
3. Mull technique.
4. Pressed pellet technique.

Solids run in solution

• Solids may be dissolved in non-aqueous inert solvent and a drop of this solution is placed on an alkali metal disc and solvent is allowed to evaporate, leaving a thin film of solute (or the entire solution is placed in a liquid sample cell) which is then mounted in spectrometer.
• If the solution of solid can be prepared in a suitable solvent then the solution is run in concentration of cells for liquids.
• Some solvents used are chloroform, carbon tetrachloride, acetone, Cyclohexane etc.
Demerit:
• This method can't be used for all solids because suitable solvents are limited in number & there is no single solvent which is transparent throughout IR region. Precautions: • Solute chemical interaction with the solvent must be taken into consideration especially for compounds having property of H-bonding. • The solvent should not absorb in the studied range

Solid films

• If a solid is polymer resins & amorphous solids, the sample is dissolved in any reasonable volatile solvent & this solution is poured on a rock salt plate (Nacl or KBr) & solvent is evaporated by gentle heating.
• If solid is non-crystalline, a thin homogenous film is deposited on the plate which can be mounted and scanned directly.
• Sometimes polymers can be "hot pressed" onto plates. Merit and Demerit:
• This method is useful for rapid qualitative analysis but becomes useless for carrying out quantitative analysis

Mull technique:

• In this technique a small quantity of sample is thoroughly ground in a clean mortar until the powder is very fine.
• After grinding, the mulling agent (mineral oil or Nujol) is introduced in small quantities just sufficient to take up the powder (mixture approximates the consistency of a toothpaste).
• The mixture is then transferred to the mull plates & the plates are squeezed together to adjust the thickness of the sample between IR transmitting windows.
• This is then mounted in a path of IR beam and the spectrum is run

Pressed pellet technique:

• In this technique a small amount of finely ground solid sample is intimately mixed with about 100 times its weight of powdered Potassium bromide, in a vibrating ball mill. • This finely ground mixture is then pressed under very high pressure (25000 p sig) in evacuable die or minipress to form a small pellet (about 1-2 mm thick and 1cm in diameter). • The resulting pellet is transparent to IR radiation and is run as such.
The powder (KBr + sample) is introduced in between the 2 bolts and the upper screw A is tightened until the powder is compressed to a thin disc. • After compressing the sample bolts A & A1 are removed and a steel cylinder with pellet inside it is placed in path of the beam of IR spectrometer and a blank KBr pellet of identical thickness is kept in the path of reference beam

Advantages of this technique over mull technique:

• The use of KBr eliminates the problem of bands which appear in IR spectrum due to the mulling agent as in this case no such bands appear.
• KBr pellets can be stored for longer periods of time.
• As concentration of the sample can be suitably adjusted in pellets, it can be used for quantitative analysis.
• The resolution of spectrum in KBr is superior to that obtained with mulls

Q.24 Describe KBr pellet method and mull method in IR spectroscopy

Mull technique:

• In this technique a small quantity of sample is thoroughly ground in a clean mortar until the powder is very fine.
• After grinding, the mulling agent (mineral oil or Nujol) is introduced in small quantities just sufficient to take up the powder (mixture approximates the consistency of a toothpaste).

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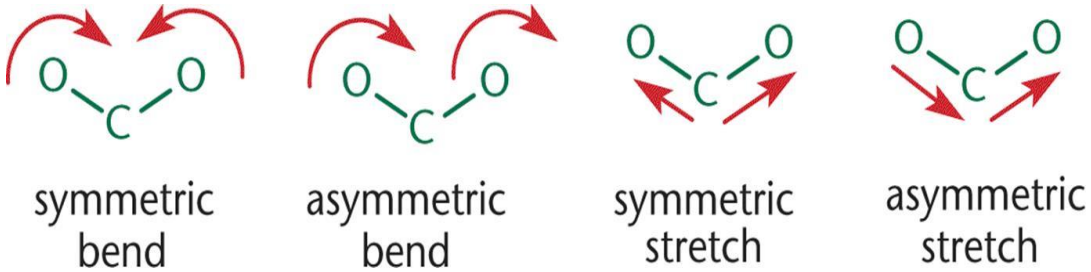
Q.25 With the help of neat diagrams explain different types of vibrations in IR spectroscopy

Stretching or bonding vibrations (ν) alter the bond lengths; Bending or deformation vibrations alter the bond angles, while the bond lengths remain unchanged;
They can be subdivided into in-plane (δ) and out-of-plane modes (γ);
These modes are often referred to as twisting, wagging, and rocking vibration of a fragment; Torsional vibrations involve an alternation of the torsion angle; A further division into symmetric (s), antisymmetric (as), and degenerated (e) vibrations is possible



- Stretching: a change in the length of a bond, such as C–H or C–C
- Bending: a change in the angle between two bonds, such as the HCH angle in a methylene group
- Rocking: a change in angle between a group of atoms, such as a methylene group and the rest of the molecule.
- Wagging: a change in angle between the plane of a group of atoms, such as a methylene group and a plane through the rest of the molecule,

- Twisting: a change in the angle between the planes of two groups of atoms, such as a change in the angle between the two methylene groups.
- Out–of–plane: a change in the angle between any one of the C–H bonds and the plane defined by the remaining atoms of the ethylene molecule. Another example is in BF_3 when the boron atom moves in and out of the plane of the three fluorine atoms.

In a rocking, wagging or twisting coordinate the bond lengths within the groups involved do not change. The angles do. Rocking is distinguished from wagging by the fact that the atoms in the group stay in the same plane.

Q.26 Describe various sources used in IR spectroscopy

Radiation sources

IR instruments require a source of radiant energy which emit IR radiation which must be steady, intense enough for detection and extend over the desired wavelength. Various sources of IR radiations are as follows.

a) Nernst glower
b) Incandescent lamp
c) Mercury arc
d) Tungsten lamp
e) Glober source
f) Nichrome wire

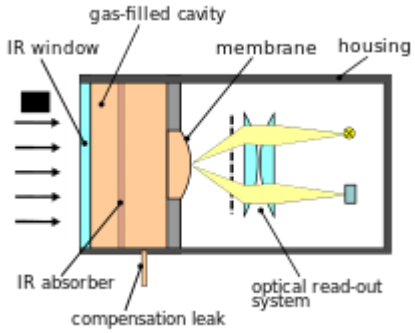
A typical source is a mercury arc inside a quartz envelope where most of the radiation is generated by the hot quartz. Either a **Nernst filament** or a **globar** (SiC) is used as a source of mid-infrared radiation within 200-400nm . **Tungsten filaments** is used in the visible and near infrared spectral range 320-2500nm.

Different types of **gas discharge lamps** are common light sources in ultraviolet and visible spectral region 180-800nm. In a **xenon discharge lamp** an electrical discharge excites xenon atoms to excited states which then emit ultraviolet radiation. At high pressure (several kPa) the output of a xenon lamp consists of sharp lines superimposed on a board intense background due to emission from plasma. High pressure xenon lamps are widely used as a source of radiation which is similar to the black body radiation at 6000 K. There are also many other widely used lamps which use discharge in **deuterium**, **mercury**, **neon**, **krypton** and produce polychromatic many-line radiation at different wave lengths.

Very important modern source of radiation from IR till X-rays spectral range is **synchrotron radiation**. A typical synchrotron storage ring consists of a high energy electron beam travelling in a circular path many meters in diameter. The electrons move around the circle under influence of a strong magnetic field which is perpendicular to the circle plane and generate radiation in very wide spectral range. The polychromatic beam is dispersed by a diffraction grating and quasi monochromatic radiation is separated by a slit. Except in the microwave region, synchrotron radiation is much more intense than can be obtained by most other conventional sources.

Q.27 With the help of a neat diagram explain the construction and working of a Golay cell

The **Golay cell** is a type of opto-acoustic detector mainly used for infrared spectroscopy. It consists of a gas-filled enclosure with an infrared absorbing material and a flexible diaphragm or membrane. When infrared radiation is absorbed, it heats the gas, causing it to expand.

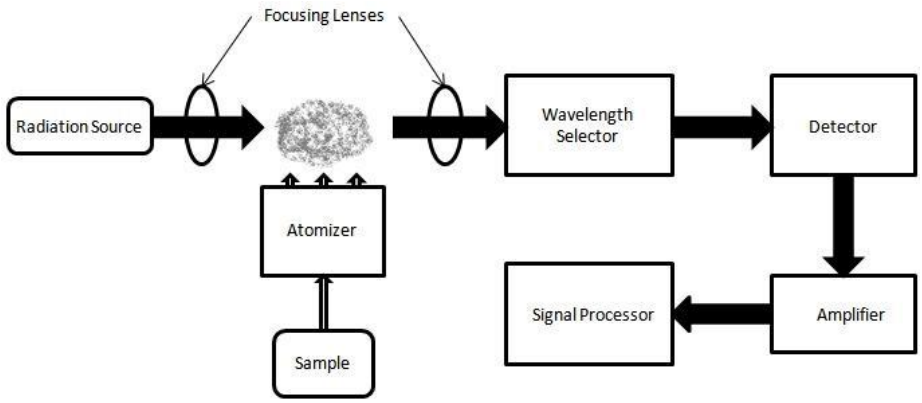


1. Golay cell consists of a small metal cylindrical closed by a rigid blackened metal plate.
2. Pneumatic chamber is filled with xenon gas.
3. At one end of cylinder a flexible silvered diaphragm and at the other end Infra red transmitting window is present.
4. When infra red radiation is passed through infrared transmitting window the blackened plate absorbs the heat. By this heat the xenon gas causes expand.
5. The resulting pressure of gas will cause deformation of diaphragm. This motion of the diaphragm detects how much IR radiation falls on metal plate.
6. Light is made to fall on diaphragm which reflects light on photocell.

Q.28 With the help of neat diagrams, describe absorption profiles for various metallic ions in atomic spectroscopy

The basic principles of atomic absorption spectroscopy can be expressed by three simple statements: x All atoms can absorb light. x The wavelength at which light is absorbed is specific for each element. If a sample containing nickel, for example, together with elements such as lead and copper is exposed to light at the characteristic wavelength for nickel, then only the nickel atoms will absorb this light. x The amount of light absorbed at this wavelength will increase as the number of atoms of the selected element in the light path increases, and is proportional to the concentration of absorbing atoms. x The relationship between the amount of light absorbed and the concentration of the analyte present in known standards can be used to determine unknown concentrations by measuring the amount of light they absorb. An atomic absorption spectrometer is simply

an instrument in which these basic principles are applied to practical quantitative analysis.



Q.29 Compare laminar flow burners with turbulent flow burners in atomic absorption spectroscopy.

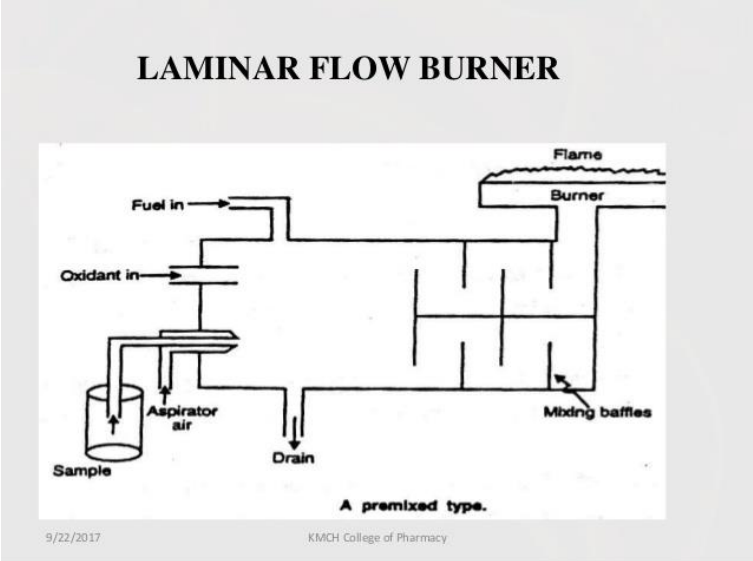
Turbulent flow burners	**laminar flow burners**
It Produces shorter and broader flame	It produces longer and narrower flame
Representative sample reaches the flame	Most of the sample is drained out at the bottom of the chamber
There is a possibility of clogging of the tip of the burner	Clogging of the tip of the burner does not occur
There is no risk of explosion	Explosion can occur in the mixing chamber
This burner is a noisy burner from the auditory as well as electronic point of view	This burner produces the silent flame

Q.30 With the help of a neat diagram explain the working of a laminar flow burner

laminar flow burner is described that provides several advantages in atomic absorption flame photometry. Included in its design is a heated spray chamber followed by a condensing system. This combination improves the concentration level of the analyte in the flame and keeps solvent concentration low. Therefore, sensitivities are significantly improved for most elements relative to cold chamber burners. The burner also contains several safety features. These various design features are discussed in detail, and performance data are given on (a) signal size, (b) signal-to-noise ratio, (c) linearity, (d) working range, (e) precision, and (g) accuracy.

In this type of the burner, aspirated sample, fuel and oxidant are thoroughly mixed before reaching the burner opening and then entering the flame. ϖ Important feature of this is that only a small portion (about 5%) of the sample reaches the flame in the form of small droplets and is easily decompose.

ADVANTAGES: ϖ Premix burner is non-turbulent ,noiseless and stable. ϖ Easy decomposition which leads to high atomization. ϖ Can handle solution up to several % without clogging. DEMERITS ϖ When it contains 2 solvents, the more vol. will evaporate and lesser will remain undissociated.



Q.31 Explain flame absorption profile and its significance.

Each element emits its own characteristic line spectrum, qualitative analysis can be performed here by observing what wavelengths are emitted and comparing these with various standards. However, since the detector is capable of measuring light intensity, quantitative analysis, as well as qualitative analysis, is possible. The intensity of the emitted light increases with concentration, and the relationship is usually linear:

$I = K c$

Thus, unknown concentrations can be determined by comparison with one or a series of standards in the same manner as described for the molecular techniques in UV-Vis Absorption spectroscopy.

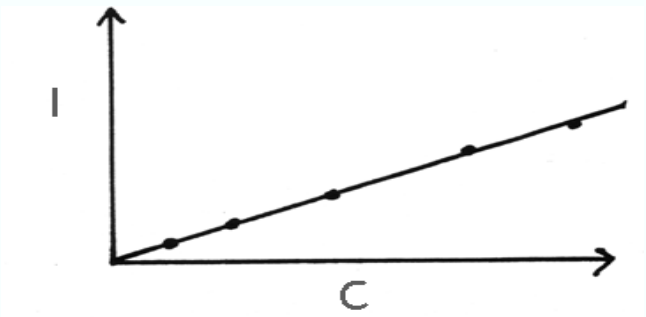


Figure 7 A plot of intensity (I) vs concentration (C) representing quantitative analysis.

In short, flame photometry (FP) is an atomic technique which measures the wavelength and intensity of light emitted by atoms in a flame resulting from the drop from the excited state (formed due to absorption of energy from the flame) to lower states. No light source is required since the energy imparted to the atoms comes from the flame. Thus, FP is different from atomic absorption spectroscopy (AA), which is described in the next section.

Q.32 Explain the effect of temperature variation on flame spectra

Both emission and absorption spectra are affected in a complex way by variations in flame temperature. Higher temperatures tend to increase the total atom population of the flame and sensitivity. With certain elements, such as the alkali metals, however, this ii-increase in atom population is more than offset by the loss of atoms by ionization. Higher temperatures cause greater broadening of lines. This effect is often negligible but it can be the dominant broadening mechanism in low-pressure gases. This effect is called doppler broadening.

Q.33 Compare atomization of compounds by flame and non-flame atomizers

Flame Atomization

After being nebulized by gaseous oxidant and mixed with fuel, the sample is carried into a flame where the heat allows atomization to occur. Once the sample reaches the flame, three more steps occur, desolvation, volatilization, and dissociation. First a molecular aerosol is produced when the solvent evaporates (desolvation), then the aerosol is formed into gaseous molecules (volatilization) and finally the molecules dissociate and produces atomic gas (dissociation). During this process cations and electrons can also be formed when the atomic gas is ionized.

a- Flame atomizer

b- b- Flameless or non flame atomizer

It is a graphite furnace heated electrically up to 6000oC and contains a ribbon or boat in which one can inject the sample. Upon heating the furnace the sample is ashen, then atomized by action of heat.

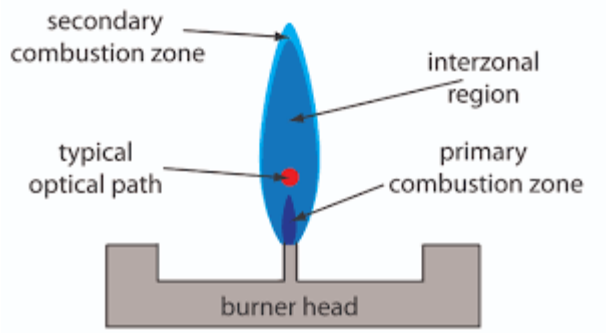
Advantages of non flame atomizer

-The sample volume is small .

- Unusual high sensitivity -Solid sample can be used directly.
- No need for fuel -oxidant mixture.
- No flame noise.
- Heat distribution is uniform and temperature is steady

Q.34 With the help of a neat diagram explain different parts of the flame and also the reactions that can occur in those parts

The flames can be categorized from several points of view. One is based on the mixing way of the combustible gases and the combustion feeding gases. When the gases are mixed before the combustion as in the case of Bunsen burner (Fig. 5.), we can speak about premixed flame. When the oxygene feeding the combustion gets to the flame from air, the flame is called diffusion flame as in the case of the flame of a candle.

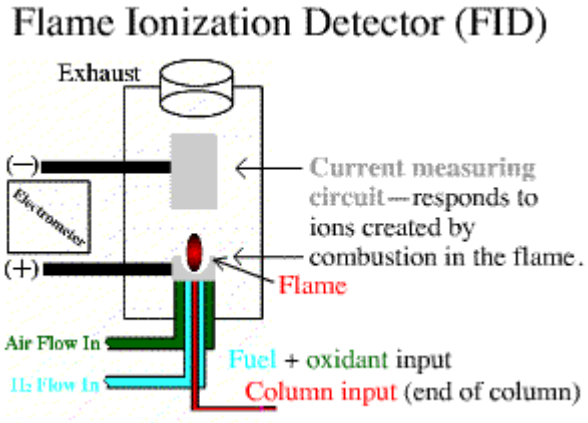


1 open end of the burner; 2 prewarming zone; 3 reaction zone; 4 inner combustion zone; 5 outer combustion zone; ν is the flow rate of the gas mixture; uf is the rate of combustion of the flame

From the liquid drop the solvent evaporates first, and solid aerosol particles (microsized crystals of salts) are formed, in the next step it looses its'crystalline water (if possesed) then the crystals melt and evaporate that is molecule vapour forms. In the higher regions of the flame the thermal dissociation of the molecules occurs: ground state atoms are formed (for atomic absorption measurements only these particles are useful). Of course, when the temperature of the flame makes it possible, the thermal prcesses go further, by the side of the ground state atoms excited atoms, even ions will be present in the flame (these excited particles are useful only for emission measurements).

Q.35 Flame ionization detector

A **flame ionization detector** (**FID**) is a scientific instrument that measures analyte in a gas stream. It is frequently used as a**detector** in gas chromatography.



The sample gas is introduced into a hydrogen flame inside the FID. Any hydrocarbons in the sample will produce ions when they are burnt. Ions are detected using a metal collector which is biased with a high DC voltage. The current across this collector is thus proportional to the rate of ionisation which in turn depends upon the concentration of HC in the sample gas.

The ionisation process is very rapid, so the slow time response of conventional FIDs is mainly due to sample handling. A typical slow analyser might have a response time of 1-2 seconds.

The Cambustion HFR fast response FID analyzers use conventional detection principles and a unique patented sampling system to give millisecond response times.

Q.36 Draw a neat diagram of an Eel's nephelometer. How do you calculate concentration of an unknown sample using it? (Show only calculations).

A powerful light from electric lamp passes through filter which is just put in place only where instrument is to be utilized for luminescence studies, and falls on glass plate. Some part of beam is reflected from this plate and falls on glass attenuator, while part of it enters cell filled with solution under study.

Now the light beam passing through cell is extinguished in light trap. The part of luminous flux reflected by particles in solution passes through lens, adjustable diaphragm, lens and that is directed by rhombic prism through filter into eye piece where it illuminates only one half of the optical field.

The luminous flux from attenuator traverses a similar path through lens, adjustable diaphragm, lens, rhombic prism, filter and enters eye piece to illuminate second half of the optical field. Now by varying slit width of adjustable diaphragms and luminous fluxes can be equalized, i.e. optical equilibrium is attained.

While working with this instrument solution under study should be placed in cell, dials of adjustable diaphragms are set to zero and intensities of luminous fluxes are brought close by putting in interchangeable attenuators. Then luminous fluxes are equalized by means of adjustable diaphragms.

Such measurements are made for a series of solutions containing definite quantities of substance analyzed and then a calibration curve is plotted relating the adjustable diaphragm readings to the concentration of solutions. After this, the unknown concentration can be determined from the diaphragm readings by using this calibration curve.

Calculation:

The concentration of metals or ions can be determined from the formula:

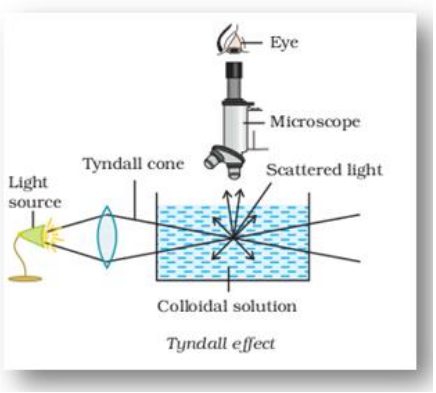
$C_1 = C_0\ 1_1/1_2$

where C_1 and C_2 are concentration of standard and unknown solution respectively.

1_1 and 1_2 are layer thickness in nephelometer cells.

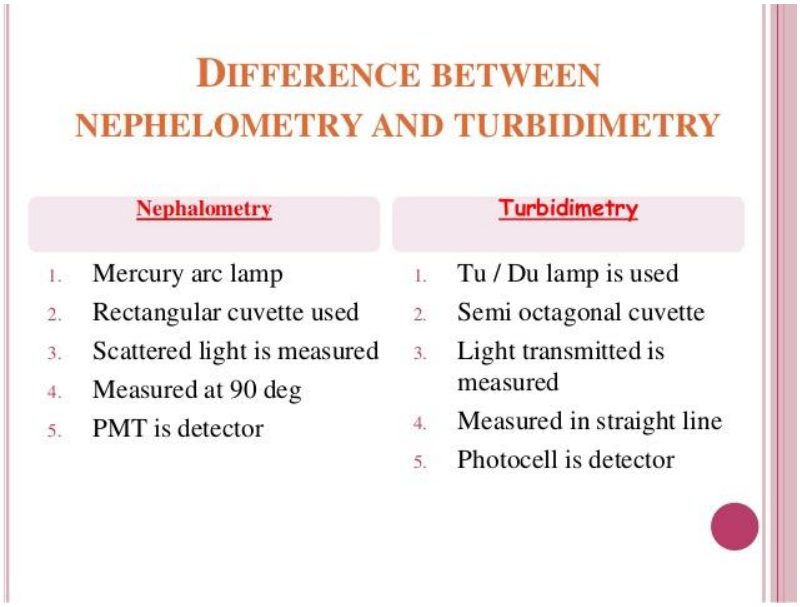
Q.37What is Tyndall effect? Explain important applications of the light scattering phenomena

The **Tyndall effect** is the**scattering** of **light** as a **light** beam passes through a colloid. The individual suspension particles **scatter** and reflect **light**, making the beam visible. The amount of**scattering** depends on the frequency of the **light** and density of the particles.



Light scattering provides information concerning the size, shape, number, and time dependence of the physical nonuniformities of a system. Measurements of the scattered intensity as a function of both scattering angle and wavelength describe static properties, whereas the spectral distribution of the scattered radiation is related to time dependent phenomena. The applications of light scattering are discussed, including critical phenomena, molecular weight determination, air pollution analysis, and diffusion phenomena.

Q 38



Differentiate between nephelometry and turbidometry

Nephelometry is the measurement of the scattered light by the suspended particles at right angles to the incident beam. This method is mainly used for the determination of the low concentration suspensions.

Turbidimetry is the measurement of the transmitted light by the suspended particles to the incident beam. This is used for the determination of the high concentration suspensions.

Q.39 Draw a neat diagram of Eel's nephelometer and explain its advantages over Duboscq nephelometer

A **nephelometer** is an instrument for measuring the concentration of suspended particulates in a liquid or gas colloid. A **nephelometer** measures suspended particulates by employing a light beam (source beam) and a light detector set to one side (often 90°) of the source beam

Advantages;

1. The measurement of intensity of scattered radiation is not done visually in Eel's nephelometer.Hence,it does not involve man to man variation.
2. Eel's nephelometer provides higher accuracy as compared to Doboscq nepheometer
3. It does not cause problem of fatigue to the eye of the operator

The basic principle of Duboscq colorimeter is based on Beer's Law[2], which is expressed as: A = ebc, where A is the absorbance, e is the molar absorptivity of a solution, b is the path length, and c is the molar concentration. Therefore we can compare path length and concentration of two solutions**.** The Duboscq colorimeter is used to determine concentration of an unknown coloured solution (sample) by comparing its visual appearances (hue, purity, and brightness[1]) with a standard solution.

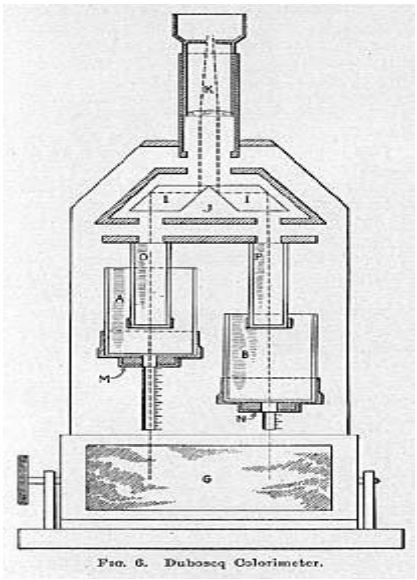


Fig. 6. Duboscq Colorimeter.

Q.40 Applications of nephelometry and turbidometry

Nephelometric and turbidimetric measurements are used in the determination of suspended material in natural waters and in processing streams. The technique is also used for determination of sulfur in coal, oil, and other organic materials; the sulfur is precipitated as barium sulfate

Nephlo-turbidimetric method no doubt is an ideal inexpensive technique used for multi-facet measurements some of which are precisely discussed below;

1. Determination of particle size present in suspensions.
2. Determination of average molecular weight of polymer in solution.
3. Measurement of atmospheric pollutants.
4. Determining concentration of solute in solution.

5. Growth of bacterial cell in a liquid nutrient medium.
6.Turbidimetry and nephelometry has numerous applications in water treatment plants, sewage work, steam generating plant, beverage bottling industry, in pulp and paper manufacturing, petroleum refining and pharmaceutical industries.
7. Determination of carbon dioxide, sugar products and clarity of citric acid juice.
8. Determining end point of precipitation titration

Clinical applications of nephelometry.

Widely used to determine concentrations of unknowns where there is antigen-antibody reactions such as

1. Determination of immunoglobulins (total, IgG, IgE, IgM, IgA) in serum and other biological fluids
2. Determination of the concentrations of individual serum proteins; hemoglobin, haptoglobin, transferring, c-reactive protein, !1-antitrypsin, albumin (using antibodies specific for each protein)
3. Determination of the size and number of particles (laser-nephelometr}

Q.41: Sample injection system in HPLC

The injection system is positioned after the pump head.

• The injection of a sample at atmospheric pressure into the system, at high pressure, represents a critical step in the chromatographic process.

• Sample injection valves, or switching valves, are used to introduce reproducible amounts of sample into the HPLC eluent stream without causing changes in pressure or flow

The injector is located on the high pressure side of the pump.

• Sample injection valves allow effective sample introduction without interrupting the flow or altering the system pressure. Components of the sample injection valve

• A needle or syringe to pierce the vial septum

• A metering device to measure the aspirated amount of sample liquid

• A loop or holding device to retain the sample prior to injection

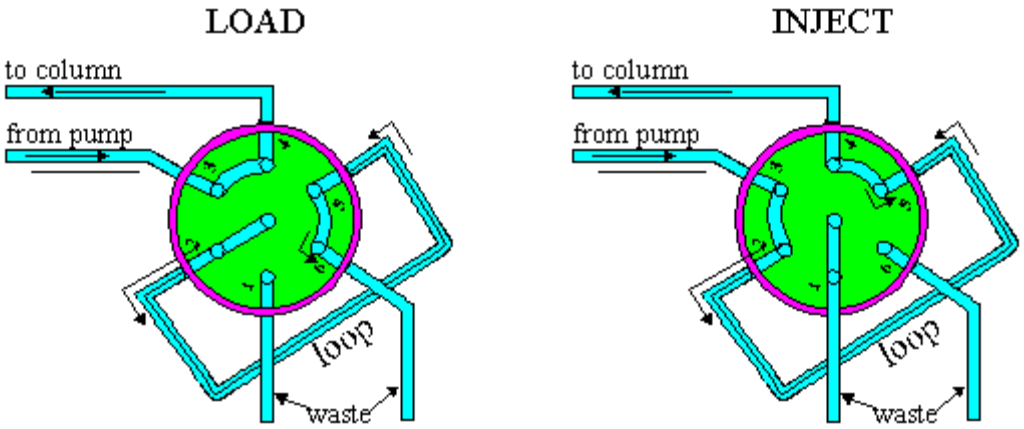
• A valve which is used to alter the hydraulic path of the eluent through the device in order to affect direct injection of the sample plug into the eluent stream under pressure

Manual Injection Systems

• Manual sample injectors for HPLC transfer sample at atmospheric pressure from a syringe to a Sample Loop. The loop is then connected via a change in valve configuration, to the high-pressure mobile phase stream, which carries the sample onto the column. There are 2 methods of filling

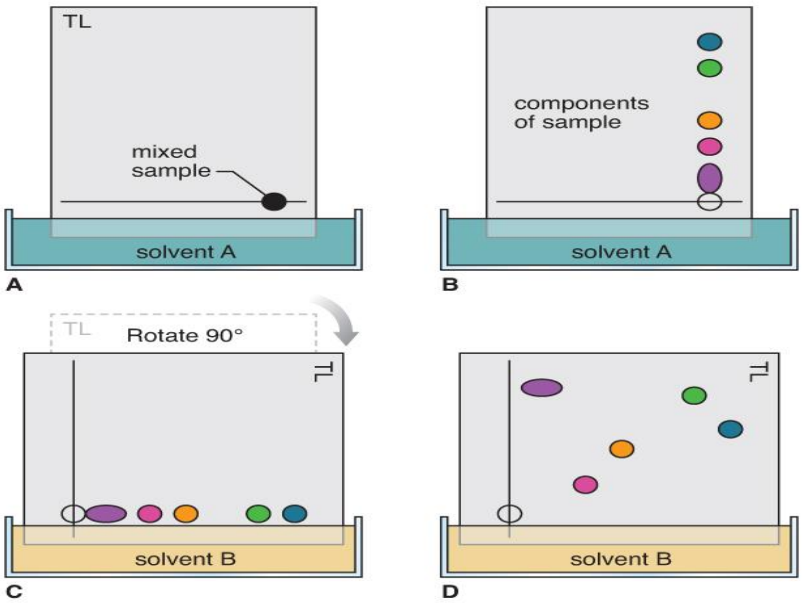
• Complete-filling –where the loop size chosen has the desired injection volume and is totally filled with sample

• Partial-filling –where the loop chosen is at least twice the required sample volume and is only partially filled



Q.42 With the help of neat diagrams describe two dimensional technique used in TLC to develop the plate

Two-dimensional TLC can provide improved resolution and consequently is very advantageous in the separation of complex mixtures. The apparatus for two-dimensional TLC is very similar to that used for the forced-flow procedure depicted in figure 8 except that a square plate is used and there are *two solvent inlets* and *two solvent outlets*. The sample is initially spotted on the top right-hand corner of the plate and the plate developed by forced flow downwards. This produces a series of solute bands or spots down the right-hand side of the plate. After a predetermined time, the vertical downward flow is stopped and the plate is developed employing a different second solvent that is passed by forced-flow from right to left across the plate. The resolving power of the 2D TLC method has great application, especially in the areas of biochemistry, biology, natural products, pharmaceuticals, and environmental analysis.



Q.43 Note-Paper Chromatography

The principle involved is partition chromatography wherein the substances are distributed or partitioned between liquid phases. One phase is the water, which is held in the pores of

the filter paper used; and other is the mobile phase which moves over the paper. The compounds in the mixture get separated due to differences in their affinity towards water (in stationary phase) and mobile phase solvents during the movement of mobile phase under the capillary action of pores in the paper.

The principle can also be adsorption chromatography between solid and liquid phases, wherein the stationary phase is the solid surface of paper and the liquid phase is of mobile phase. But most of the applications of paper chromatography work on the principle of partition chromatography, i.e. partitioned between to liquid phases.

Applications of Paper Chromatography

Paper chromatography is specially used for the separation of a mixture having polar and non-polar compounds.

The paper is the stationary phase. This uses capillary action to pull the solutes up through the paper and separate the solutes. Paper is comprised of cellulose, which is a polymer of the simple sugar glucose, and as such is very polar due to the –OH groups present in glucose. Because of the many exposed –OH groups, cellulose interacts strongly with polar water molecules. This interaction is so strong that "dry" paper is approximate 22% water by weight .It is this water adsorbed on the paper surface that is the stationary phase in paper chromatography. In general, the polarity of the mobile phase is adjusted by trial and error to affect the desired separation. Often for paper chromatography the mobile phase is a mixture of water and an alcohol. This mobile phase is fairly polar, but less polar than the stationary phase. Thus as the mixture moves up the paper by capillary action, the more polar components will travel up the paper more slowly than polar ones.

- To check the control of purity of pharmaceuticals,
- To the detection of adulterants,
- To detect the contaminants in foods and drinks,
- To the study of ripening and fermentation,
- For the detection of drugs and dopes in animals & humans
- To the analysis of cosmetics
- To the analysis of the reaction mixtures in biochemical labs.
- For separation of amino acids.
- It is used to determine organic compounds, biochemicals in urine, etc.
- In the pharma sector it is used for the determination of hormones, drugs, etc.

Sometimes it is used for evaluation of inorganic compounds like salts and complexes

Q.44 Describe different methods used to locate position of compounds on the plate in TLC

Non-destructive methods

As a general visualization procedure, before treating the TLC plate with any destructive methods, UV-active compounds can be viewed under an ultraviolet lamp (*usually for polyconjugated compounds like benzophenones and anthracenes*). Furthermore, an iodine chamber can be useful for thiols, phosphines, and alkenes but it works in about 50% of cases for alkanes. It is recommended to circle the spots with a pencil on the TLC plate prior to visualization by destructive methods.

Destructive methods

For compounds that are not UV-active, there are several varieties of stains that can be used depending on the nature of the compound of interest. To use a stain, simply dip the TLC plate into the staining solution as quickly as possible, and then immediately absorb the excess stain with paper and heat carefully with a heat gun or on a hot plate at 110°C until spots are revealed

Q.45 Describe the following with respect to HPLC.

Column efficiency

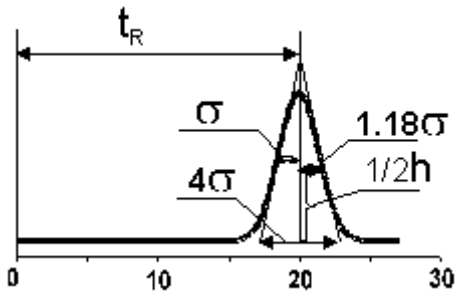
Column selectivity

Resolution

Efficiency-The higher the column band broadening, the smaller the number of components that can be separated in a given time. In other words, the sharpness of the peak is an indication of how good, or efficient a column is.

The peak width is an indication of peak sharpness and, in general, an indication of the column efficiency. However, the peak width is dependent on a number of parameters (column length, flow rate, particle size). Flow rate is the only parameter which can be changed from run to run on the same column. Thus, it is better to consider a relative value to express column efficiency.

In absence of the specific interactions or sample overloading, the chromatographic peak can be represented by a Gaussian curve with the standard deviation (**s**). The ratio of standard deviation to the peak retention time (s/t_R) is called the relative standard deviation, which is independent on the flow rate.



In practice, the square of the reciprocal value is normally used $N - (t_R / \sigma)^2$. This has become the accepted expression of column efficiency. The reason for using the second power has come from statistics, and it is related to the fact that not the standard deviation (σ), but its square, the variance $(\sigma)^2$, is the basic measure of normal distribution. The value ***N*** is called the plate number or the number of theoretical plates. Term "theoretical plate" comes form the analogy with the distillation theory.

In practice, it is more convenient to measure peak width either at the base line, or at the half height, and not at 0.609 of the peak height, which actually correspond to 2σ.

$$N = 16 \left(\frac{t_R}{w_b}\right)^2 \quad (2)$$

$$N = 5.545 \left(\frac{t_R}{w_b}\right)^2 \quad (3)$$

The plate number depends on column length: the longer the column, the larger the plate number. Therefore, the plate height term has been introduced to measure how efficiently column has been packed, ***h = L/N*** .

The lower the plate height and the higher the plate number, the more efficient the chromatographic column.

Selectivity -is the ratio of the capacity factors of both peaks, or the ratio of its adjusted retention times. Selectivity represents the separation power of particular adsorbent to the mixture of this particular components.

$$\alpha = \frac{V_{R,1} - V_o}{V_{R,2} - V_o} = \frac{k'_1}{k'_2} \quad (4)$$

This parameter is independent of the column efficiency, it only depends on the nature of the components, eluent type, eluent composition, and adsorbent surface chemistry. In general, if the selectivity of two components is equal to 1, then there is no way to separate them by improving the column efficiency.

Resolution- is the parameter describing the separation power of the complete chromatographic system relative to the particular components of the mixture.

By convention, resolution (***R***) is expressed as the ratio of the distance between two peak maxima to the mean value of the peak width at the base line:

$$R = 2\frac{V_{R,2} - V_{R,1}}{w_1 + w_2} \quad (5)$$

If we approximate peaks by symmetric triangles, then, if ***R*** is equal to or more than 1 then components are completely separated. If ***R*** is less than 1, then components are overlapped.

By using the expressions for capacity factor and column efficiency the equation for ***R*** could be transferred to the form:

$$R = \frac{\sqrt{N}}{2}\frac{k'_2 - k'_1}{k'_2 + k'_1 + 2}$$

Q.46 Gel chromatography

It is a chromatographic technique that separates dissolved molecules on the basis of their size by pumping them through specialized columns containing a microporous packing material(gel). Separation is achieved using a porous matrix to which the molecules, for steric reasons, have different degrees of access--i.e., smaller molecules have greater access and larger molecules are excluded from the matrix. Hence, proteins are eluted from the GF column in decreasing order of size. The gel filtration matrix consists of microscopic beads that contain pores and internal channels. The larger the molecule, the more diffi cult it is for it to pass through the pores and penetrate the beads. Larger molecules tend to fl ow around and in between the beads. The total volume of buffer between the beads is the "void volume". Smaller molecules tend to spend more time in the maze of channels and pores in the bed. Consequently, the larger, higher molecular weight molecules are eluted from the column before smaller molecules. Larger molecules take the faster, more direct path that involves less time in the beads

Advantages and disadvantages

1. Advantages:
2. Short analysis time.
3. Well defined separation.
4. Narrow bands and good sensitivity.
5. There is no sample loss.
6. Small amount of mobile phase required.
7. The flow rate can be set.

Disadvantages:

1. -Limited number of peaks that can be resolved within the short time scale of the GPC run.
2. -Filtrations must be performed before using the instrument to prevent dust and other particulates from ruining the columns and interfering with the detectors.
3. The molecular masses of most of the chains will be too close for the GPC separation to show anything more than broad peaks.

Applications of GPC

1. Proteins fractionation
2. Purification
3. Molecular weight determination.
4. Separation of sugar, proteins, peptides, rubbers and others on the basis of their size.
5. This technique can be use to determine the quaternary structure of purified protein

Q.47 Explain how principles of chromatography can be applied to the separation of compounds using ion-exchange resins.

Ion-Exchange Chromatography (IEC) allows for the separation of ionizable molecules on the basis of differences in charge properties. Its large sample-handling capacity, broad applicability (particularly to proteins and enzymes), moderate cost, powerful resolving ability, and ease of scale-up and automation have led to it becoming one of the most versatile and widely used of all liquid chromatography (LC) techniques. This technique

exploits the interaction between charged molecules in a sample and oppositely charged moieties in the stationery phase of the chromatography matrix. This type of separation is difficult using other techniques as charge is easily manipulated by the pH of buffer used. Two types of ion exchange separation is possible - cation exchange and anion exchange. In anion exchange the stationary phase is positively charged whilst in cation exchange it is negatively charged. Ion exchange resins have positively or negatively charged functional groups covalently linked to a solid matrix. Matrices are usually made of cellulose, polystyrene, agarose, and polyacrylamide. Some of the factors affecting resin choice are anion or cation exchanger, flow rate, weak or strong ion exchanger, particle size of the resin, and binding capacity. The stability of the protein of interest dictates the selection of an anion or a cation exchanger – either exchanger may be used if the stability is of no concern.

Q. 48 Explain the theory of HPTLC technique. Discuss the advantages and Detection system in HPTLC

HPTLC have similar approach and employ the same physical principles of TLC (adsorption chromatography) i.e. the principle of separation is adsorption. ϖ The mobile phase solvent flows through because of capillary action. The components move according to their affinities towards the adsorbent. The component with more affinity towards the stationary phase travels slower. The component with lesser affinity towards the stationary phase travels faster. Thus the components are separated on a chromatographic plate

Advantages-

Technically, it is simple to learn and operate.

- Several analysts work simultaneously on the system.
- Lower analysis time and less cost per analysis.
- Low maintenance cost.
- Visual detection possible – as it is an open system.
- Availability of a great range of stationary phases with unique selectivity for mixture components. Chromatographic layer (sorbent) requires no regeneration as TLC/HPTLC plates are disposable.
- Ability to choose solvents for the mobile phase is not restricted by low UV transparency or the need for ultra-high purity. Corrosive and UV-absorbing mobile phases can be employed.
- No prior treatment for solvents like filtration and degassing.
- There is no possibility of interference from previous analysis as fresh stationary and mobile phases are used for each analysis. No carry over, hence no contamination.
- Repetition of densitometric evaluation of the same sample can be achieved under different conditions without repeating the chromatography to optimize quantification, since all sample fractions are stored on the TLC/HPTLC plate.
- Samples rarely require cleanup.
- High sample throughput since several samples can be chromatographed simultaneously.
- Lower expenditure of solvent purchase and disposal since the required amount of mobile phase per sample is small. In addition, it minimizes exposure risks of toxic

organic effluents and reduces possibilities of environment pollution.

- Accuracy and precision of quantification is high because samples and standards are chromatographed and measured under the identical experimental conditions on a single TLC/HPTLC plate.
- Sensitivity limits of analysis are typically at nanogram (ng) to pictogram (pg) levels.
- Use of different universal and selective detection

1. Detection

Detection under UV light is first choice - non destructive - Spots of fluorescent compounds can be seen at 254 nm (short wave length) or at 366 nm (long wave length) - Spots of non fluorescent compounds can be seen - fluorescent stationary phase is used - silica gel GF UV CABINET

2. Detection and visualization

•Detection under UV light is first choice - non destructive.

•Non UV absorbing compounds like ethambutol, dicylomine etc - dipping the plates in 0.1% iodine solution.

Quantification

•Sample and standard should be chromatographed on same plate after development chromatogram is scanned.

•Concentration of analyte in the sample is calculated by considering the sample initially taken and dilution factors.

3. Densitometry measurements ¬ Measures visible, UV absorbance or Fluorescence. ¬ Convert the spot/band into chromatogram consisting of peaks.

Q.49 Instrumentation of GC

Gas chromatography is mainly composed of the following parts:

1. **Carrier gas in a high-pressure cylinder with attendant pressure regulators and flow meters**

- Helium, N_2, H, Argon are used as carrier gases.
- Helium is preferred for thermal conductivity detectors because of its high thermal conductivity relative to that of most organic vapors.
- N_2 is preferable when a large consumption of carrier gas is employed.
- Carrier gas from the tank passes through a toggle valve, a flow meter, (1-1000 ml/min), capillary restrictors, and a pressure gauge (1-4 atm).
- Flow rate is adjusted by means of a needle valve mounted on the base of the flow meter and controlled by capillary restrictors.
- The operating efficiency of the gas chromatograph is directly dependant on the maintenance of constant gas flow.

2. **Sample injection system**

- Liquid samples are injected by a microsyringe with a needle inserted through a self-scaling, silicon-rubber septum into a heated metal block by a resistance heater.
- Gaseous samples are injected by a gas-tight syringe or through a by-pass loop and valves.

- Typical sample volumes range from 0.1 to 0.2 ml.

3. **The separation column**

- The heart of the gas chromatography is the column which is made of metals bent in U shape or coiled into an open spiral or a flat pancake shape.
- Copper is useful up to 250^0
- Swege lock fittings make column insertion easy.
- Several sizes of columns are used depending upon the requirements.

4. **Liquid phases**

- An infinite variety of liquid phases are available limited only by their volatility, thermal stability and ability to wet the support.
- No single phase will serve for all separation problems at all temperatures.

Non-Polar – Parafin, squalane, silicone greases, apiezon L, silicone gum rubber. These materials separate the components in order of their boiling points.

Intermediate Polarity – These materials contain a polar or polarizable group on a long non-polar skeleton which can dissolve both polar and non-polar solutes. For example. diethyl hexyl phthalate is used for the separation of high boiling alcohols.

Polar – Carbowaxes – Liquid phases with a large proportion of polar groups. Separation of polar and non-polar substances.

Hydrogen bonding – Polar liquid phases with high hydrogen bonding e.g. Glycol.

Specific purpose phases – Relying on a chemical reaction with solute to achieve separations. e.g AgNO3 in glycol separates unsaturated hydrocarbons.

5. **Supports**

- The structure and surface characteristics of the support materials are important parameters, which determine the efficiency of the support and the degree of separation respectively.
- The support should be inert but capable of immobilizing a large volume of liquid phase as a thin film over its surface.
- The surface area should be large to ensure the rapid attainment of equilibrium between stationary and mobile phases.
- Support should be strong enough to resist breakdown in handling and be capable of packed into a uniform bed.
- Diatomaceous earth, kieselguhr treated with Na 2CO 3 for 900^0 C causes the particle fusion into coarser aggregates.
- Glass beads with a low surface area and low porosity can be used to coat up to 3% stationary phases.
- Porous polymer beads differing in the degree of cross-linking of styrene with alkyl-vinyl benzene are also used which are stable up to 250^0

6. **Detector**

- Detectors sense the arrival of the separated components and provide a signal.
- These are either concentration-dependent or mass dependant.

- The detector should be close to the column exit and the correct temperature to prevent decomposition.
-

7. **Recorder**

- The recorder should be generally 10 mv (full scale) fitted with a fast response pen (1 sec or less). The recorder should be connected with a series of good quality resistances connected across the input to attenuate the large signals.
- An integrator may be a good addition.

ASSIGNMENT

Note- Solve any four questions

Question	Details	Marks	Unit no. as per syllabus	CO mapped	Bloom's Taxonomy Level
1	Write the principle involved in UV spectroscopy	5	**1**	**CO1**	**1**
2	Explain in brief detectors used in UV spectroscopy	5	**1**	**CO1**	**2,3**
3	Explain sampling technique of IR	5	**2**	**CO1**	**3**
4	Describe the vibrations in IR spectroscopy	5	**2**	**CO1**	**1**
5	Applications of IR spectroscopy	5	**2**	**CO3**	**3**

CLASS TEST-I

Note- Solve any four questions

Question	Details	Marks	Unit no. as per syllabus	CO mapped	Bloom's Taxonomy Level
1	Differentiate between total consumption burner and laminar flow burner	5	**2**	**CO1**	**1**
2	Explain the quenching and factors affecting quenching of fluroscence	5	**1**	**CO1**	**2**
3	Explain different atomizer used in AAS	5	**2**	**CO1**	**3**
4	What is Tyndall effect? Explain important applications of the light scattering phenomena	5	**2**	**CO3**	**2**
5	Describe sample preparation in IR spectroscopy for gaseous, liquid and solid samples	5	**2**	**CO3**	**4**

CLASS TEST-II

Question	Details	Unit no. as per syllabus	CO mapped	Bloom's Taxonomy Level
1	With the help of neat diagrams explain relation between resolution, selectivity factor, column efficiency and capacity factor	**4**	**CO3**	**2**
2	Plate development techniques in TLC	**3**	**CO1**	**3**
3	Short Note: Sample injection system in HPLC	**4**	**CO3**	**2**
4	Explain sample injection in HPLC	**3**	**CO3**	**4**

SUBJECT II

BP702T INDUSTRIAL PHARMACY-II

THEORY

SCHEME

BP702T Industrial Pharmacy-II -Theory

SCHEME FOR TEACHING

Course of study for semester VII

Course Code	Course Name	No. of Hours per week			Credit Points
		Theory	Practical	Tutorial	
BP702T	IP-II	03	0	01	04

SCHEME FOR INTERNAL AND END SEMESTER EXAMINATIONS

Course code	Name of the course	Internal Assessment				End Semester Exams		Total Marks
		Continuous Assessment	Sessional Exams		Total	Marks	Duration	
			Marks	Duration				
BP702T	IP-II	10	15	01 hrs	25	75	03 hrs	100

SYLLABUS

BP702T Industrial Pharmacy-II -Theory

Course Content

Scope: This course is designed to impart fundamental knowledge on pharmaceutical product development and translation from laboratory to market.

UNIT-I **10 Hours**

Pilot plant scale up techniques: General considerations - including significance of personnel requirements, space requirements, raw materials,Pilot plant scale up considerations for solids, liquid orals, semi solids and relevant documentation, SUPAC guidelines, Introduction to platform technology.

UNIT-II **10 Hours**

Technology development and transfer: WHO guidelines for Technology Transfer(TT): Terminology, Technology transfer protocol, Quality risk management, Transfer from R & D to production (Process, packaging and cleaning), Granularity of TT Process (API, excipients, finished products, packaging materials) Documentation, Premises and equipments, qualification and validation, quality control, analytical method transfer, Approved regulatory bodies and agencies, Commercialization - practical aspects and problems (case studies), TT agencies in India - APCTD, NRDC, TIFAC, BCIL, TBSE / SIDBI; TT related documentation - confidentiality agreement, licensing, MoUs,legal issues.

UNIT-III **10 Hours**

Regulatory affairs: Introduction, Historical overview of Regulatory Affairs, Regulatory authorities, Role of Regulatory affairs department, Responsibility of Regulatory Affairs Professionals Regulatory requirements for drug approval: Drug Development Teams, Non-Clinical Drug Development, Pharmacology, Drug Metabolism and Toxicology, General considerations of Investigational New Drug (IND) Application, Investigator's Brochure (IB) and New Drug Application (NDA), Clinical research / BE studies, Clinical

Research Protocols, Biostatistics in Pharmaceutical Product Development, Data Presentation for FDA Submissions, Management of Clinical Studies.

UNIT-IV **08 Hours**

Quality management systems: Quality management & Certifications: Concept of Quality, Total Quality Management, Quality by Design (QbD), Six Sigma concept, Out of Specifications (OOS), Change control, Introduction to ISO 9000 series of quality systems standards, ISO 14000, NABL, GLP

UNIT-V **07 Hours**

Indian Regulatory Requirements: Central Drug Standard Control Organization (CDSCO) and State Licensing Authority: Organization, Responsibilities, Certificate of Pharmaceutical Product (COPP), Regulatory requirements and approval procedures for New Drugs.

Recommended Books: (Latest Editions)

1. Regulatory Affairs from Wikipedia, the free encyclopedia modified on 7th April available at http,//en.wikipedia.org/wiki/Regulatory_ Affairs.

2. International Regulatory Affairs Updates, 2005. available at http://www.iraup.com/about.php

3. Douglas J Pisano and David S. Mantus. Text book of FDA Regulatory Affairs A Guide for Prescription Drugs, Medical Devices, and Biologics' Second Edition.

4. Regulatory Affairs brought by learning plus, inc. available at http.//www.cgmp.com/ra.htm

LESSION PLAN

BP702T Industrial Pharmacy-II -Theory

Name of the faculty: Ms. N. S. Kadbhane

Lect No.	Topics / Sub-Topics	COs Addressed	BL Level	Reference (Text Book, Website)
1	**Pilot plant scale up techniques:**	2	1	Regulatory Affairs brought by learning plus, inc. available at http.//www.cgmp.com/ra.htm
2	General considerations -	1	2	Regulatory Affairs from Wikipedia, the free encyclopedia modified on 7th April available at http,//en.wikipedia.org/wiki/Regulatory_Affairs.
3	including significance of personnel requirements, space requirements,	2	1	International Regulatory Affairs Updates, 2005. available at http://www.iraup.com/about.php
1 T	-			
4	raw materials,	2	2	Douglas J Pisano and David S. Mantus. Text book of FDA Regulatory Affairs A Guide for Prescription Drugs, Medical Devices, and Biologics' Second Edition.
5	Pilot plant scale up considerations for solids	1	2	Regulatory Affairs from Wikipedia, the free encyclopedia modified on 7th April available at http,//en.wikipedia.org/wiki/Regulatory_Affairs.
6	semi solids and relevant documentation,, liquid orals,	1	1	International Regulatory Affairs Updates, 2005. available at http://www.iraup.com/about.php
2 T				
7	, Introduction to platform technology.	1	2	International Regulatory Affairs Updates, 2005. available at http://www.iraup.com/about.php
8	Introduction to	2	2	International Regulatory Affairs

	platform technology.			Updates, 2005. available at http://www.iraup.com/about.php
9	Introduction to platform technology. SUPAC guidelines	3	2	Douglas J Pisano and David S. Mantus. Text book of FDA Regulatory Affairs A Guide for Prescription Drugs, Medical Devices, and Biologics' Second Edition.
3 T				
10	Technology development and transfer:	2	2	International Regulatory Affairs Updates, 2005. available at http://www.iraup.com/about.php
11	WHO guidelines for Technology Transfer(TT):	3	2	Regulatory Affairs brought by learning plus, inc. available at http.//www.cgmp.com/ra.htm
12	Terminology, Technology transfer protocol.	2	2	Douglas J Pisano and David S. Mantus. Text book of FDA Regulatory Affairs A Guide for Prescription Drugs, Medical Devices, and Biologics' Second Edition.
4 T				
13	Quality risk management, Transfer from R & D to production	2	2	
14	(Process, packaging and cleaning),	3	2	Regulatory Affairs from Wikipedia, the free encyclopedia modified on 7th April available at http,//en.wikipedia.org/wiki/Regulatory_Affairs.
15	Granularity of TT Process (API, excipients, finished products, packaging materials)	2	2	International Regulatory Affairs Updates, 2005. available at http://www.iraup.com/about.php
5 T				
16	Documentation, Premises and equipments, qualification and validation,	2	3	Douglas J Pisano and David S. Mantus. Text book of FDA Regulatory Affairs A Guide for Prescription Drugs, Medical Devices, and Biologics' Second Edition.
17	quality control,	2	2	

	analytical method transfer,			
18	Approved regulatory bodies and agencies,	3	2	International Regulatory Affairs Updates, 2005. available at http://www.iraup.com/about.php
6 T	MoUs,legal issues	2	3	Regulatory Affairs from Wikipedia, the free encyclopedia modified on 7th April available at http,//en.wikipedia.org/wiki/Regulatory_ Affairs.
19	Commercialization - practical aspects and problems (case studies),	2	2	Regulatory Affairs from Wikipedia, the free encyclopedia modified on 7th April available at http,//en.wikipedia.org/wiki/Regulatory_ Affairs.
20	TT agencies in India - APCTD, NRDC, TIFAC, BCIL, TBSE / SIDBI;	3	2	International Regulatory Affairs Updates, 2005. available at http://www.iraup.com/about.php
21	TT related documentation - confidentiality agreement, licensing, MoUs,legal issues	2	2	nternational Regulatory Affairs Updates, 2005. available at http://www.iraup.com/about.php
7 T				
22	**UNIT-III** **10 Hours** Regulatory affairs	3	2	International Regulatory Affairs Updates, 2005. available at http://www.iraup.com/about.php
23	Introduction, Historical overview of Regulatory Affairs,	3	2	Regulatory Affairs from Wikipedia, the free encyclopedia modified on 7th April available at http,//en.wikipedia.org/wiki/Regulatory_ Affairs.
24	Regulatory authorities, Role of Regulatory affairs department,	3	2	

8 T				
25	Responsibility of Regulatory Affairs Professionals	3	2	Regulatory Affairs from Wikipedia, the free encyclopedia modified on 7th April 1available at ttp,//en.wikipedia.org/wiki/Regulatory_ Affairs.
26	Regulatory requirements for drug approval: Drug Development Teams,	3	2	
27	Non-Clinical Drug Development, Pharmacology,	3	3	Douglas J Pisano and David S. Mantus. Text book of FDA Regulatory Affairs A Guide for Prescription Drugs, Medical Devices, and Biologics' Second Edition.
9 T				
28	Biostatistics in Pharmaceutical Product Development, Data Presentation for FDA Submissions,	3	2	International Regulatory Affairs Updates, 2005. available at http://www.iraup.com/about.php
29	General considerations of Investigational New Drug (IND) Application,	4	2	
30	Investigator's Brochure (IB)	3	2	
10 T				
31	and New Drug Application (NDA), Clinical research / BE studies, Clinical Research Protocols,	3	2	International Regulatory Affairs Updates, 2005. available at http://www.iraup.com/about.php
32	**UNIT-IV 08 Hours** Quality management	4	2	Douglas J Pisano and David S. Mantus. Text book of FDA Regulatory Affairs A Guide for Prescription Drugs, Medical Devices, and Biologics' Second Edition.

	systems: Quality management & Certifications:			
33	Concept of Quality	4	2	
11 T	Total Quality Management,	4	2	
34	Quality by Design (QbD)	4	2	
35	Six Sigma concept, Out of Specifications (OOS),	4	2	
36	Change control, Introduction to ISO 9000 series of quality systems standards,	4	2	International Regulatory Affairs Updates, 2005. available at http://www.iraup.com/about.php
12 T				
37	ISO 14000, NABL, GLP	4	2	
38	Indian Regulatory Requirements: Central Drug Standard Control Organization (CDSCO)	4	2	International Regulatory Affairs Updates, 2005. available at http://www.iraup.com/about.php
39	and State Licensing Authority: Organization,	4	2	Douglas J Pisano and David S. Mantus. Text book of FDA Regulatory Affairs A Guide for Prescription Drugs, Medical Devices, and Biologics' Second Edition.
13 T				
40	Regulatory requirements and Responsibilities, Certificate of Pharmaceutical Product (COPP),	4	2	International Regulatory Affairs Updates, 2005. available at http://www.iraup.com/about.php
41	Regulatory requirements	4	2	

42	approval procedures for New Drugs.	4	3	Douglas J Pisano and David S. Mantus. Text book of FDA Regulatory Affairs A Guide for Prescription Drugs, Medical Devices, and Biologics' Second Edition.
14 T				
43	approval procedures for New Drugs.	4	2	
44	approval procedures for New Drugs.	4	3	Douglas J Pisano and David S. Mantus. Text book of FDA Regulatory Affairs A Guide for Prescription Drugs, Medical Devices, and Biologics' Second Edition.
45	Management of Clinical Studies Drug Metabolism and Toxicology,	4	2	Regulatory Affairs from Wikipedia, the free encyclopedia modified on 7th April available at http,//en.wikipedia.org/wiki/Regulatory_Affairs.
15 T				

Note: 1.Home Assignment will be given after completion of each unit.

2. Class Test I & II will be conduct as per the schedule of Academic Calendar.

COURSE DELIVERY, OBJECTIVES, OUTCOMES

BP702T Industrial Pharmacy-II -Theory

Course Delivery:

The course will be delivered through lectures, class room interaction, and presentations.

Course Objectives:

Upon the completion of the course student shall be able to

1. Understand the chemistry of drugs with respect to their pharmacological activity
2. Understand the drug metabolic pathways, adverse effect and therapeutic value of drugs
3. Know the Structural Activity Relationship of different class of drugs
4. Study the chemical synthesis of selected drugs

Course Outcomes (COs):

After successful completion of course student will able to

Upon the completion students are able to **CO-PO**

CO1	Know the process of pilot plant and scale up of pharmaceutical dosage forms
CO2	Understand the process of technology transfer from lab scale to commercial batch
CO3	Know different Laws and Acts that regulate pharmaceutical industry
CO4	Understand the approval process and regulatory requirements for drug products

Mapping of Course Outcome (CO) with Program Outcome (PO) and Program Specific Outcome (PSO)

1: Slight (Low) 2: Moderate (Medium) 3: Substantial (High)

If there is no correlation, put "-"

CO	PO1	PO2	PO3	PO4	PO5	PO6	PO7	PO8	PO9	PO10	PO11	PSO1	PSO2	PSO3	PSO4
CO1	3	2	1	1	2	-	-	-	-	-	-	3	3	1	2
CO2	3	2	1	1	2	-	-	-	-	-	-	3	3	1	2
CO3	3	2	1	3	2	-	-	-	-	-	-	3	3	1	2
CO4	3	1	1	-	-	-	-	-	-	-	-	3	3	1	1

Justification of CO-PO Mapping

CO1 with PO1	CO1 is aligned with PO1 because CO1 gives the highly basic knowledge of the pharmacy.
CO1 with PO2	CO1 is aligned with PO2 because it deals with the technology transfer in industries
CO1 with PO3	CO1 is aligned with PO3 because it deals with the method of technology transfer
CO1 with PO4	CO1 is aligned with PO4 because it deals with experimental work and analysis of results of scale ups
CO1 with PO5	CO1 is aligned with PO5 because it deals with modern techniques and tools for pilots plant scale up
CO 1 with PO 12	CO1 is aligned with PO12 because it correlate the pharmaceutical principals, demonstrate the knowledge and apply it at work place for sustainable development.
CO2 with PO1	CO2 is aligned with PO1 because it Highly deals with the basic pharmacy knowledge
CO2 with PO2	CO2 is aligned with PO2 because it deals basic knowledge of technology transfer.
CO2 with PO3	CO2 is aligned with PO3 because it moderately deals with industrial importance and implementation of pilot plant scale up principal in pharmaceutical processing and industry by understanding scale up procedure ,indstrument handling alonfg with their mechanisam.
CO2 with PO4	CO2 is aligned with PO4 relevant to theoretical as well as practical knowledge of importance and implementation of scale up tech in pharmaceutical processing and industry by understanding scale up procedure ,indstrument handling along with their mechanisam.
CO2 with PO5	CO2 is aligned with PO5 because it deals with modern tools for understanding and analyzing pharmacy practice.

CO 2with PO 12	CO2 is aligned with PO12 because it deals with application of pharmacy knowledge for Pilot plant tech.
CO3 with PO1	CO3 is aligned with PO1 because it gives the Highly basic knowledge of the sterility testing of pharmaceutical products
CO3 with PO2	CO3 is aligned with PO2 because it deals with practical knowledge of Solid liquid ,semisolid Dosage form. Regulatory requirement
CO3 with PO3	CO3 is aligned with PO3 because it deals with design and evaluation of scale up procedure acc. Regulatory requirement .
CO3 with PO4	CO3 is aligned PO4 relevant to theoretical as well as practical knowledgeRegulatory guideline
CO3 with PO5	CO3 is aligned with PO5 because it deals with modern tools and techniques for legal guideline of pharmaceutical products
CO 3 with PO 12	CO3 is aligned with PO12 because it deals with application of sterility testing of pharmaceutical products principles in pharmacy practice.
CO4 with PO1	CO4 is aligned with PO1 because it Highly deals with the basic pharmacy knowledge
CO4 with PO2	CO4 is aligned with PO2 because it slightly deals with the Regulatory requirement of drug
CO4 with PO3	CO4 is aligned with PO3 because it moderately deals with design and regulatory requirement of Pharmaceuticals.including approval of drug products
CO4 with PO4	CO4 is aligned with PO4 relevant to perform testing according to guideline
CO4 with PO5	CO4 is aligned with PO5 because it deals with modern tools and techniquesfor approval of drugs
CO 4 with PO 12	CO4 is aligned with PO12 because it deals with Understanding and implementing theoretical and practical knowledge in Drug approvals.
CO5with PO1	CO5 is aligned with PO1 because it Highly deals with the basic pharmacy knowledge
CO5 with PO2	CO5 is aligned with PO2 because it slightly deals with the Drug approval Process
CO5 with PO3	CO5 is aligned with PO3 because it moderately deals with drug approval process.
CO5 with PO4	CO5 is aligned with PO4 relevant to drug approval process.
CO5 with PO5	CO5 is aligned with PO5 because it deals with modern techniques and tools related to regulatory requirement of drug .
CO 5 with PO 12	CO5 is aligned with PO12 because it deals with implementation of pharma based system in drug approval process
CO1 with PSO 1,2,3,4	Student apply fundamental knowledge to differnts methods & technique of drug approval,Technology Transfer ,scale up tech so it correlate to PSO1 & PSO2,PSO3, PSO4
CO2 with PSO 1,2,3,4	Student apply fundamental knowledge differnts methods & technique of knowledge of importance and implementation of regulatory

	guideline along with their mechanisam to implement PSO1 & PSO2,PSO3, PSO4
CO3 with PSO 1,2,3,4	Student apply fundamental knowledge to physical pharmaceutics to scale up tech pharmaceutical products so it correlate to PSO1 & PSO2,PSO3, PSO4
CO4 with PSO 1,2,3,4	Student apply fundamental knowledge to design and regulatory guideline so it correlate to PSO1 & PSO2,PSO3, PSO4

QUESTION BANK

BP702T Industrial Pharmacy-II -Theory

UNIT 1

2 MARKS Questions

1. Define pilot and scale up?
2. What is the difference between pilot scale and scale-up?
3. Why to conduct pilot plant studies?
4. What are the advantages of pilot studies?
5. What is SUPAC?
6. What is the purpose of SUPAC guidelines?
7. Define platform technology?

5 MARKS SHORT ASSAY

1. What are the objectives and significance of pilot plants?
2. Explain SUPAC guidelines?
3. Discuss the uses of platform technology?

10 MARKS LONG ASSAY

1. Discuss the general factors to be considered in pilot plant scale up technology?
2. Discuss pilot plant scale up consideration for solids dosage solids.
3. Discuss pilot plant scale up consideration for liquid orals.
4. Discuss pilot plant scale up consideration for semi-solids.
5. what are difference platform technology and explain.

UNIT-2

2 MARKS SHORT ASSAY

1. Define the technology transfer according to WHO and how it is classified?
2. What are the goal of technology transfer?
3. What are the advantage of technology transfer?
4. What is good manufacturing practices (GMP)?
5. What do you mean by SU &RU
6. Define quality risk management (QRM) and write its principle

7. What do you mean by intercompany and intracompany?
8. What is standard operating procedure (SOP) ?
9. What is validation and process validation?
10. What is validation protocol (VP) and validation report (VR) ?
11. what is the drug master file (DMF) ?
12. What is analytical method transfer?
13. What is design qualification (DQ) and installation qualification (IQ) ?
14. What is operational qualification (OQ) and performance qualification (PQ) ?

5 MARKS SHORT ASSAY

1. Explain technology transfer sample protocol in pharmaceuticals
2. Discuss technology transfer from R & D to production as per WHO guidelines?
3. Discuss granularity of TT process (API, excipients, finished products, packaging material) as per WHO guidelines for TT ?
4. Discuss about documentation, premises, and equipments for TT as per WHO guidelines
5. Discuss about qualification and validation for TT as per WHO guidelines?
6. How analytical methods are exchanged in a technology transfer ?

10 MARKS QUESTIONS

1. Discuss stage involved in TT in pharmaceutical industry?

UNIT 3

2 MARKS QUESTIONS

1. What is regulatory affairs ? what its goal?
2. what is investigational new drug and application?
3. what is New drug application (NDA) /
4. what is clinical trial?
5. what is clinical trial protocol?
6. what are BE & BA studies? why they are required?
7. Mention the major regulatory bodies in the world?
8. What is the organisational structure of regulatory affairs ?
9. Which is the health care product regulated by RA ?
10. What is CTD ?

5 MARKS QUESTIONS

1. Discuss the role and responsibilities of RA professional.
2. Write a note on Drug development team and their functions.
3. Discuss regulatory authorities and their responsibilities.
4. Write a note on Non-clinical drug development process.
5. Write a note on Investigator's Brochure (IB).
6. Discuss the different phase of clinical trial.
7. How Bioequivalence are documented.
8. Write a note on clinical Research protocol.
9. Discuss about Management of clinical studies.
10. Discuss the various Modules in CTD.

10 MARKS QUESTIONS

1. Explain Regulatory Requirement Approval for obtaining NDA.
2. Discuss general consideration of Investigational New drug Application.

SUBJECT NOTES
BP702T Industrial Pharmacy-II -Theory

Technology development and transfer:

WHO guidelines for Technology Transfer(TT): Terminology, Technology transfer protocol, Quality risk management, Transfer from R & D to production (Process, packaging and cleaning), Granularity of TT Process (API, excipients, finished products, packaging materials) Documentation, Premises and equipments, qualification and validation, quality control, analytical method transfer, Approved regulatory bodies and agencies, Commercialization - practical aspects and problems (case studies), TT agencies in India - APCTD, NRDC, TIFAC, BCIL, TBSE / SIDBI; TT related documentation - confidentiality agreement, licensing, MoUs, legal issues. PREPARED BY Dr. Ch. Niranjan Patra (BPUT TEACHER REGISTRATION NUMBER: T090326703) Vice principal cum Professor, Roland Institute of Pharmaceutical Sciences, Berhampur, Odisha. Technology Development and Transfer Abstract In today's scenario, interest in the profitable exploitation of a firm's technological assets, through technology transfer, has intensified. Appropriate technology transfer is both vital and critical to drug discovery and development for novel medicinal products and is also essential to upgrade drug quality intended during research and development and to finishing product during manufacturing as well as to assure constant quality transferred. Successful growth and commercialization of innovative technologies is always apprehensive with difficulties, multifaceted endeavor, and a range of development tools exist to uphold this activity, by far the most popular approach to directly supporting successful innovation is through technology transfer. To develop appropriate clinical good manufacturing practice facilities, specify and design specialized process equipment, finalize process details, and correctly determine scale-up parameters requires the integrated efforts of a highly skillful technology transfer team. Successful technology transfer requires carefully studying conditions like careful evaluation of ultimate manufacturing requirements early in research and development and the consequent improvement of robust developments that endure large-scale operation, the assembly of a detailed technology transfer document that provides manufacturing with both "know how" and "know why," and will serve as the basis for facilities and equipment design as well as operator training and standard operating procedure generation in successful manufacturing. Introduction What is technology transfer? • Transfer of technology is defined as a "logical procedure that controls the transfer of any process together with its documentation and professional expertise between developments or between manufacture sites." • Technology transfer is both integral and critical to the drug discovery and development process for new medical products. • Technology transfer is helpful to develop dosage forms in various ways as it provides efficiency in process, maintains quality of product, helps to achieve standardized process which facilitates cost effective production. It is the process by which by an original innovator of technology makes it technology available to commercial partner that will exploit the technology. • In pharmaceutical industry, "Technology transfer "refers to the processes of successful progress from drug discovery to product development, clinical

trials and ultimately full scale commercialization. • Technology transfer is important for such researcher to materialize on a larger scale for commercialization especially in the case of developing product. Technology transfer includes not only patentable aspects of production but also includes the business processes such as knowledge and skills. • The different stages involved in technology transfer are presented in figure 1. INVENTION IDEA & TECHNOLOGY FEASIBILITY PROTOTYPE /SCALE UP PRODUCT DEVELOPMENT INITIAL MANUFACTURE COMMERCIALIZATION TRANSLATION Figure 1, Different stages of technology transfer Facts of technology transfer The transfer of technology could happen in following ways • Government labs to private sector firms. • Between private sector firms of same country. • Between private sector firms of different country. • From academia to private sector firms. WHO guidelines for Technology Transfer (TT): [1] These guiding principles on transfer of technology are intended to serve as a framework which can be applied in a flexible manner rather than as strict rigid guidance. Focus has been placed on the quality aspects, in line with WHO's mandate. 1. Transfer of processes to an alternative site occurs at some stage in the life-cycle of most products, from development, scale-up, manufacturing, production and launch, to the postapproval phase. 2. Transfer of technology is defined as "a logical procedure that controls the transfer of any process together with its documentation and professional expertise between development and manufacture or between manufacture sites". It is a systematic procedure that is followed in order to pass the documented knowledge and experience gained during development and or commercialization to an appropriate, responsible and authorized party. 3. Literature searches revealed little information on the subject originating from national or regional regulatory bodies. Guidance on intra-company transfers was prepared by the International Society for Pharmaceutical Engineering (ISPE). 4. The ever changing business strategies of pharmaceutical companies increasingly involve intraand intercompany transfers of technology for reasons such as the need for additional capacity, relocation of operations or consolidations and mergers. The WHO Expert Committee on Specifications for Pharmaceutical Preparations, therefore, recommended in its 42nd report that WHO address this issue through preparation of WHO guidelines on this matter. 5. Transfer of technology requires a documented, planned approach using trained and knowledgeable personnel working within a quality system, with documentation of data covering all aspects of development, production and quality control. Usually there is a sending unit (SU), a receiving unit (RU) and the unit managing the process, which may or may not be a separate entity. 6. For successful transfer, the following general principles and requirements should be met: • The project plan should encompass the quality aspects of the project and be based upon the principles of quality risk management (QRM). • The capabilities of the SU and the RU should be similar, but not necessarily identical, and facilities and equipment should operate according to similar operating principles. • A comprehensive technical gap analysis between the SU and RU including technical risk assessment and potential regulatory gaps, should be performed as needed. • Adequately trained staff should be available or should be trained at the RU: Regulatory requirements in the countries of the SU and the RU, and in any countries where the product is intended

to be supplied, should be taken into account and interpreted consistently throughout any transfer programme project and there should be effective process and product knowledge transfer. 7. Technology transfer can be considered successful if there is documented evidence that the RU can routinely reproduce the transferred product, process or method against a predefined set of specifications as agreed with the SU. 8. In the event that the RU identifies particular problems with the process during the transfer, the RU should communicate them back to the SU to ensure continuing knowledge management. 9. Technology transfer projects, particularly those between different companies, have legal and economic implications. If such issues, which may include intellectual property rights, royalties, pricing, conflict of interest and confidentiality, are expected to impact on open communication of technical matters in any way, they should be addressed before and during planning and execution of the transfer. Any lack of transparency may lead to ineffective transfer of technology. 10. Some of the responsibilities outlined in this document for the SU may also be considered to be part of the management unit responsibilities. The guidelines address the following areas • Transfer of development and production (processing, packaging and cleaning). • Transfer of analytical methods for quality assurance and quality control. • Skills assessment and training. • Organization and management of the transfer. • Assessment of premises and equipment. • Documentation; and qualification and validation. Terminologies used in technology Transfer Acceptance criteria Measurable terms under which test results will be considered acceptable. Bracketing An experimental design to test only the extremes of, for example, dosage strength. The design assumes that the extremes will be representative of all the samples between the extremes. Change control (C/C) A formal system by which qualified representatives of appropriate disciplines review proposed or actual changes that might affect a validated status. The intent is to determine the need for action that would ensure that the system is maintained in a validated state. Commissioning The setting up, adjustment and testing of equipment or a system to ensure that it meets all the requirements, as specified in the user requirement specification, and capacities as specified by the designer or developer. Commissioning is carried out before qualification and validation. Corrective action (C/A) Any action to be taken when the results of monitoring at a critical control point indicate a loss of control. Critical Having the potential to impact product quality or performance in a significant way. Critical control point (CCP) A step at which control can be applied and is essential to prevent or eliminate a pharmaceutical quality hazard or reduce it to an acceptable level. Design qualification (DQ) Documented evidence that the premises, supporting systems, utilities, equipment and processes have been designed in accordance with the requirements of good manufacturing practices (GMP). Design space The multidimensional combination and interaction of input variables (e.g. material attributes) and process parameters that have been demonstrated to provide assurance of quality. Drug master file (DMF) Detailed information concerning a specific facility, process or product submitted to the drug regulatory authority, intended for the incorporation into the application for marketing authorization. Gap analysis Identification of critical elements of a process which are available at the SU but are missing from the RU. Good Manufacturing Practices (GMP)

That part of quality assurance which ensures that products are consistently produced and controlled to the quality standards appropriate to their intended use and as required by the marketing authorization. Inter-company transfer A transfer of technology between sites of different companies. Intra-company transfer A transfer of technology between sites of the same group of companies. In-process control (IPC) Checks performed during production in order to monitor and, if necessary, to adjust the process to ensure that the product conforms to its specifications. The control of the environment or equipment may also be regarded as a part of in-process control. Installation qualification (IQ) The performance of tests to ensure that the installations (such as machines, measuring devices, utilities and manufacturing areas) used in a manufacturing process are appropriately selected and correctly installed and operate in accordance with established specifications. Operational qualification (OQ) Documented verification that the system or subsystem performs as intended over all anticipated operating ranges. Performance qualification (PQ) Documented verification that the equipment or system operates consistently and gives reproducibility within defined specifications and parameters for prolonged periods. Process validation Documented evidence which provides a high degree of assurance that a specific process will consistently result in a product that meets its predetermined specifications and quality characteristics. Quality assurance (QA) Quality assurance is a wide-ranging concept covering all matters that individually or collectively influence the quality of a product. The totality of the arrangements made with the objective of ensuring that pharmaceutical products are of the quality required for their intended use. Quality control (QC) Quality control covers all measures taken, including the setting of specifications, sampling, testing and analytical clearance, to ensure that starting materials, intermediates, packaging materials and finished pharmaceutical products conform with established specifications for identity, strength, purity and other characteristics. Qualification Action of proving and documenting that any premises, systems and equipment are properly installed, and/or work correctly and lead to the expected results. Qualification is often a part (the initial stage) of validation, but the individual qualification steps alone do not constitute process validation. Quality risk management (QRM) Quality risk management is a systematic process for the assessment, control, communication and review of risks to the quality of the pharmaceutical product across the product life-cycle. Receiving unit (RU) The involved disciplines at an organization where a designated product, process or method is expected to be transferred. Sending unit (SU) The involved disciplines at an organization where a designated product, process or method is expected to be transferred from. Spiking The addition of a known amount of a compound to a standard, sample or placebo, typically for the purpose of confirming the performance of an analytical procedure. Standard operating procedure (SOP) An authorized written procedure giving instructions for performing operations not necessarily specific to a given product or material (e.g. equipment operation, maintenance and cleaning; validation; cleaning of premises and environmental control; sampling and inspection). Transfer of technology (TOT) A logical procedure that controls the transfer of an established process together with its documentation and professional expertise to site capable of reproducing the process and its support functions to a predetermined level of performance. Validation Action of proving and documenting that any process,

procedure or method actually and consistently leads to the expected results. Validation master plan (VMP) A high-level document that establishes an umbrella validation plan for the entire project and summarizes the manufacturer's overall philosophy and approach, to be used for establishing performance adequacy. It provides information on the manufacturer's validation work programme and defines details of and timescales for the validation work to be performed, including a statement of the responsibilities of those implementing the plan. Validation protocol (or plan) (VP) A document describing the activities to be performed in a validation, including the acceptance criteria for the approval of a manufacturing process – or a part thereof – for routine use. Validation report (VR) A document in which the records, results and evaluation of a completed validation programme are assembled and summarized. It may also contain proposals for the improvement of processes and/or equipment. Technology Transfer Protocol The transfer protocol should list the intended sequential stages of the transfer. The protocol should include: • objective; • scope; • key personnel and their responsibilities; • a parallel comparison of materials, methods and equipment; • the transfer stages with documented evidence that each critical stage has been satisfactorily accomplished before the next commences; • identification of critical control points; • experimental design and acceptance criteria for analytical methods; • information on trial production batches, qualification batches and process validation; • change control for any process deviations encountered; • assessment of end-product; • arrangements for keeping retention samples of active ingredients, intermediates and finished products, and information on reference substances where applicable; and • Conclusion, including signed-off approval by project manager. Quality risk management [2] Two primary principles of quality risk management are: ⎪ The evaluation of the risk to quality should be based on scientific knowledge and ultimately link to the protection of the patient; and ⎪ The level of effort, formality and documentation of the quality risk management process should be commensurate with the level of risk. Quality risk management is a systematic process for the assessment, control, communication and review of risks to the quality of the drug (medicinal) product across the product lifecycle. A model for quality risk management is outlined in the Figure 2. Responsibilities Quality risk management activities are usually, but not always, undertaken by interdisciplinary teams. When teams are formed, they should include experts from the appropriate areas (e.g., quality unit, business development, engineering, regulatory affairs, production operations, sales and marketing, legal, statistics and clinical) in addition to individuals who are knowledgeable about the quality risk management process. Initiating a Quality Risk Management Process Quality risk management should include systematic processes designed to coordinate, facilitate and improve science-based decision making with respect to risk. Possible steps used to initiate and plan a quality risk management process might include the following : • Define the problem and/or risk question, including pertinent assumptions identifying the potential for risk; • Assemble background information and/ or data on the potential hazard, harm or human health impact relevant to the risk assessment; • Identify a leader and necessary resources; • Specify a timeline, deliverables and appropriate level of decision making for the risk management process. Figure 2, Overview of a typical

Quality risk management process Risk Assessment Risk assessment consists of the identification of hazards and the analysis and evaluation of risks associated with exposure to those hazards. Quality risk assessments begin with a well-defined problem description or risk question. Three fundamental questions are often helpful: • What might go wrong? • What is the likelihood (probability) it will go wrong? • What are the consequences (severity)? • Risk Identification It is a systematic use of information to identify hazards referring to the risk question or problem description. Information can include historical data, theoretical analysis, informed opinions, and the concerns of stakeholders. Risk identification addresses the "What might go wrong?" question, including identifying the possible consequences Risk analysis Risk analysis is the estimation of the risk associated with the identified hazards. It is the qualitative or quantitative process of linking the likelihood of occurrence and severity of harms. Risk Evaluation It compares the identified and analyzed risk against given risk criteria. The output of a risk assessment is either a quantitative estimate of risk or a qualitative description of a range of risk. When risk is expressed quantitatively, a numerical probability is used. Alternatively, risk can be expressed using qualitative descriptors, such as "high", "medium", or "low", which should be defined in as much detail as possible. Risk Control Risk control includes decision making to reduce and/or accept risks. The purpose of risk control is to reduce the risk to an acceptable level. Risk control might focus on the following questions: • Is the risk above an acceptable level? • What can be done to reduce or eliminate risks? • What is the appropriate balance among benefits, risks and resources? • Are new risks introduced as a result of the identified risks being controlled? Risk Reduction Risk reduction focuses on processes for mitigation or avoidance of quality risk when it exceeds a specified (acceptable) level. Risk reduction might include actions taken to mitigate the severity and probability of harm. Processes that improve the detectability of hazards and quality risks might also be used as part of a risk control strategy. Risk communication Risk communication is the sharing of information about risk and risk management between the decision makers and others. Parties can communicate at any stage of the risk management process. The output/result of the quality risk management process should be appropriately communicated and documented. Risk review A mechanism to review or monitor events should be implemented. The output/results of the risk management process should be reviewed to take into account new knowledge and experience. The frequency of any review should be based upon the level of risk. Risk review might include reconsideration of risk acceptance decisions. Risk management methodology Quality risk management supports a scientific and practical approach to decision-making. It provides documented, transparent and reproducible methods to accomplish steps of the quality risk management process based on current knowledge about assessing the probability, severity and sometimes detectability of the risk. The pharmaceutical industry and regulators can access and manage risk using recognized risk management tools and/or internal procedures (e.g., standard operating procedures). Below is a non-exhaustive list of some of these tools. • Basic risk management facilitation methods (flowcharts, check sheets etc.); • Failure Mode Effects Analysis (FMEA); • Failure Mode, Effects and Criticality Analysis (FMECA); • Fault Tree Analysis (FTA); • Hazard

Analysis and Critical Control Points (HACCP); • Hazard Operability Analysis (HAZOP); • Preliminary Hazard Analysis (PHA); • Risk ranking and filtering; • Supporting statistical tools. Transfer from R & D to production (Process, packaging and cleaning) • It should be established at the outset whether the intention is to perform single-batch manufacture, continuous production or campaigns, and whether the RU can accommodate the intended production capacity. • Consideration should be given to the level and depth of detail to be transferred to support production and any further development or process optimization at the RU as intended under the transfer project plan. • The SU and the RU should jointly develop a protocol for the transfer of relevant information related to the manufacturing process under consideration from the SU to the RU, as well as the development of an equivalent process at the RU. Process The SU should provide a detailed characterization of the product, including its qualitative and quantitative composition, physical description, method of manufacture, in-process controls and specifications, packaging components and configurations, and any special safety and handling considerations. The SU should provide any information on the history of process development which may be required to enable the RU to perform any further development and/or process optimization intended after successful transfer. Such information may include the following: • information on clinical development, e.g. information on the rationale for the synthesis, route and form selection, technology selection, equipment, clinical tests, and product composition; • information on scale-up activities: process optimization, statistical optimization of critical process parameters, pilot report and/or information on pilot-scale development activities indicating the number and disposition of batches manufactured; and • information or report on full-scale development activities, indicating the number and disposition of batches manufactured, and deviation and change control reports which led to the current manufacturing. The SU should provide to the RU information on any health, safety and environmental issues associated with the manufacturing processes to be transferred, and resulting implications, e.g. need for gowning or protective clothing. The SU should provide to the RU information on current processing and testing, including but not limited to: • a detailed description of facility requirements and equipment ; • process technology selection; • information on starting materials, applicable MSDs and storage requirements for raw materials and finished products; • description of manufacturing steps (narrative and process maps or flow charts), including qualification of in-processing hold times and conditions, order and method of raw material addition and bulk transfers between processing steps; • description of analytical methods; • in-process controls, including, e.g. identification of critical performance aspects for specific dosage forms, identification of process control points, product quality attributes and qualification of critical processing parameter ranges, statistical process control (SPC) charts; • validation information, e.g. validation plans and reports, and annual product reviews; • stability information; and an authorized set of SOPs and work instructions for manufacturing. Packaging It should follow the same procedural patterns as those of the production transfer. • Information on packaging to be transferred from the SU to the RU include specifications for a suitable container/closure system, as well as any relevant additional information on design,

packing, processing or labeling requirements needed for qualification of packaging components at the RU. • For quality control testing of packaging components, specifications should be provided for drawings, artwork, and material (glass, card, fibre board, etc.). Based on the information provided, the RU should perform a suitability study for initial qualification of the packaging components. Packaging is considered suitable if it provides adequate protection (preventing degradation of the drug due to environmental influences), safety (absence of undesirable substances released into the product), compatibility (absence of interaction possibly affecting drug quality) and performance (functionality in terms of drug delivery). Cleaning During the manufacturing process, pharmaceutical products and APIs can be contaminated by other pharmaceutical products or APIs if processing different products. To minimize the risk of contamination and cross-contamination, operator exposure and environmental effects, adequate cleaning procedures are essential. The SU should provide information on cleaning procedures in use at the SU to minimize crosscontamination due to residues from previous manufacturing steps, operator exposure and environmental impact, including: solubility information of active ingredients, excipients and vehicles. Granularity of TT Process (API, excipients, finished products, packaging materials) Starting materials The specifications of the starting materials (APIs and excipients) to be used at the RU should be consistent with reference batches (development batches, biobatches or batches manufactured at the SU). Any properties which are likely to influence the process or product should be identified and characterized. Active Pharmaceutical Ingredients (API) The SU should provide the drug master file (DMF) and any relevant additional information on the API to the RU to be checked against the specifications of the API. The following information should be provided: • manufacturer; • flow chart of synthetic pathway, outlining the process, including entry points for raw materials, critical steps, process controls and intermediates; • definitive form of the API (including photomicrographs and other relevant data) and any polymorphic and solvate forms; • solubility profile; • partition coefficient (including the method of determination); • intrinsic dissolution rate (including the method of determination); • particle size and distribution (including the method of determination); • bulk physical properties, including data on bulk and tap density, surface area and porosity as appropriate; • water content and determination of hygroscopicity, including water activity data and special handling requirements; • microbiological considerations (including sterility, bacterial endotoxins and bioburden levels where the API supports microbiological growth) in accordance with regional pharmacopoeial requirements; • specifications and justification for release and end-of-life limits; • summary of stability studies conducted in conformity with current guidelines, including conclusions and recommendations on retest date; • listing of potential and observed synthetic impurities, with data to support proposed specifications and typically observed levels; • information on degradants, with a listing of potential and observed degradation products and data to support proposed specifications and typically observed levels; • potency factor, indicating observed purity and justification for any recommended adjustment to the input quantity of API for product manufacturing, providing example calculations; and • special considerations with implications for storage

and/or handling, e.g. safety and environmental factors and sensitivity to heat, light or moisture. Excipients The excipients to be used have a potential impact on the final product. Their specifications as well as the DMF should, therefore, be made available by the SU for transfer to the RU site. The following information should be provided for all types of excipients: • description of functionality, with justification for inclusion of any antioxidant, preservative or any excipient above recommended guidelines; • manufacturer; • specifications, i.e. monographs and additional information that may affect product processing or quality for compendia excipients, or a complete listing of specifications, including analytical methods and justification for release limits for non-compendial excipients. For excipients used for the first time in a human drug product or by a new route of administration, the same level of detail as for a drug substance should be provided; • special considerations with implications for storage and/or handling, including but not limited to safety and environmental factors (e.g. as specified in material safety data sheets) and sensitivity to heat, light or moisture solubility; and • regulatory considerations, i.e. compendial status and appropriate regulatory information for non-compendial excipients; information on residual solvents or organic volatile impurities; and documentation to support compliance with transmissible animal spongiform encephalopathy certification requirements (where applicable). Finished Products Depending on the type of dosage form, the SU should provide relevant information on physical properties of excipients to the RU, including: • definitive form (for solid and inhaled dosage forms); • solubility profile (for solid, inhaled and transdermal dosage forms); • partition coefficient, including the method of determination (for transdermal dosage forms); • intrinsic dissolution rate, including the method of determination (for transdermal dosage forms); • particle size and distribution, including the method of determination (for solid, inhaled and transdermal dosage forms); • bulk physical properties, including data on bulk and tap density, surface area and porosity as appropriate (for solid and inhaled dosage forms); • compaction properties (for solid dosage forms); • melting point range (for semi-solid/topical dosage forms); • pH range (for parenteral, semi-solid/topical, liquid and transdermal dosage forms); • ionic strength (for parenteral dosage forms); • specific density/gravity (for parenteral, semi-solid/topical, liquid and transdermal dosage forms); • viscosity and/or viscoelasticity (for parenteral, semi-solid/topical, liquid and transdermal dosage forms); • osmolarity (for parenteral dosage forms); • water content and determination of hygroscopicity, including water activity data and special handling requirements (for solid and inhaled dosage forms); • moisture content range (for parenteral, semi-solid/topical, liquid and transdermal dosage forms); • microbiological considerations in accordance with regional pharmacopoeial requirements (for parenteral, semi-solid/topical, liquid, inhaled and transdermal dosage forms); and • information on adhesives supporting compliance with peel, sheer and adhesion design criteria (for transdermal dosage forms). Packaging • Information on packaging to be transferred from the SU to the RU include specifications for a suitable container/closure system, as well as any relevant additional information on design, packing, processing or labeling requirements needed for qualification of

packaging components at the RU. For quality control testing of packaging components, specifications should be provided for drawings, artwork, material. Documentation: The documents used in technology transfer are presented in table 1. Table 1. Documentation for transfer of technology (TOT) Key task Documentation provided by SU Transfer documentation Project definition Project plan and quality plan (where separate documents), protocol, risk assessments, gap analysis Project implementation plan TOT protocol Quality agreement Facility assessment Plans and layout of facility, buildings (construction, finish) Qualification status (DQ, IQ, OQ) and reports Side-by-side comparison with RU facility and buildings; gap Analysis Qualification protocol and report Health & Safety assessment Product-specific waste management plans Contingency plans Skill set analysis and training SOPs and training documentation (product-specific operations, analysis, testing) Training protocols, assessment results Analytical method transfer Analytical method specifications and validation, including in-process quality control Analytical methods transfer protocol and report Starting material Evaluation Equipment selection and transfer Specifications and additional information on APIs, excipients Inventory list of all equipment and systems, including makes, models, qualification status (IQ, OQ, PQ). Drawings, manuals, logs, SOPs (e.g. set-up, operation, cleaning, maintenance, calibration, storage) Side-by-side comparison with RU equipment (makes, models, qualification status) Gap analysis. Qualification and validation protocol and report Process transfer: manufacturing and packaging Reference batches (clinical, dossier, bio-batches) Development report (manufacturing process rationale),History of critical analytical data Rationale for specifications, Change control documentation, Critical manufacturing process Parameters Process validation reports Drug master file. API validation status and report(s) Product stability data Current master batch manufacturing and packaging records List of all batches produced Deviation reports, Investigations, complaints, recalls Annual product review History of process development at RU, Experiences at RU should be recorded for future reference Provisional batch mfg document (RU to develop) Provisional batch packaging document (RU to develop) Description of process at RU (narrative, process map, fl ow chart) Process validation protocol and report Cleaning Cleaning validation, Solubility information; therapeutic doses; category (toxicology); existing cleaning SOPs; validation reports chemical and micro; agents used; recovery study Product- and site-specifi c cleaning SOPs at RU Cleaning validation protocol and report Premises and Equipment Premises • The SU should provide information to the RU on the layout, construction and finish of all buildings and services (heating, ventilation and air-conditioning (HVAC), temperature, relative humidity, water, power, compressed air) impacting the product, process or method to be transferred. • The SU should provide information on relevant health, safety and environmental issues, including: • inherent risks of the manufacturing processes (e.g. reactive chemical hazards, exposure limits, fire and explosion risks). • health and safety requirements to minimize operator exposure (e.g. atmospheric containment of pharmaceutical dust). • Differences in building, construction layout and services between the SU and the RU should be listed and compared in view of the following considerations: • buildings and services at the RU should be capable of accommodating

the product, process or method under transfer to the agreed quality standard and production volume in compliance with GMP; DQ, design qualification; IQ, installation qualification; OQ, operational qualification; API, active pharmaceutical ingredient; SOPs, standard operating procedures; RU, receiving unit. • quality control laboratories should be equipped and capable of testing all APIs, excipients, intermediate and finished products, packaging components and cleaning validation samples; • buildings intended for production of a highly sensitizing nature (e.g. penicillins and cytotoxic materials) should be dedicated for this purpose and located in a different facility from other production units; and • health, safety and environmental issues, including waste management, emergency planning, minimization of operator exposure and environmental impact, should be addressed at the RU in compliance with any regulatory or company-developed rules, regulations and limits. Equipment The SU should provide a list of equipment, makes and models involved in the manufacture, filling, packing and/or control of the product, process or method to be transferred, together with existing qualification and validation documentation. Relevant documentation may include: • drawings; • manuals; • maintenance logs; • calibration logs; and • SOPs (e.g. equipment set up, operation, cleaning, maintenance, calibration, storage). The RU should review the information provided by the SU together with its own inventory list including the qualification status (IQ, OQ, PQ) of all equipment and systems, and perform a sideby-side comparison of equipment at the two sites in terms of their functionality, makes, models and qualification status. Based on the side-by-side comparison, the RU should perform a gap analysis to identify requirements for adaptation of existing equipment, or acquisition of new equipment, to enable the RU to reproduce the process being transferred. GMP requirements should be satisfied, and intended production volumes and batch sizes (e.g. same, scaled-up or campaign) should be considered. Factors to be compared include: • minimum and maximum capacity; • material of construction; • critical operating parameters; • critical equipment components (e.g. filters, screens, temperature/pressure sensors); and • range of intended use. The facility- and building-specific location of all equipment at the RU should be considered at the time of drawing up process maps or flow charts of the manufacturing process to be transferred, including movement of personnel and material. The impact of manufacturing new products on products currently manufactured with the same equipment should be determined. Where existing producing equipment needs to be adapted to be capable of reproducing the process being transferred, a detailed development project should be included in the transfer protocol. New equipment should be designed and constructed to facilitate the process and ease cleaning and maintenance operations. Any newly acquired equipment should undergo a qualification protocol up to and including OQ level. Applicable operating procedures for set-up, operation, cleaning, storage and maintenance should be developed by the conclusion of OQ. Supporting documents such as drawings of equipment and piping installations, manuals, maintenance logs and calibration logs should be retained. Qualification and Validation General ⟩ Qualification and validation of facilities, equipment, systems and procedures are essential to demonstrate that all critical stages of the transfer project have been completed successfully, enabling the RU to

reproduce the product, process or method routinely to the specifications agreed with the SU. ⏐ Validation performed as part of the transfer project should be documented in a validation master plan (VMP). The VMP should identify the stages which need to be validated and define acceptance criteria. ⏐ For intra-company transfers, the RU should operate under the same VMP as the SU. For intercompany transfers, a VMP should be in place at the RU before the transfer. ⏐ The RU should prepare a validation protocol (VP) for each sequential step. Successful execution of each VP should be documented in a validation report (VR). ⏐ Setting up and commissioning of systems at the RU need to be completed before qualification and validation can be performed at the RU. The steps required for this purpose have been described in this guideline for buildings, services and equipment, manufacturing, packaging and cleaning and analytical testing. In brief, the following basic steps apply equally to each of these areas: • the SU should provide information on materials, systems and procedures involved in the manufacturing of the product, process or method to be transferred; • the RU should review the information provided by the SU, and audit its current systems, equipment and processes, including non-process related practices and support services that impact the process; • based on this review, the RU should either accept the information provided or develop it further to prepare site-specific procedures, SOPs, training programmes and protocols which will form the basis of the qualification and validation; and • relevant staff, e.g. operators and analysts, should be trained in any new processes as required. ⏐ Once the required systems and procedures have been commissioned at the RU, and successful training has been documented, qualification and validation of facility and equipment should be executed, followed by validation of analytical test methods, process validation for manufacturing and packaging, and cleaning validation. ⏐ The RU should review the gap analysis and prepare, where appropriate, VPs for the facility, services and equipment. ⏐ Both new and existing equipment should satisfy the VPs associated with purchase and design specifications, factory acceptance tests (FAT) if possible, IQ and OQ. ⏐ Performance qualification, including a further assessment of operating parameters with relation to product characteristics, should be established on commencement of trial batches. ⏐ Successful completion of qualification and validation should be documented in a report. Quality Control: Transfer of analytical methods should accommodate all the analytical testing required to demonstrate compliance of the product to be transferred with the registered specification. Transfer of analytical methods used to test pharmaceutical products, their ingredients and cleaning (residue) samples, needs to be in place before process validation studies of manufacturing operations can be carried out. The SU should prepare a protocol defining the steps to be undertaken for analytical method transfer. The analytical methods transfer protocol should describe the objective; scope; responsibilities of the SU and the RU; materials, methods and equipment; the experimental design and acceptance criteria; documentation (including information to be supplied with the results, and report forms to be used if any); deviations; references; signed approval; and details of reference samples (APIs, intermediates and finished products). The SU's responsibilities for the transfer of analytical methods are to: • provide method-specific training for analysts and other quality control staff; • provide acceptance criteria and validation

protocols for any RU training exercises; • assist in analysis of quality control testing results; • define and justify all methods to be transferred for testing a given product, ingredient or cleaning sample; • define experimental design, sampling methods and acceptance criteria; • provide any validation reports for methods under transfer, and demonstrate their robustness; • provide data for the equipment used and any standard reference samples; and • provide approved SOPs used in testing. The RU's responsibilities are to: • review analytical methods provided by the SU, and formally agree on acceptance criteria before execution of the transfer protocol; • ensure that the necessary equipment for quality control is available and qualified at the RU site. Equipment should be replicated where possible, but it is accepted that different models, e.g. spectrometers and chromatographs, could already be in place; • ensure that adequately trained and experienced personnel is in place for analytical testing; • provide a documentation system capable of recording receipt and testing of samples. A suggested analytical training protocol would be as follows: • SU and RU analysts assay two retained samples from SU; • SU and RU analysts then assay two sub-potent samples (available from SU or spiked); • SU and RU analysts assay samples taken from RU production; • RU analyst provides sufficient replicate analyses to enable a significance test (e.g. student's t) against the established method at the SU site; and • a similar exercise should be undertaken for analysis of low levels of APIs. • All training activities and outcomes should be documented. Analytical methods Transfer The analytical methods transfer protocol should cover the following sections: • objective; • scope; • responsibilities of the SU and the RU; • materials, methods and equipment; • the experimental design and acceptance criteria; • documentation (including information to be supplied with the results, and report forms to be used if any); • deviations; • references; • signed approval; and • details of reference samples (APIs, intermediates and finished products). Successful transfer and validation of analytical methods should be documented in a report. Approved regulatory bodies and agencies The principal regulatory bodies entrusted with the responsibility of ensuring the approval, production and marketing of quality drugs in India at reasonable prices are: ⁾ The Central Drug Standards and Control Organization (CDSCO), located under the aegis of the Ministry of Health and Family Welfare. The CDSCO prescribes standards and measures for ensuring the safety, efficacy and quality of drugs, cosmetics, diagnostics and devices in the country. Regulates the market authorization of new drugs and clinical trials standards; supervises drug imports and approves licences to manufacture the above-mentioned products. ⁾ The Drugs Controller General of India (DCGI), With respect to licencing and quality control issues, market authorization is regulated by the Central Drug Controller, Ministry of Health and Family Welfare, Department of Biotechnology, Ministry of Science and Technology (DST) and Department of Environment, Ministry of Environment and Forests. State drug controllers have the authority to issue licences for the manufacture of approved drugs and monitor quality control, along with the Central Drug Standards Control Organization (CDSCO). ⁾ The Food and Drug Administration (FDA or USFDA) is a federal agency of the United States Department of Health and Human Services, one of the United States federal

executive departments. The FDA is responsible for protecting and promoting public health through the Control and supervision of food safety, tobacco products, dietary supplements, prescriprion and over the counter pharmaceutical drugs (medications), vaccines, biopharmaceuticals, blood transfusions, medical, electromagnetic radiation emitting devices (ERED), cosmetics, animal foods & feed[4] and veterinary products. ⎫ The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health, and is responsible for regulating therapeutic goods including prescription medicines, vaccines, sunscreens, vitamins and minerals, medical devices, blood and blood products. Almost any product for which therapeutic claims are made must be entered in the Australian Register of Therapeutic Goods (ARTG) before it can be supplied in Australia. ⎫ Medicines and Healthcare products Regulatory Agency (MHRA) regulates medicines, medical devices and blood components for transfusion in the UK. Commercialization - practical aspects and problems (case studies) Technology transfer are discussed with certain practical studies. Case Study 1 The blending of drug with excipients is presented in table 2. [3] Factors considered in the proposed technology transfer (scale up) Geometric Similarity: Ratio of all lengths constant (constant fill ratio) Dynamic Similarity: Maintenance of Forces (Froude number) Kinematic Similarity: Maintaining a consistent number or revolutions Table 2, Scale-up in QbD Approach: Blending Scale Amount (kg) Blender Capacity Blending Speed (rpm) Blending Time (min) Nrev Volume Fill Ratio (%) Laboratory 2 8 qt 25 12 300 ~50 Pilot 40 7.5 cu.ft 15 20 300 ~50 Commercial 180 30 cu. Ft 10 30 300 ~50 Conclusion of case study 1: The desired content uniformity was attained by modifying the above parameters such as blending speed and blending time. Case Study 2 (Drug layering on MCC spheres) [3] Equipment of production having greatest similitude (geometric) to the intended to commercial scale process, similar particle trajectories and dynamics enables maintenance of process parameters through scale-up with the exception of air-flow which is linearly scaled (Figure 3, Table 3). Conclusion of case study 2 Air flow rate and total spray rate were adjusted to obtain uniform coating of drug on MCC spheres. Assay of the formulation was 99.9% in both pilot batch and commercial batch. Table 3, Parameters for pilot and verification batches at commercial scale Pilot batches Commercial scale Starting Batch Size 40 kg 140 kg Ending Batch Size 56 kg 198 kg Estimated use of capacity 50%-70% 56%-79% Number of Partition(s) 1 3 Partition height 30-50 mm 30-50 mm Nozzle 1.2 mm 1.2 mm Product Temperature 44-48 C 44-48 C Air Flow Rate 810±90 cfm 2430±270 cfm Spray Rate per nozzle 135±25 g/min 135±25 g/min Total Spray Rate 135±25 g/min 405±75 g/min Atomization Pressure per nozzle 2.5-2.9 bar 2.5-2.9 bar Figure 3A Pilot Scale Studies (40 kg each) using 18'' Wurster HS insert Figure 3B Commercial Scale (140 kg) using 32'' Wurster HS insert TT agencies in India - APCTD, NRDC, TIFAC, BCIL, TBSE /SIDBI [4] Asian and Pacific Centre for Transfer of Technology (APCTT) • It is a United Nations Regional Institution under the Economic and Social Commission for Asia and the Pacific (ESCAP) established in 1977 in Bangalore, India. In 1993, the Centre moved to New Delhi, India. APCTT promotes transfer of technology to and from small- and medium-scale enterprises (SMEs) in Asia and the Pacific. APCTT implements development projects funded by international donors

aimed at strengthening the environment for technology transfer among SMEs. The objective of APCTT is to strengthen the technology transfer capabilities in the region and to facilitate import/export of environmentally sound technologies to/from the member countries. National Research Development Corporation (NRDC) • National Research Development Corporation (NRDC) was established in 1953 by the Government of India, with the primary objective to promote, develop and commercialise the technologies / know-how / inventions / patents / processes emanating from various national R&D institutions / Universities and is presently working under the administrative control of the Dept. of Scientific & Industrial Research, Ministry of Science & Technology. During the past six decade of its existence and in pursuance of its corporate goals, NRDC has forged strong links with the scientific and industrial community in India and abroad. It is recognized as a large repository of wide range of technologies spread over almost all areas of industries, viz. Agriculture and Agro-processing, Chemicals including Pesticides, Drugs and Pharmaceuticals, Bio Technology, Metallurgy, Electronics and Instrumentation, Building Materials, Mechanical, Electrical and Electronics etc. It has licensed the indigenous technology to more than 4800 entrepreneurs and helped to establish a large number of small and medium scale industries. NRDC also undertakes number of activities such as meritorious inventions awards, TechnoCommercial support, Technical and financial assistance for IPR Protection, Value addition services and support for further development of technologies and much more. Technology information, Forecasting and assesmement Council (TIFAC) • TIFAC is an autonomous organization set up in 1988 under the Department of Science & Technology to look ahead in technology domain, assess the technology trajectories, and support innovation by networked actions in selected areas of national importance TIFAC embarked upon the major task of formulating a Technology Vision for the country in various emerging technology areas. Under the leadership of Dr. APJ Abdul Kalam, Technology Vision 2020 exercise led to set of 17 documents, including sixteen technology areas and one on services. In more than 25 years of its service to the nation, it has delivered number of technology assessment and foresight reports. While inaugurating the 103rd Indian Science Congress in Mysuru, Hon'ble Prime Minister of India Shri Narendra Modi released the Technology Vision 2035 prepared by TIFAC.This is being followed by release of Technology Roadmaps in 12 thematic areas of national priorities and importance • Education, Medical Science & Health Care, Food and Agriculture, Water, Energy, Environment, Habitat, Transportation, Infrastructure, Manufacturing, Materials and Information & Communication Technologies (ICT). Biotech Consortium India Limited (BCIL) Biotech Consortium India Limited (BCIL), New Delhi was incorporated as public limited company in 1990 under The Companies Act, 1956. The consortium is promoted by the Department of Biotechnology, Government of India and financed by the All India Financial Institutions and some corporate sectors BCIL 's major functions include the development and transfer of technology for the commercialisation of biotechnology products, project consultancy, biosafety awareness and human resource development BCIL has been successfully managing several Flagship schemes and Programmes of the Department of Biotechnology, Government of India. Most notable

include Biotechnology Industry Partnership Programme, 2. Biotechnology Industrial Training Programme and Small Business Innovation Research Initiative Technology Bureau for Small Enterprises (TBSE)/ Small Industries Development Bank of India (SIDBI). • The Technology Bureau for Small Enterprises (TBSE) is a platform for MSMEs to tap opportunities at the global level for the acquisition of technology or establishing business collaboration. TBSE is a result of the cooperative initiative of the United Nations' Asian and Pacific Centre for Transfer of Technology (APCTT) and Small Industries Development Bank of India (SIDBI) in 1995. TBSE also receives partial funding from the Office of DC (SSI), Government of India. Features of TBSE Offering a professionally managed system for the reasons of technology and collaboration exploration helping in the building up of confidence between potential partner. It providing an opportunity to global technology market through the process of networking. Taking up project appraisal and the preparation of a business plan. The new technologies for the reason of transfer are sourced from countries namely China, Philippines, South Korea, Australia, Germany, as well as the U.S. TT related documentation - confidentiality agreement, licensing, MoUs, legal issues. [5] Confidentiality Agreements The aim of a confidentiality agreement is to protect all information of party entering negotiations. Before any concrete negotiations on the transfer of a technology can really start all parties involved must be able to evaluate the technology offered. Both the technological and the commercial possibilities of the offer will thereby be taken into account. Before giving anybody access to your technology a confidentiality agreement should be drafted with discussion on the main topics to be addressed in such agreement keeping in mind that all the standard clauses of an agreement should also be included (parties, term and termination, applicable law). The first item in any confidentiality agreement should be a brief but clear description of the technology that will be transferred. What are the main specifications of this technology and what is its relevant application? In this same disposition of the agreement a reference to the property rights of the party offering can be made. Licensing The legal core of the transfer of technology is constituted by a licensing agreement. By signing this agreement the owner of a technology, the licenser, gives the right to another company, the licensee, to make use of this technology. A licence does not alter the property rights of the owner: he remains the only proprietor of the technology. He could also sell his technology whereby the buyer becomes the owner and replaces the seller. But if an owner of a technology prefers to enter into an agreement with a licensee he will give him limited rights. The licensee cannot dispose of the technology but he can use it. This use will be more or less limited. A limitation in time, in geographical market, in product market or in the application can be introduced in a licence. The licence will determine the relationship between the licenser and licensee for the whole duration of their co-operation and a lot of questions will have to be answered before this relationship can start. Memoranda of Understanding (MOUs) Often collaborative research efforts with outside institutions are defined in Memoranda of Understanding (MOU) before other agreements are executed. An MOU typically defines how intellectual property will be shared and the roles and responsibilities of the involved parties. If you are planning to enter into a collaborative relationship with an outside party, it is important to discuss the possibility of an MOU. Office of Technology Commercialization is responsible for

drafting MOUs related to collaborative research. MOUs typically identify a lead institution for managing intellectual property and provide details on how licensing income will be shared.

Legal Issues The following types legal issues are generally observed in technology transfer.

- Legal contractual agreements
- Tax implications
- Legal issues in intellectual property transaction • Problems associated with IPR litigation
- Legislations covering IPRs in India References

1. WHO Technical Report Series, Annex 7, No. 961, 2011.

2. Guidance for Industry Q10 Pharmaceutical Quality System. U.S. Department of Health and Human Services Food and Drug Administration, ICH, April 2009.

3. Raw AS. QbD Scale-up Considerations Linking Exhibit Batches to Commercial Production. GPhA/FDA Quality by Design Workshop for ANDAs, FDA – CDER - Office of Generic Drugs, May 5, 2011.

4. Dave V, Pareek A, Yadav S, Sharma S, Paliwal S. Pharmaceutical industry and technology transfer agencies in India. The Pharma Review, jan-Feb, 2013, 116-112.

5. Dogra R, Garg R and Jatav P. Technology Transfer in Pharmaceutical Industry: Transfer of Process from Development to Commercialization. IJPSR, 4(5), 2013, 1692-1708.

Tutorial No. 01

1. Define Pilot Plant Scale up
2. Explain objective of Pilot plant Scale up
3. Explain general consideration of Pilot plant Scale up
4. Explain use of Pilot plant scale up

Tutorial No. 02

Q. 1.Draw a flow chart for pilot plant of liquid oral.

Q. 2.Draw a flow chart for pilot plant of semisolids.

Q. 3.Write application of pilot plant scale up.

Q. 4.Define SUPAC and its type.

Tutorial No 03

1.Write a note on Technology transfer protocol & explain how Quality risk management important in TT.

2. How one can go for transfer
from R & D to production (for Process, packaging and cleaning),

3.Explain in details granularity of TT Process (For API, excipients, finished products, packaging
materials)

4.Explain with reference to tecchnlogy transfer for,
A.Documentation,B.Premises and equipments, C) Qualification and validation, D)Quality control, E)Analytical method transfer,

Tutorial No 04

1. What is technology transfer?
2. Explain WHO guidelines for Technology Transfer (TT).
3.Explain following terminology
    1.Change control (C/C).
    2.Corrective action (C/A)
    3.Design qualification (DQ)
    4.Drug master file (DMF

SUBJECT II

BP703T PHARMACY PRACTICE

SCHEME

BP703T Pharmacy Practice-Theory

SCHEME FOR TEACHING

Course of study for semester VII

Course Code	Course Name	No. of Hours per week			Credit Points
		Theory	Practical	Tutorial	
BP703T	Pharmacy Practice	03	0	01	04

SCHEME FOR INTERNAL AND END SEMESTER EXAMINATIONS

Course code	Name of the course	Internal Assessment				End Semester Exams		Total Marks
		Continuous Assessment	Sessional Exams		Total	Marks	Duration	
			Marks	Duration				
BP703T	Pharmacy Practice	10	15	01 hrs	25	75	03 hrs	100

SYLLABUS

BP703T Pharmacy Practice-Theory

Course Content

Scope: In the changing scenario of pharmacy practice in India, for successful practice of Hospital Pharmacy, the students are required to learn various skills like drug distribution, drug information, and therapeutic drug monitoring for improved patient care. In community pharmacy, students will be learning various skills such as dispensing of drugs, responding to minor ailments by providing suitable safe medication, patient counselling for improved patient care in the community set up.

Unit I: **10 Hours**

a) Hospital and it's organization

Definition, Classification of hospital- Primary, Secondary and Tertiary hospitals, Classification based on clinical and non- clinical basis, Organization Structure of a Hospital, and Medical staffs involved in the hospital and their functions.

b) Hospital pharmacy and its organization

Definition, functions of hospital pharmacy, Organization structure, Location, Layout and staff requirements, and Responsibilities and functions of hospital pharmacists.

c) Adverse drug reaction

Classifications - Excessive pharmacological effects, secondary pharmacological effects, idiosyncrasy, allergic drug reactions, genetically determined toxicity, toxicity following sudden withdrawal of drugs, Drug interaction- beneficial interactions,

adverse interactions, and pharmacokinetic drug interactions, Methods for detecting drug interactions, spontaneous case reports and record linkage studies, and Adverse drug reaction reporting and management.

d) Community Pharmacy

Organization and structure of retail and wholesale drug store, types and design, Legal requirements for stablishment and maintenance of a drug store, Dispensing of proprietary products, maintenance of records of retail and wholesale drug store.

Unit II: **10 Hours**

a) Drug distribution system in a hospital

Dispensing of drugs to inpatients, types of drug distribution systems, charging policy and labelling, Dispensing of drugs to ambulatory patients, and Dispensing of controlled drugs.

b) Hospital formulary

Definition, contents of hospital formulary, Differentiation of hospital formulary and Drug list, preparation and revision, and addition and deletion of drug from hospital formulary.

c) Therapeutic drug monitoring

Need for Therapeutic Drug Monitoring, Factors to be considered during the Therapeutic DrugMonitoring, and Indian scenario for Therapeutic Drug Monitoring.

d) Medication adherence

Causes of medication non-adherence, pharmacist role in the medication adherence, and monitoring of patient medication adherence.

e) Patient medication history interview

Need for the patient medication history interview, medication interview forms.

f) Community pharmacy management

Financial, materials, staff, and infrastructure requirements.

Unit III: 10 Hours

a) Pharmacy and therapeutic committee

Organization, functions, Policies of the pharmacy and therapeutic committee inincluding drugs into formulary, inpatient and outpatient prescription, automatic stop order, and emergency drug list preparation.

b) Drug information services

Drug and Poison information centre, Sources of drug information, Computerised services, and storage and retrieval of information.

c) Patient counseling

Definition of patient counseling; steps involved in patient counseling, and Special cases that require the pharmacist

d) Education and training program in the hospital

Role of pharmacist in the education and training program, Internal and external training program, Services to the nursing homes/clinics, Code of ethics for community pharmacy, and Role of pharmacist in the interdepartmental communication and community health education.

e) Prescribed medication order and communication skills

Prescribed medication order- interpretation and legal requirements, and Communication skills- communication with prescribers and patients.

Unit IV **8 Hours**

a) Budget preparation and implementation

Budget preparation and implementation

b) Clinical Pharmacy

Introduction to Clinical Pharmacy, Concept of clinical pharmacy, functions and responsibilities of clinical pharmacist, Drug therapy monitoring - medication chart review, clinical review, pharmacist intervention, Ward round participation, Medication history and Pharmaceutical care. Dosing pattern and drug therapy based on Pharmacokinetic & disease pattern.

c) Over the counter (OTC) sales

Introduction and sale of over the counter, and Rational use of common over the counter medications.

Unit V **7 Hours**

a) Drug store management and inventory control

Organisation of drug store, types of materials stocked and storage conditions, Purchase and inventory control: principles, purchase procedure, purchase order, procurement and stocking, Economic order quantity, Reorder quantity level, and Methods used for the analysis of the drug expenditure

b) Investigational use of drugs

Description, principles involved, classification, control, identification, role of hospital pharmacist, advisory committee.

c) Interpretation of Clinical Laboratory Tests

Blood chemistry, hematology, and urinalysis

Recommended Books (Latest Editions):

1. Merchant S.H. and Dr. J.S.Quadry. *A textbook of hospital pharmacy*, 4th ed. Ahmadabad: B.S. Shah Prakakshan; 2001.
2. Parthasarathi G, Karin Nyfort-Hansen, Milap C Nahata. *A textbook of Clinical Pharmacy Practice- essential concepts and skills*, 1st ed. Chennai: Orient Longman Private Limited; 2004.
3. William E. Hassan. *Hospital pharmacy*, 5th ed. Philadelphia: Lea & Febiger; 1986.
4. Tipnis Bajaj. *Hospital Pharmacy*, 1st ed. Maharashtra: Career Publications; 2008.
5. Scott LT. *Basic skills in interpreting laboratory data*, 4thed. American Society of Health System Pharmacists Inc; 2009.
6. Parmar N.S. *Health Education and Community Pharmacy*, 18th ed. India: CBS Publishers & Distributers; 2008.

Journals:

1. Therapeutic drug monitoring. ISSN: 0163-4356
2. Journal of pharmacy practice. ISSN : 0974-8326
3. American journal of health system pharmacy. ISSN: 1535-2900 (online)
4. Pharmacy times (Monthly magazine)

LESSION PLAN

BP703T Pharmacy Practice-Theory

Name of the faculty: Ms. Sheetal B. Gosavi

Lect. No.	Topics / Sub- Topics	COs	BL Level	Reference (Text Book, Website)
0	Orientation to Syllabus			
1	**Hospital and it's organization** Definition, Classification of hospital- Primary, Secondary and Tertiary hospitals,	CO1	1,2	1,2,3
2	Classification based on clinical and non- clinical basis, Organization Structure of a Hospital, and Medical staffs involved in the hospital and their functions.	CO1	1,2	1,3,4
3	**Hospital pharmacy and its organization** Definition, functions of hospital pharmacy, Organization structure, Location, Layout and staff requirements,	CO1	1,2,3	1,2,3
1 T	TUTORIAL:1			
4	Responsibilities and functions of hospital pharmacists.	CO1	1,2,3	2,3
5	**Adverse drug reaction** Classifications - Excessive pharmacological effects, secondary pharmacological effects,	CO2	1,2,3	1,3,4
6	idiosyncrasy, allergic drug reactions, genetically determined toxicity, toxicity following sudden withdrawal of drugs,	CO2	1,2,3	1,2,3

2 T	TUTORIAL:2			
7	Drug interaction- beneficial interactions, adverse interactions, and pharmacokinetic drug interactions,	CO2	1,2,3	1,2,4
8	Methods for detecting drug interactions, spontaneous case reports and record linkage studies, and Adverse drug reaction reporting and management.	CO2	1,2,3	1,3,4
9	**Community Pharmacy** Organization and structure of retail and wholesale drug store, types and design, Legal requirements for establishment and maintenance of a drug store,	CO1	1,2,3	1,2,3
3 T	TUTORIAL:3			
10	Dispensing of proprietary products, maintenance of records of retail and wholesale drug store.	CO2	1,2,3	1,2,4
11	**Hospital formulary** Definition, contents of hospital formulary, Differentiation of hospital formulary and Drug list, preparation	CO3	2,3	1,2,3
12	revision, and addition and deletion of drug from hospital formulary.	CO3	2,3	1,2,4
4 T	TUTORIAL:4			
13	**Therapeutic drug monitoring** Need for Therapeutic Drug Monitoring,	CO3		1,2,3
14	Factors to be considered during the Therapeutic Drug Monitoring, and Indian scenario for Therapeutic	CO3	2,3	1,2,4,5

	Drug Monitoring.			
15	**Medication adherence** Causes of medication non-adherence	CO3	2,3	1,2,3
5 T	TUTORIAL:5			
16	Pharmacist role in the medication adherence, and monitoring of patient medication adherence.	CO3	2,3	1,2,4
17	**Introduction to Patient medication history interview**	CO3	1,2	1,2,3
18	Need for the patient medication history interview, medication interview forms.	CO3	1,2	2,3,4
6 T	TUTORIAL:6			
19	Introduction to **Community pharmacy management**	CO1	1,2	1,2,3
20	Financial, materials, staff, and infrastructure requirements.	CO1	1,2	2,3,4
21	**Pharmacy and therapeutic committee** Organization, functions, Policies of the pharmacy and therapeutic committee in including drugs into formulary,	CO3	2,3	1,2,5
7 T	TUTORIAL:7			
22	inpatient and outpatient prescription, automatic stop order, and emergency drug list preparation.	CO3	2,3	1,2,3
23	**Drug information services** Drug and Poison information centre, Sources of drug information,	CO3	1,2	3,4,5
24	Computerised services, and storage	CO3	2,3	1,2,3

	and retrieval of information.			
8 T	TUTORIAL:8			
25	**Patient counseling** Definition of patient counseling; steps involved in patient counseling, and Special cases that require the pharmacist	CO3	1,2,3	1,2,3
26	**Education and training program in the hospital** Role of pharmacist in the education and training program, Internal and external training program,	CO3	1,2,3	4,5,6
27	Services to the nursing homes/clinics, Code of ethics for community pharmacy,	CO3	2,3	3,5
9 T	TUTORIAL:9			
28	Role of pharmacist in the interdepartmental communication and community health education.	CO3	2,3	2,3
29	**Prescribed medication order and communication skills** Prescribed medication order-interpretation and legal requirements,	CO3	2,3	2,3
30	Communication skills-communication with prescribers and patients.	CO3	2,3	2,3
10 T	TUTORIAL:10			
31	**Budget preparation and implementation** Budget preparation and implementation	CO3	2,3	1,2,3
32	**Introduction to Clinical Pharmacy**	CO3		3,4

33	Concept of clinical pharmacy, functions and responsibilities of clinical pharmacist,	CO3	2,3	3,4
11 T	TUTORIAL:11			
34	Drug therapy monitoring - medication chart review, clinical review,	CO3	1,2	5,6
35	pharmacist intervention, Ward round participation, Medication history and Pharmaceutical care.	CO3	2,3	1,2,3
36	Dosing pattern and drug therapy based on Pharmacokinetic & disease pattern.	CO3	2,3	2,3,5
12 T	TUTORIAL:12			
37	**Over the counter (OTC) sales- Introduction**	CO3	1,2	2,3,4
38	sale of over the counter, and Rational use of common over the counter medications.	CO3	2,3	1,2,4
39	**Drug store management and inventory control** Organisation of drug store, types of materials stocked and storage conditions,	CO4	2,3	2,3
13 T	TUTORIAL:13			
40	Purchase and inventory control:	CO4	1,2	1,2,3
41	principles, purchase procedure, purchase order, procurement and stocking, Economic order quantity,	CO4	2,3	2,3,4
42	Reorder quantity level, and Methods used for the analysis of the drug expenditure	CO4	2,3	3,4,5

14 T	TUTORIAL:14			
43	**Investigational use of drugs** Description, principles involved, classification,	CO4	1,2	1,2,3
44	control, identification, role of hospital pharmacist, advisory committee.	CO4	2,3	1,2,3
45	**Interpretation of Clinical Laboratory Tests** Blood chemistry, hematology, and urinalysis	CO4	2,3	2,3,4
15 T	TUTORIAL:15			

Note: 1.Home Assignment will be given after completion of each unit.

2. Class Test I & II will be conduct as per the schedule of Academic Calendar.

COURSE DELIVERY, OBJECTIVES, OUTCOMES

BP703T Pharmacy Practice-Theory

Course Delivery:

The course will be delivered through lectures, class room interaction, and presentations.

Course Objectives:

Upon the completion of the course student shall be able to

5. Understand the mechanism of drug action and its relevance in the treatment of different infectious diseases
6. Comprehend the principles of toxicology and treatment of various poisonings and appreciate correlation of pharmacology with related medical sciences.

Course Outcomes (COs):

After successful completion of course student will able to

Upon the completion students are able to **CO-PO**

CO1	Get in-depth knowledge [**L2: Understanding]** about various hospitals and its organizations, its functioning, functions **[L3:Applying]** of hospital pharmacist, setting up of community pharmacy
CO2	Understand [**L2: Understanding]** adverse drug reactions, drug-drug interactions, mechanism involved and its predisposing factors.
CO3	Know [**L2: Understanding]** functioning **[L3: Applying]** and role of hospital pharmacy and practice of rational drug therapy with regards to pharmacy therapeutic committee, hospital formulary and therapeutic drug monitoring.
CO4	Know [**L2: Understanding]** Drug store management and inventory control and interpret **[L3: Applying]** clinical laboratory tests of specific disease state.

Mapping of Course Outcome (CO) with Program Outcome (PO) and Program Specific Outcome (PSO)

1: Slight (Low) 2: Moderate (Medium) 3: Substantial (High)

If there is no correlation, put "-"

CO	PO1	PO2	PO3	PO4	PO5	PO6	PO7	PO8	PO9	PO10	PO11	PSO1	PSO2	PSO3	PSO4
CO1	3	3	2	-	2	3	3	2	3	-	3	3	2	-	-
CO2	3	3	2	-	2	3	3	2	3	-	3	3	2	-	-
CO3	3	3	2	-	2	3	3	2	3	-	3	3	2	-	-
CO4	3	3	2	-	2	3	3	2	3	-	3	3	2	-	-

Justification of CO-PO Mapping

CO1 with PO1	CO1 is aligned with PO1 because it demonstrates the basic knowledge about various hospitals and its organizations, its functioning, functions of hospital pharmacist, setting up of community pharmacy
CO1 with PO2	CO1 is aligned with PO2 because it develops an ability to develop and implement basic knowledge about various hospitals and its organizations, its functioning, functions of hospital pharmacist, setting up of community pharmacy
CO1 with PO3	CO1 is aligned with PO3 because it effectively identifies various hospitals and its organizations, its functioning, functions of hospital pharmacist, setting up of community pharmacy
CO1 with PO5	CO1 is aligned with PO5 as it help to develop leadership skills and its implementation of hospitals and its organizations, its functioning, functions of hospital pharmacist, setting up of community pharmacy
CO1 with PO6	CO1 is aligned with PO6 because it deals with an ability to recognize about hospitals and its organizations, its functioning, functions of hospital pharmacist, setting up of community pharmacy
CO1 with PO7	CO1 is aligned with PO7 as it uses professional ethics in hospitals and its organizations, its functioning, functions of hospital pharmacist, setting up of community pharmacy
CO1 with PO8	CO1 is aligned with PO8 because it helps them to report and write any problem in the organization of hospital and communicate the same for well being of society.
CO1 with PO9	CO1 is aligned with PO9 because it helps to overcome the societal, health and legal problems by providing better knowledge of hospital organization and its functioning.
CO1 with PO11	CO1 is aligned with PO11 it helps them to get the basic knowledge and use the same for advancement to know different interaction of drugs so as to engage them in life long learning.
CO2 with PO1	CO2 is aligned with PO1 because it demonstrates the basic knowledge about adverse drug reactions, drug-drug interactions, mechanism involved and its predisposing factors.

CO2 with PO2	CO2 is aligned with PO2 because it develops an ability to develop and implement basic knowledge about adverse drug reactions, drug-drug interactions, mechanism involved and its predisposing factors.
CO2 with PO3	CO2 is aligned with PO3 because it effectively identifies various adverse drug reactions, drug-drug interactions, mechanism involved and its predisposing factors.
CO2 with PO5	CO2 is aligned with PO5 as it help to develop leadership skills and its implementation of adverse drug reactions, drug-drug interactions, mechanism involved and its predisposing factors.
CO2 with PO6	CO2 is aligned with PO6 because it deals with an ability to recognize adverse drug reactions, drug-drug interactions, mechanism involved and its predisposing factors.
CO with PO7	CO2 is aligned with PO7 as it uses professional ethics in adverse drug reactions, drug-drug interactions, mechanism involved and its predisposing factors.
CO2 with PO8	CO2 is aligned with PO8 because it helps them to report and write any interaction and communicate the same for well being of society.
CO2 with PO9	CO2 is aligned with PO9 because it helps to overcome the societal, health and legal problems by providing better knowledge of drug drug interaction.
CO2 with PO11	CO2 is aligned with PO11 it helps them to get the basic knowledge and use the same for advancement to know different interaction of drugs so as to engage them in life long learning.
CO3 with PO1	CO3 is aligned with PO1 because it demonstrates the basic knowledge about role of hospital pharmacy and practice of rational drug therapy with regards to pharmacy therapeutic committee, hospital formulary and therapeutic drug monitoring.
CO3 with PO2	CO3 is aligned with PO2 because it develops an ability to develop and implement basic knowledge about role of hospital pharmacy and practice of rational drug therapy with regards to pharmacy therapeutic committee, hospital formulary and therapeutic drug monitoring.
CO3 with PO3	CO3 is aligned with PO3 because it effectively identifies various role of hospital pharmacy and practice of rational drug therapy with regards to pharmacy therapeutic committee, hospital formulary and therapeutic drug monitoring.
CO3 with PO5	CO3 is aligned with PO5 as it help to develop leadership skills and its implementation of role of hospital pharmacy and practice of rational drug therapy with regards to pharmacy therapeutic committee, hospital formulary and therapeutic drug monitoring.
CO3 with PO6	CO3 is aligned with PO6 because it deals with an ability to role of hospital pharmacy and practice of rational drug therapy with regards to pharmacy therapeutic committee, hospital formulary and therapeutic drug monitoring.
CO3 with PO7	CO3 is aligned with PO7 as it uses professional ethics in role of hospital pharmacy and practice of rational drug therapy with regards to pharmacy therapeutic committee, hospital formulary and therapeutic drug monitoring.
CO3 with	CO3 is aligned with PO8 because it helps them to report and write role

PO8	of hospital pharmacy and practice of rational drug therapy with regards to pharmacy therapeutic committee, hospital formulary and therapeutic drug monitoring. interaction and communicate the same for well being of society.
CO3 with PO9	CO3 is aligned with PO9 because it helps to overcome the societal, health and legal problems by providing better knowledge of role of hospital pharmacy and practice of rational drug therapy with regards to pharmacy therapeutic committee, hospital formulary and therapeutic drug monitoring..
CO3 with PO11	CO3 is aligned with PO11 it helps them to get the basic knowledge and use the same for advancement to know role of hospital pharmacy and practice of rational drug therapy with regards to pharmacy therapeutic committee, hospital formulary and therapeutic drug monitoring.so as to engage them in life long learning.
CO4 with PO1	CO4 is aligned with PO1 because it demonstrates the basic knowledge about drug store management and inventory control and interpret clinical laboratory tests of specific disease state.
CO4 with PO2	CO4 is aligned with PO2 because it develops an ability to develop and implement basic knowledge drug store management and inventory control and interpret clinical laboratory tests of specific disease state.
CO4 with PO3	CO4 is aligned with PO3 because it effectively identifies drug store management and inventory control and interpret clinical laboratory tests of specific disease state.
CO4 with PO5	CO4 is aligned with PO5 as it help to develop leadership skills and its implementation of drug store management and inventory control and interpret clinical laboratory tests of specific disease state.
CO4 with PO6	CO4 is aligned with PO6 because it deals with an ability of drug store management and inventory control and interpret clinical laboratory tests of specific disease state.
CO4 with PO7	CO4 is aligned with PO7 as it uses professional ethics in role of drug store management and inventory control and interprets clinical laboratory tests of specific disease state.
CO4 with PO8	CO4 is aligned with PO8 because it helps them to report and write drug store management and inventory control and interpret clinical laboratory tests of specific disease state and communicate the same for well being of society.
CO4 with PO9	CO4 is aligned with PO9 because it helps to overcome the societal, health and legal problems by providing better knowledge of drug store management and inventory control and interpret clinical laboratory tests of specific disease state.
CO4 with PO11	CO4 is aligned with PO11 it helps them to get the basic knowledge and use the same for advancement to know drug store management and inventory control and interpret clinical laboratory tests of specific disease state so as to engage them in life long learning.
CO1 with PSO1	CO1 is aligned with PSO1 because it deals with the technical knowledge of subject essential for health care system.
CO1 with	CO1 is aligned with PSO2 because it helps to learn, select and apply the

PSO2	knowledge of hospitals and its organizations, its functioning, functions of hospital pharmacist, setting up of community pharmacy
CO2 with PSO1	CO2 is aligned with PSO1 because it deals with the technical knowledge of subject essential for health care system.
CO2 with PSO2	CO2 is aligned with PSO2 because it helps to learn, select and apply the knowledge of about adverse drug reactions, drug-drug interactions, mechanism involved and its predisposing factors.
CO3 with PSO1	CO3 is aligned with PSO1 because it deals with the technical knowledge of subject essential for health care system.
CO3 with PSO2	CO3 is aligned with PSO2 because it helps to learn, select and apply the knowledge of role of hospital pharmacy and practice of rational drug therapy with regards to pharmacy therapeutic committee, hospital formulary and therapeutic drug monitoring.
CO4with PSO1	CO4 is aligned with PSO1 because it deals with the technical knowledge of subject essential for health care system.
CO4 with PSO2	CO4 is aligned with PSO2 because it helps to learn, select and apply the knowledge of drug store management and inventory control and interpret clinical laboratory tests of specific disease state.

QUESTION BANK

BP703T Pharmacy Practice-Theory

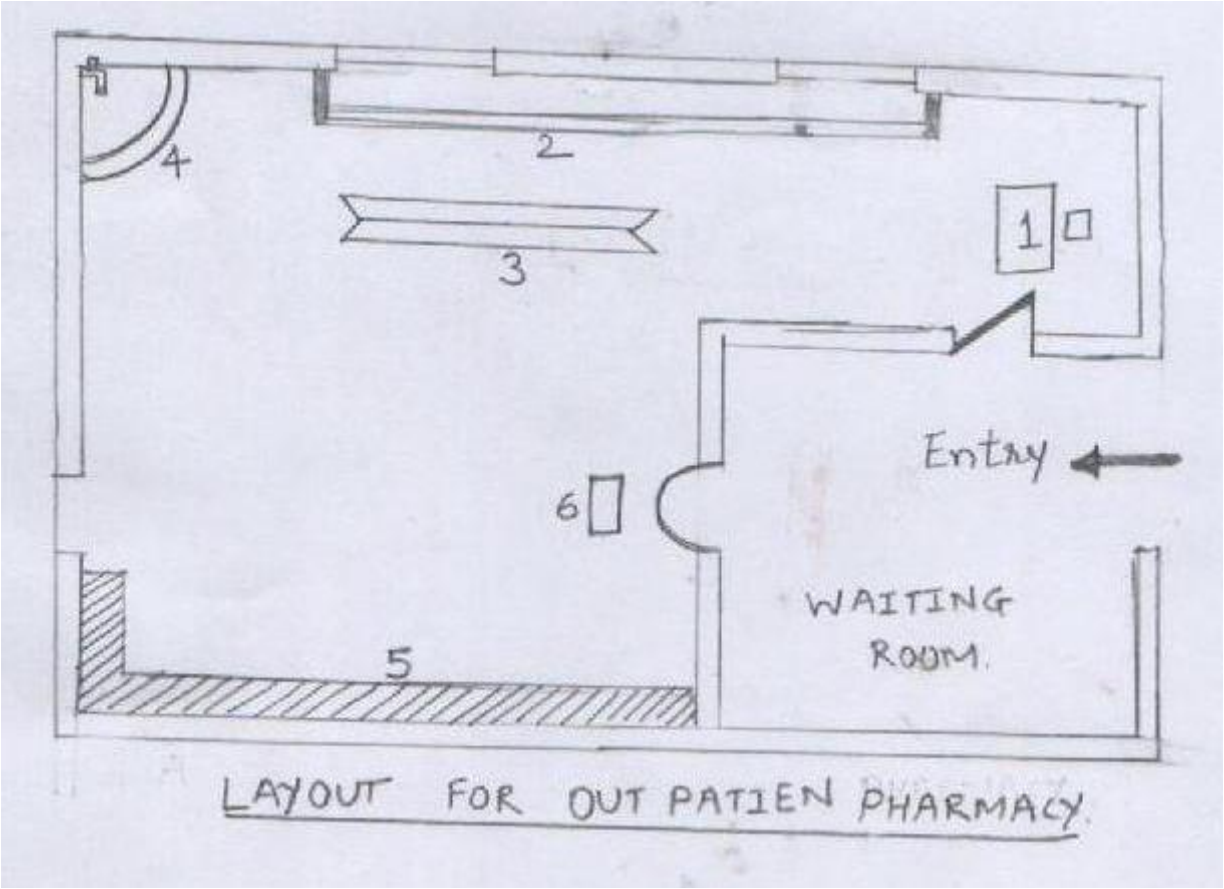
SR. NO.	QUESTIONS	CO ATTAINED
1	Draw a layout of outpatient pharmacy.	CO1
2	Define Adverse Drug Reaction. Classify ADR with examples.	CO2
3	Give any six functions of hospital.	CO1
4	Enlist different abilities a hospital pharmacist should possess & explain any one ability.	CO1
5	Discuss the role of PTC in drug safety.	CO3
6	Explain the role of pharmacist in Patient counselling.	CO3
7	Explain how purchase order is prepared.	CO1
8	Define clinical pharmacy. Give different roles of clinical pharmacist.	CO1
9	Write three administrative patterns of Central Sterile Services Department.	CO1
10	Comment on various sources of Drug information.	CO3
11	Enlist methods of Drug distribution in hospital. Give advantages & disadvantages of floor stock system.	CO1
12	Explain food-drug interactions with examples.	CO2
13	Define patient compliance. Discuss factors that influence patient compliance.	CO3
14	Explain role of computers in purchase and inventory control in hospitals.	CO4
15	Explain factors influencing make or buy decision in hospitals. What are the different methods of estimation of demand ?	CO4
16	Define Hospital formulary. Write about the guiding principles while using a hospital formulary.	CO3
17	What are the objectives of hospital pharmacy ?	CO1
18	Give the functions of PTC.	CO3
19	Discuss drug-food interactions.	CO2
20	Define clinical pharmacy. What is the scope of clinical pharmacy ?	CO1
21	Enlist the different softwares used in Hospital pharmacy. Explain the use of computer in Inventory control.	CO4
22	What are the objectives and functions (any three of each) of Hospital pharmacy ?	CO1
23	Define outpatient. Explain the Receipt and Issue system to	CO1

	outpatient.	
24	What is (ADR) – Adverse Drug Reaction ? Give the classification of ADR. Give the reasons for Adverse Drug Reaction.	**CO2**
25	Describe procurement or purchase procedure step-by-step	**CO4**
26	Write guiding principle while using hospital formulary.	**CO3**
27	Explain how purchase order is prepared and distributed.	**CO4**
28	Explain the role of PTC in drug safety.	**CO3**
29	What is patient compliance ? Discuss the factors contributing to non-compliance	**CO3**
30	Explain the abilities required for a hospital pharmacist.	**CO1**
31	Define Hospital. Classify it on the basis of clinical parameter.	**CO1**
32	What is hospital formulary ? Discuss the contents of hospital formulary.	**CO3**
33	Give requirements and list the technical abilities of Hospital Pharmacist.	**CO1**
34	Give objectives of inventory control. Explain procedure for purchasing.	**CO4**
35	Write A Note On TDM.	**CO3**
36	Explain The Role Of Pharmacist In Medication Adherance.	**CO3**
37	Classify drug interaction. Explain in brief drug interaction during absorption and distribution with suitable examples.	**CO2**
38	Explain the role of hospital pharmacist in practice of rational drug therapy.	**CO3**

MODEL ANSWERS

BP703T Pharmacy Practice-Theory

Q.1. Draw a layout of outpatient pharmacy.



1. Table and chair 2.Preparation table 3.Storage rack
4. Sink with tap 5. Medicine platform 6.Dispensing window

Q.2). Classify drug interaction. Explain in brief drug interaction during absorption and distribution with suitable examples.

Types of drug Interactions

1.Drug-drug interactions.
2.Drug-food interactions.
3.Chemical-drug interactions.
4.Drug-laboratory test interactions.
5.Drug-disease interactions.

Pharmacokinetic interactions

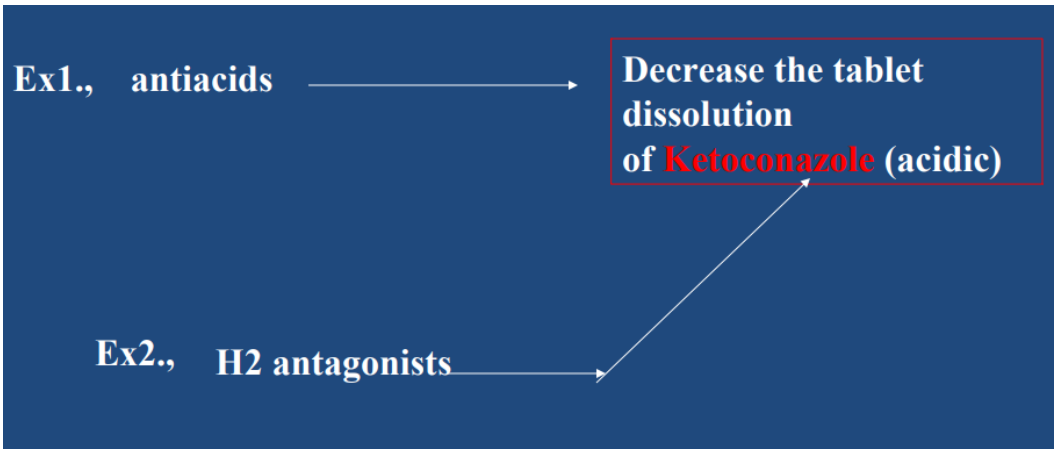
Absorption Interactions:

1) **Altered GIT absorption.**
   - •Altered pH
   - •Altered bacterial flora
   - • formation of drug chelates or complexes

• drug induced mucosal damage
• altered GIT motility.

a) Altered pH;

The non-ionized form of a drug is more lipid soluble and more readily absorbed from GIT than the ionized form does.



Therefore, these drugs must be separated by at least 2h in the time of administration of both .

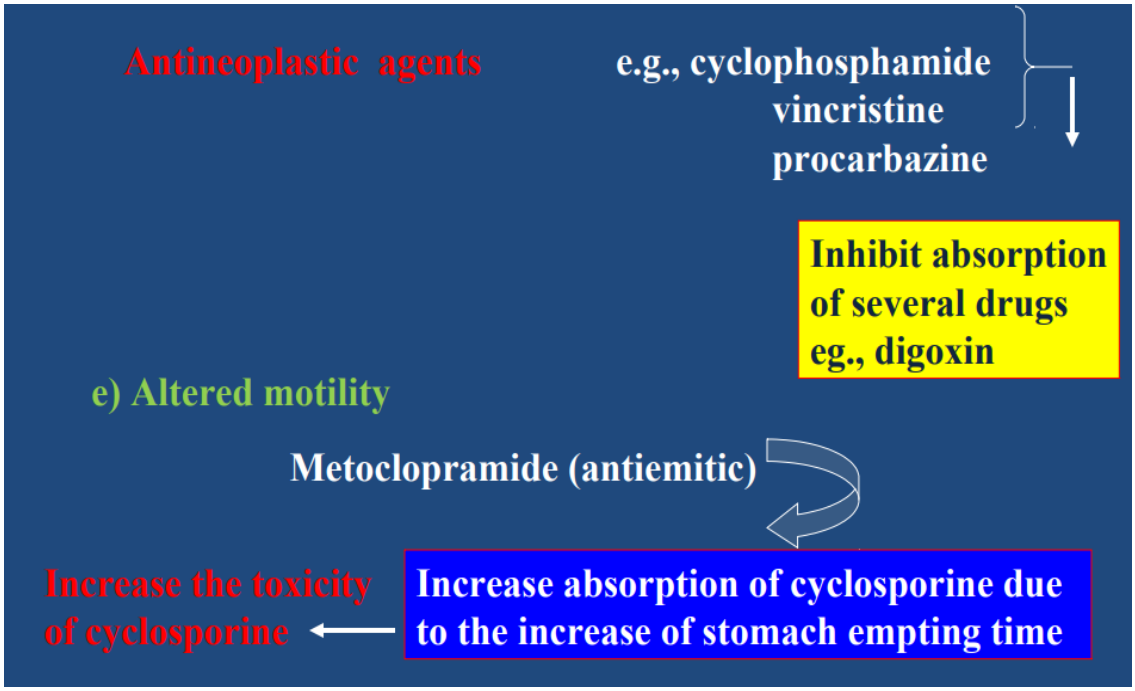
b) Altered intestinal bacterial flora ;

EX., 40% or more of the administered digoxin dose is metabolised by the intestinal flora.

c**) Complexation or chelation;**

EX1., Tetracycline interacts with iron preparations.

d) Drug-induced mucosal damage.



Distribution Interactions:

Displaced protein binding

It depends on the affinity of the drug to plasma protein. The most likely bound drugs is capable to displace others. The free drug is increased by displacement by another drug with higher affinity. Phenytoin is a highly bound to plasma protein (90%), Tolbutamide (96%), and warfarin (99%) Drugs that displace these agents are Aspirin Sulfonamides phenylbutazone

Q.3). Discuss drug food interaction with examples.

Tryamine rich food (cheese, liver, yeast product) and MAO inhibitors (Phenelzeline etc) leads Fatal risk of hypertensive crisis enhanced metabolism.

- Tetracycline or fluoroquinolones like ciprofloxacin with antacid or food containing divalent ions lead to formation of poorly soluble chelates or complexes which can not be absorbed.
- Grapefruit juice and Terfenadine
- Grapefruit juice and cyclosporin
- Grapefruit juice and felodipine
- Grapefruit contains : furanocoumarin compounds that can selectively inhibit CYP3A4.

Liquorice contain glycyrrhizin (glycyrrhizinic or glycyrrhizic acid)

- Glycyrrhizinic acid is hydrolyzed in the intestine to pharmacologically active compound glycyrrhetic acid which inhibit 11 betahydroxysteroid dehydrogenase.
- This increase cortisol in kidney and act as aldosterone (fluid retention, hypokalemia, hypertension)
- Ex: ▪ Liqourice and antihypertensive.

Q.4.) Explain in brief pharmacodynamic drug interaction with suitable examples.

It means alteration of the dug action without change in its serum concentration by pharmacokinetic factors.

They occur when the effects of a drug are changed due to presence of another drug at its site of action either directly (on the same receptor) or indirectly (on different receptor).

- Such interactions may be direct or indirect.
- 1.These are of two types
- 1.direct pharmacodynamics interactions.

2.Indirect pharmacodynamics interactions.

DIRECT INTERACTION

- Additive effect : 1 + 1 =2
- Synergistic effect : 1 +1 > 2
- Potentiation effect : 1 + 0 =2
- Antagonism : 1-1 = 0
- Antagonism:

The interacting drugs have opposing actions

Example: Acetylcholine and nor-adrenaline have opposing Effects on heart rate.

- Addition or summation:

The interacting drugs have similar actions and the resultant effect is the some of individual drug responses

Example: CNS depressants like sedatives and hypnotics,…etc

- Synergism or potentiating:

It is an enhancement of action of one drug by another

Example: Alcohol enhances the analgesics activity of aspirin.

INDIRECT INTERACTIONS

- In which both the object and the precipitant drugs have unrelated effects. but the latter in Some way alerts the effects but latter in some way alerts the effects of the former.
- Example: salicylates decrease the ability of the platelets to aggregate thus impairing the Homeostasis if warfarin induced bleeding occurs.

Q.5.) Write a note on drug-food interaction.

When a food affects medications in the body, this is called food-drug interaction. Food can prevent medicine from working the way it should and can cause medicinal side effects to become better or worse and/or cause new side effects to occur. Drugs can also change the way the body uses food. There are a variety of food and drug interactions that can occur, but here is a small list of common drugs and how food affects the way they are used in the body.

- Green, leafy vegetables, which are high in vitamin K, can decrease how well aspirin thins the blood. Consuming the same amount of green-leafy vegetables each day will decrease this interaction.
- Grapefruit juice alters the way the body absorbs statins (cholesterol-lowering drugs) like Lipitor in the blood. It can cause these drugs to be absorbed in higher than normal amounts resulting in a greater risk of side effects.
- Calcium channel blockers are prescribed for high blood pressure and are also affected by grapefruit juice. Grapefruit juice changes the way this drug breaks down in the body and may cause overly high levels of the drug in the blood, raising the risk of side effects.
- Dairy products such as milk, yogurt and cheese decrease the absorption of antibiotics. Try to eat meals one to two hours before taking these to avoid this interaction.
- Alcohol affects insulin or oral diabetic pills. Alcohol prolongs the effects of these drugs, which leads to low blood sugar.
- Moderate pain reliever drugs with acetaminophen should not be taken with alcohol because it has a higher chance of causing severe liver damage. Antihistamines, like Benadryl, should not be taken with alcohol because it will cause increased drowsiness.

This is only a small list of drugs that are affected by food, but it is important to be informed about common medications that are consumed.

Q.6) Give the reasons for increasing number of drug interactions.

- Poly pharmacy
- Multiple prescribers
- Multiple pharmacies
- Genetic make up
- Specific population like E.g., females, elderly, obese, malnourished, critically ill patient,

transplant recipient.

- Specific illness E.g. Hepatic disease, Renal dysfunction,
- Narrow therapeutic index drug: Cyclosporine, Digoxin, Insulin, Lithium , Antidepressant,

Warfarin etc.

Q.7). Discuss in detail different mechanism for drug interaction.

Mechanisms of drug interactions

1. Pharmacokinetics
2. Pharmacodynamics

Pharmacokinetics involve the effect of a drug on another drug kinetic that includes absorption ,distribution , metabolism and excretion. Pharmacodynamics are related to the pharmacological activity of the interacting drugs E.g., synergism , antagonism, altered cellular transport effect on the receptor site.

Pharmacokinetic interactions

2) Altered GIT absorption.

•Altered pH

•Altered bacterial flora

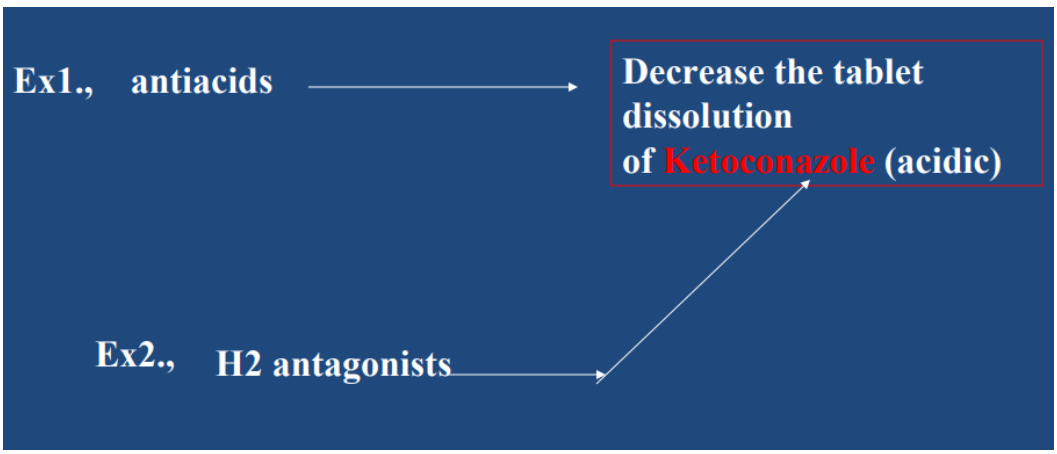
• formation of drug chelates or complexes

• drug induced mucosal damage

• altered GIT motility.

c) Altered pH;

The non-ionized form of a drug is more lipid soluble and more readily absorbed from GIT than the ionized form does.



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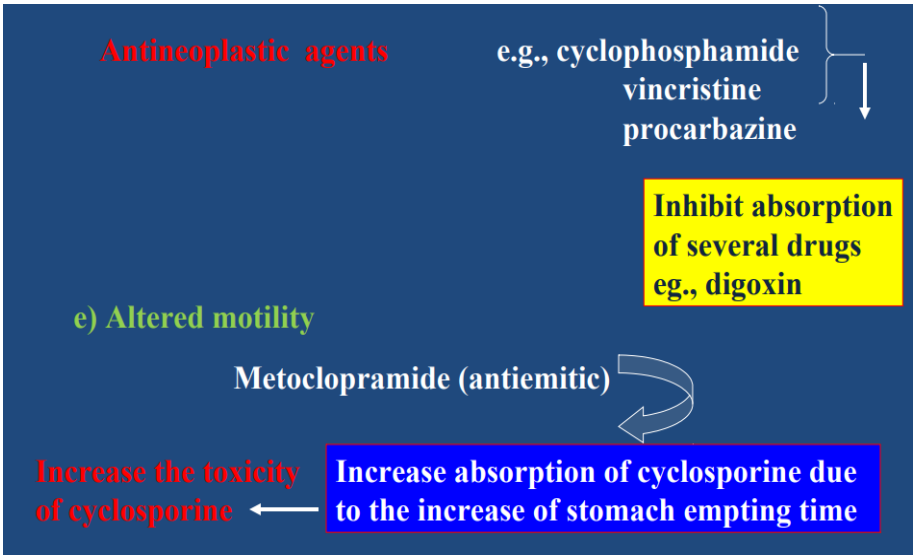

f) Displaced protein binding

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g) Altered metabolism

The effect of one drug on the metabolism of the other is well documented. The liver is the major site of drug metabolism but other organs can also do e.g., WBC,skin,lung, and GIT. CYP450 family is the major metabolizing enzyme in phase I (oxidation process). Therefore, the effect of drugs on the rate of metabolism of others can involve the following examples.

Eg., Enzyme inhibition; It is the decrease of the rate of metabolism of a drug byϖ another one . This will lead to the increase of the concentration of theϖ target drug and leading to the increase of its toxicity . Inhibition of the enzyme may be due to the competitionϖ on its binding sites , so the onset of action is short may be within 24h.

Onset of drug interaction

It may be seconds up to weeks for example in case of enzyme induction, it needs weeks for protein synthesis, while enzyme inhibition occurs rapidly. The onset of action of a drug may be affected by the half lives of the drugs e.g., cimitidine inhibits metabolism of theophylline. Cimitidine has a long half life, while, theophylline has a short one. When cimitidine is administered to a patient regimen for Theophylline, interaction takes place in one day.

First-pass metabolism:

Oral administration increases the chance for liver and GIT metabolism of drugs leading to the loss of a part of the drug dose decreasing its action. This is more clear when such drug is an enzyme inducer or inhibitor. EX., Rifampin lowers serum con. of verapamil level by increase its first pass . Also, Rifampin induces the hepatic metabolism of verapamil.

Renal excretion:

•Active tubular secretion It occurs in the proximal tubules.

♣ The drug combines with a specific protein to pass through the proximal tubules. When a drug has a competitive reactivity to the protein that is

♣ responsible for active transport of another drug .This will reduce such a drug excretion increasing its con. and hence its toxicity.

Pharmacodynemic interaction

It means alteration of the dug action without change in its serum concentration by pharmacokinetic factors.

EX., Propranolol + verapamil gives Synergistic or additive effect

Additive effect : 1 + 1 =2 Synergistic effect : 1 +1 > 2 Potentiation effect : 1 + 0 =2 Antagonism : 1-1 = 0

Pharmacodynamic interactions

• Receptor interaction – Competitive – Non-competitive
• Sensitivity of receptor – Number of receptor – Affinity of receptor
• Alter neurotransmitter release /drug transportation
• Alter water/electrolyte balance

Q.8). Give the predisposing factors leading to ADR.

- ADR to drugs are most common cause of iatrogenic disease.
- 3-5% hospitalisations due to adverse reactions results in 3,00,000 hospitalisations annually in US.
- Once hospitalised → 30% chance of ADR→ Risk of each course is 5%
- 3% chance of life threatning reactions →
- Risk of each course is 0.4 %

COMMON CAUSES OF ADRS

- Failing to take the correct dosages at the correct times.
- Overdosing.
- Allergies to chemical components of the medicine.

- Combining the medicine with alcohol.
- Taking other drugs or preparations that interact with the medicine.
- Taking a medicine that was prescribed for someone else.

FACTORS AFFECTING ADVERSE DRUG REACTIONS :

Patient-related factors

- Age
- Sex
- Genetic influences
- Concurrent diseases (renal ,liver , cardiac)
- Previous adverse drug reactions
- Compliance with dosing regimen
- Total number of medications
- Misc. (diet, smoking, environmental exposure)

AGE

Children are often at risk because their capacity to metabolize drugs is usually not fully developed. Children younger than 18 may be at risk of developing Reye's syndrome if given acetylsalicylic acid (aspirin) while infected with chickenpox or influenza.

ELDERLY

- ADRs, including drug interactions, are a common cause of admission to hospitals in the elderly
- Reasons for ADRs in the elderly:
  - Concomitant use of several medications
  - Decreased drug ADME activity due to age
  - These conditions are exacerbated by malnutrition and dehydration, common in the elderly

PREGNANCY

- Sulfonamides → Jaundice and brain damage in the fetus
- Warfarin → Birth defects, and increased risk of bleeding problems in newborns and mothers
- Lithium → Defects of the heart (Ebstein's Anomaly), lethargy, reduced muscle tone, and underactivity of the thyroid gland

BREAST FEEDING

→ Many drugs can be passed from mother to infant via breast milk

- Amantadine (antiviral)
- Cyclophosphamide (antineoplastic)
- Cocaine (Schedule 2 FDA drug)
- Carisoprodol (skeletal muscle relaxant)

FACTORS AFFECTING ADVERSE DRUG REACTIONS :

Drug-related factors

- Dose
- Duration
- Inherent toxicity of the agent
- Pharmacodynamic properties
- Pharmacokinetic properties

Q.9). Write a note on reporting of ADR.

STEPS INVOLVED IN ADR REPORTING

- Identifying adverse drug reaction (ADR).
- Assessing causality between drug and′ suspected reaction by using various algorithms.
- Documentation of ADR in patient's medical′ records.
- Reporting serious ADRs to′ pharmacovigilance centers /ADR regulating authorities

PREMARKETING STUDIES

- During the development of new medicines, their safety is tested in animal models.
- Specific animal studies for carcinogenicity,′ teratogenicity and mutagenicity are also available
- Clinical trials are carried out in 3 different′ phases prior to the submission of a marketing authorization application
- Clinical trials normally identifies ADRs of′ frequency greater that .5-1.0%

POST MARKETING SURVELLIANCE

- Pharmavigilance methodologies are used for detection of risk and for the collection of risk information
- Powerful and cost effective system for the′ identification of unknown drug-related risk is spontaneous adverse drug reactions reporting
- Health care practitioner should see it as a part of′ professional duty report ADR result in a patient under his care
- Concerned identifying product defect, intoxicants and′ abuse and unexpected lack of therapeutic effect

- **12. Define ADR, Overdose and efficacy.**
- **ADR: Adverse Drug Reaction**
- A response to a medicinal product which is noxious and unintended. Response in this context means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility. Adverse reactions may arise from use of the product within or outside the terms of the marketing authorisation or from occupational exposure. Conditions of use outside the marketing authorisation include off- label use, overdose, misuse, abuse, and medication errors.
- **Overdose:**
- Administration of a quantity of a medicinal product given per administration or cumulatively which is above the maximum recommended dose according to the authorised product information. Clinical judgement should always be applied.
- **Efficacy:**
- The ability of a drug to produce the intended effect as determined by scientific methods, for example in pre-clinical and in clinical research conditions.

Q.10). Write the composition, objectives and process of pharmacy and therapeutic committee in hospital pharmacy.

Definition

The pharmacy and therapeutics committee(PTC) is an advisory group of the

- medical staff and serves as the organizational line of communication between the medical staff and the pharmacy department. The committee is composed of physicians, the pharmacist and the other
- health professionals selected with guidance of the medical staff. This committee assists in the formulation of broad professional policies
- regarding the evaluation, selection, procurement, distribution, use, safety procedures and other matters relating to drugs use in the hospital.

Composition of PTC:

- At least three physicians
- A pharmacist
- A representative of the nursing staff
- A hospital administrator or his/her designated person and ex-officio member of the committee
- The physician may be appointed as the " Chairman " of P.T.C.
- The pharmacist is designated as the " Secretary " of the committee.

Responsibility

- Ensure safety medication to patients
- The preparations of a hospital formulary,
- Publishing of a pharmacy educational bulletin,
- The establishment of automatic stop orders for dangerous drugs,

- The supervision of investigational use drugs,
- The development of a program for reporting and investigating adverse drug
- reactions and Assisting in the preparation of emergency kits or carts for medical emergencies.

Objectives of PTC:

Advisory:

- The committee recommends the adoption of (or) assists in the formulation of the broad profession policies regarding evaluation, selection and therapeutic use of drugs in the hospital.
- The committee serves in an advisory capacity to medical staff and hospital administration in all matters pertaining to the use of drugs including the investigational drugs.

Objectives of PTC:

1. **Educational:**

- The committee recommends or assists in the formulation of functions, designed to meet the needs of the professional staff, the physicians, nurses, pharmacists and other health care practitioners, for the complete current knowledge of the matters related to drugs and their uses.
- The committee studies the problems related to the distribution and administration of medication.
- It establishes or plans suitable educational scheme for the hospital professional staff on the matters related to the use of drugs.

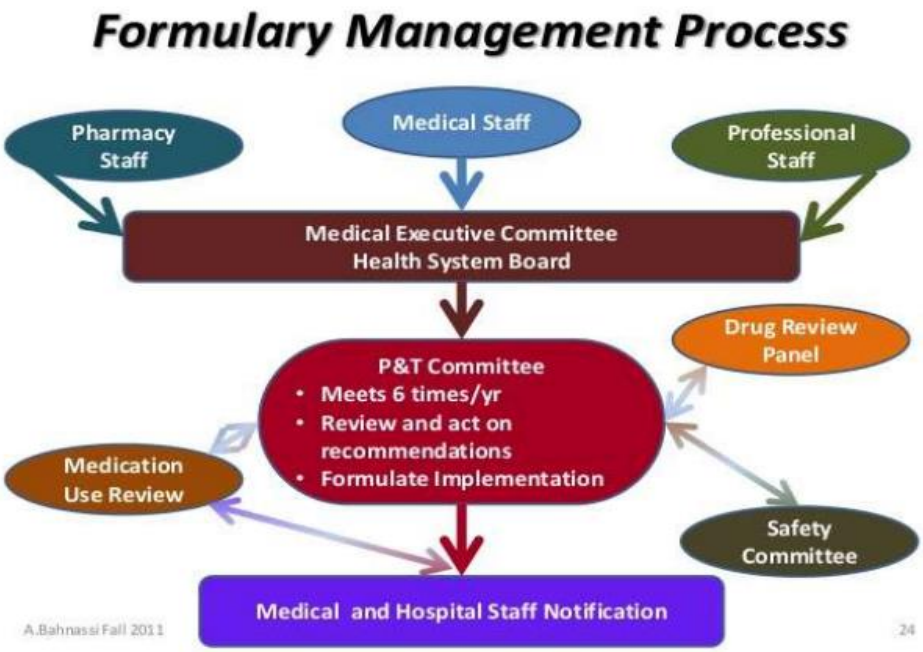
2. **Drug Safety and Adverse Drug Monitoring:**

- The safety aspects are more or less taken for granted by pharmacy, medical and nursing staff.
- As the therapeutic agents are increasing, the scope, knowledge and responsibility of the hospital pharmacist is also increasing.

Organization and Operation

- Operation PTC should meet regularly at least six times in an year and also as and when necessary.
- The committee can invite its meetings and persons within or outside the hospital who can contribute specialized or unique knowledge and skilled judgment.
- The agenda and the supplementary materials should be prepared by the secretary and furnished to the committee members sufficiently in time before the meeting.
- The pharmacy and therapeutics committee should be composed of at least three physicians, a pharmacist, a nurse and an administrator.

Management process of PTC:



Committee membership

According to the approved statement by the American Hospital Association and the American Society of Hospital Pharmacists provides for a membership of not less than three physicians and the pharmacist, the majority of the large hospitals list committees which often include representatives of the following groups:

- Surgery
- Medicine
- Pharmacist
- Administrator
- Nurse

Committee Agenda

- Minutes of the previous meeting.
- Review of a specified of the Formulary for up-dating and deletion of products.
- New drugs which have become commercially available.
- Investigational use of drugs currently in use in the hospital.
- Review of adverse drug reactions reported in the hospital since the last meeting.
- Drug safety in the hospital.
- Slow moving medication.

Role of PTC in drug safety:

- Drug safety is the moral, legal and professional obligation of pharmacist .
- It includes responsibility from dispensing of drugs to drug administration .
- Following guidelines may sub serve the committee in ascertaining the adequate safety factor of hospital pharmacy.
- The hospital must employ a qualified, at least, a registered pharmacist with at least B. Pharm degree as ‘Chief pharmacist’ and the rest are may be at least diploma holders in pharmacist.

Committee’s role in the adverse drug reaction program

- A consequence of recent advances in drug therapy is the proportionate increase in drug reactions. Reaction caused by blood and plasma products need to be reported unless a chemical agent other than the basic substance is responsible.
- An adverse Drug Reaction(ADR) Report From, should be prepared by the PTC and made available on every nursing station.
- Every case of adverse drug reaction must be reported by the attending doctor to the clinical pharmacologist, if one is available, otherwise to the chairman of PTC.
- The completed ADR from of any having adverse drug reaction, will remove from the medical record and forward to the chairman or clinical pharmacologist, after discharge of the patient.

Functions of PTC

- Preparation of hospital drug formulary.
- Selection of manufacturer and supplier, mode of procurement.
- Addition of new drugs, deletion of old drugs.
- Drugs to be supplied in OPD.
- Policy formulation for pharmacy and monitoring
- Budget demand for pharmacy
- Developing Drug Information System
- Checking of pharmacy records and drug quality
- Maintenance of drug standard and quality control
- Disposal of Expiry Drugs

Q.11). Write a note on hospital formulary.

Definition:

- Hospital Formulary is a continually revised compilation of pharmaceuticals including important ancillary information that reflects the current clinical judgement of the medical staff.
- Formulary system is method whereby the medical staff of an institution, working through the PTC, evaluates, appraises, and selects from among the numerous available drug entities & drug products those that considered most useful in patient care.

The need for Hospital Formulary:

- The increasing no. of new drugs manufactured and marketed by drug companies
- Increasing complexity of untoward effects of modern potent drugs
- Newer sales promotion strategies of pharmaceutical industry.
- The public interest in getting possible health care at lowest possible cost.

Guidelines

- A multidisciplinary PTC is appointed for organization of various hospital day to day activities.
- The formulary system shall be sponsored by the medical staff based upon the recommendations of the PTC.
- The medical staff should adopt the principles of the system to the needs of the particular institution.

- The PTC shall adopt written policies & procedures governing the formulary system.
- Non proprietary names should be included in the formulary
- Limiting the number of drug entities and drug products routinely available from the pharmacy can produce substantial patient care and financial benefits.
- The formulary system is informed to the entire medical and nursing staff.
- The pharmacist shall be responsible for the specification as to the quality, & source of supply of all drugs, chemicals, biological & pharmaceutical preparation**s.**

Pre requisites in developing a hospital formulary

- Establish a formulary committee
- Establish and secure agreement on content ,structure and format of the formulary
- Appointing an editor
- Reviewing the draft
- Revise and produce new editions

Preparation of Hospital Formulary

Introductory information

1. Acknowledgement
2. List of abbreviations
3. Intended usage of the formulary manual

2. Basic information of the drug

- Generic name, dosage form, strength
- Indications
- Pharmacological action
- Precautions
- Side effects
- Dosage – form, frequency
- Instructions
- Drug interactions

Supplementary information on each drug

- Price
- Regulatory category
- Storage guidelines
- Patient counselling information
- Brand names

Prescribing and dispensing guidelines

- Principles of prescription writing
- Name and address of the patient
- Prescribed drug should be written in formulary terminology
- Strength of prescribed medication must be given in accepted metric system.
- Correct dispensing guidelines
- Prevention and reporting of ADRs

General drug use advice

- Use of IV additives

- Prescribing in special situations
- Poisoning and antidotes

Other components

- Formulas for various diagnostic stains, diagnostic aids
- Table of common Lab-values
- Posological tables
- Index of the drugs included in the formulary
- Metric units
- Indexes(by generic name, brand name, therapeutic category)

The Format

- Pharmacist decides the format before commencing work on printing and publishing in the hospital.
- He has to collect formularies of some leading hospitals as well as their format.
- Copies of finally published formulary may be sent to bodies like directorate general of health services, Govt of India, PCI etc.

Size

- It is sufficiently small in size so that it could be easily carried by clinicians, nurses etc, in the pockets of their uniform or lab coats.
- The hospitals may determine their own size of the formulary.

Type of format

- Loose leaf or Bound
- Printed or Mimeographed
- Indexing and Assigning categories

Types of formularies

- Open formularies
- Closed formularies

Q.12). Define patient counseling. Explain different stages of patient counseling.

It is a very common knowledge that failure to take medicines, adversely affects the outcome of treatment, and places a huge burden of wasted resources on the society. Three seemingly related terms; compliance, adherence and concordance have been used to describe medicationtaking behaviour in chronic illnesses. This evolution in the terminology is not merely a change in definitions but it tends to be a constructive development embraces the idea of a partnership between the patient and providers which is needed to address the patient's needs better.

Compliance is defined as "the extent to which the patient's behaviour matches the prescriber's recommendations" 1. However, studies over the past few decades have questioned the validity of this term because it refers to a process where the clinician decides on a suitable treatment and the patient is expected to comply with unquestioningly, without given any consideration to the patients' perspectives in taking their medications.

As a result the term adherence has been introduced as a replacement for compliance in an effort to place the clinician-patient relationship in its proper perspective; hence adherence refers to a process, in which the appropriate treatment is decided after a proper

counselling with the patient. The term compliance also implies that the patient is under no compulsion to accept a particular treatment, and is not to be held solely responsible for the occurrence of nonadherence. Accordingly, adherence has been defined as "the extent to which a person's behaviour, in taking medication, following a diet, and/or executing lifestyle changes, corresponds with agreed recommendations from a health care provider"

Lately the concept of concordance has evolved from a narrower view, emphasizing an agreement between the clinician and the patient, which takes into account each other's perspective on medication taking, to a broader process consisting of open discussions with the patient regarding medication-taking, imparting information and supporting patients on long-term medication. It is a process, which entertains patients' views on medication taking, and acknowledges that patients' views have to be respected even if they make choices, which appear to be in conflict with the clinician's views.

Pharmacists encounter similar patients in their daily practice, and many may struggle to find effective strategies to address non-adherence. Pharmacists are in a unique position to address non-adherence. Their drug expertise, along with their accessibility, makes them ideal candidates to address this significant problem. Peer-reviewed short stories similar to the three cases presented in this issue of SJRUM may address the misperceptions underlying nonadherence.

Although none of these terms are ideal solution to understand the complex process of medication-taking behaviour of patients, the move from compliance to adherence and concordance represents genuine progress in this field, which puts the patient's perceptions at the centre of the whole process. A number of strategies have been suggested to improve adherence including: the simplification of regimen by adjusting timing, frequency and dosage to match patients' activities; imparting knowledge by discussion with physician, nurse and pharmacists modifying patient's beliefs, involving patients in decisions tailoring the education to patients' level of understanding and evaluating adherence by self-reporting, bill counting 4 . Perhaps, the best therapeutic outcomes can be realized, at least in part, by tailoring the treatment to the patient's lifestyle, not the other way around.

Adherence vs compliance

• Compliance suggests a process in which dutiful patients passively follow the advice of their physicians. • Adherence suggests how most of the patients actively participate in their care and decide themselves when and whether to follow their doctor's advice.

Patient non-adherence to medications can be attributed to 4 key reasons :

• Language barrier
• Low education level
• Poor doctor – patient interaction
• System related obstacles

Degree of non-compliance is expressed as a percentage of the deal compliance

• % compliance = (NDP-NME)*100/NDP
– NDP = number of doses prescribed
– NME = number of medication errors
– Any arbitrary value less than 90% indicates suboptimal use of medication

Conditions necessary for adherence : The patient must –

• Understand and believe the diagnosis
• Be interested in their health
• Correctly assess the impact of the diagnosis
• Believe in the efficacy of the prescribed treatment
Know exactly how and how long to use their medication
• Know onset of action
• Value outcome of the treatment more than the cost
• Be ready to use the medication

Non-adherence is of most concern when–

Chronic illness
• Asymptomatic
• Progressive
• Complex regimen
• Side effects
• Patient knowledge and understanding is limited

Q.13). Give the Strategies to improve compliance

Strategies to improve compliance

1. **Simplification of therapeutic regimen**
   Minimizing the complexity – minimum number of drugs with well defined dosage schedule
   • Use of sustained release and long acting oral preparations
   • Single dose drugs (phenytoin, propranolol or antidepressants) promote compliance by reducing adverse effects
   • Fixed dose combinations for- – Synergism (Cotrimoxazole) – Improved efficacy (oestrogen-progesterone contraceptives) – Reduction in side effects (levodopa and decarboxylase inhibitor)
2. **Development of suitable medication packing**
   • Unit dose package – blister pack – encourage degree of self monitoring – improved compliance in intelligent and motivated patients
   • Medication box – all the different drugs to be taken at a specific time are grouped together in one compartment
3. **Supplementary labeling –**
   • Precautions or recommendations that enhance the advice of the prescriber
   • Based on potential clinical significance for the benefit of patients
   • Should be concise, uncomplicated and foolproof – Description of drug action given in lay terminology – Symbols and graphics to emphasize correct time of administration – 'Daily calendar' or 'Tablet identification card' bearing details of administration schedule.
4. **Patient counseling and education**
   • Pharmacist should inform, educate and counsel patients about following items about each medication in the dosage regimen –
   – Name (trade name, generic name and common name)
   – Intended use and expected action

– Route, dosage form, dosage and administration schedule
– Special directions
– Common side effects
– Techniques for self-monitoring
– Proper storage
– Drug-drug or drug-food interactions
– Prescription refill information
– Action to be taken in event of a missed dose
– Selection of OTC drugs and their use

Methods for imparting patient education depend on type and extent of advice needed :

– Verbal counseling – Printed information
• Warning cards
• Medication instruction sheet
• Leaflets and booklets describing drugs
• Patient package inserts
– In-patient medication training programmes
– Compliance clinics
• Routine counseling is both undesirable and impractical.
• Priority should be given to cases where –
– Prophylactic treatment is required in absence of symptoms (tuberculosis)
– Drugs having low safety margin (warfarin)
– Premature withdrawal may have serious consequences (corticosteroids)
– Long term therapy for chronic conditions (epilepsy)

Q.14). Give the role of hospital pharmacist in hospital committees.

HOSPITAL PHARMACIST:-

■ Dispenses oral medications.
■ Prepare & dispenses parenteral medications.
■ Educates & counsels patients.
■ Provides drug information services.
■ Provides patient counselling services.
■ Monitor patient compliance & drug interactions & therapeutics response to drugs, & to recognize & report adverse drug reactions
■ Planning & implementation of clinical trials.
■ Procurement & inventory management of drugs.
■ Participating in teaching programs.
■ Maintenance of medial & nursing staff & patients.
■ Maintenance of central sterile supply services in hospital pharmacy.
■ Screens, monitor, & advices for self-treatment with over –the-counter (OTC) products sold without a prescription. Providing therapeutic drug monitoring services.
Sometimes specializes, with advanced training in an area of patient care.
■ Administers department
■ Develops policies & procedures.

■ Purchases drugs & supplies.
■ Monitors drug use in the hospital

Q.15). Give the methods of determining patient compliance.

• Many ways to evaluate – no "Gold standard" method
• Information reported by patients – orally or in writing – unreliable due to – inability to remember or false reporting to please or avoid disapproval of the physician

Indirect methods –

1. Interrogation – – Use of standard questionnaires to assess compliance level and inconvenience of the regimen, incidence of side effects and overall level of comprehension – Too subjective – not always reliable
2. 2. Pill count (Residual tablet counting) – At every visit, according to requirements, the patients received a supply sufficient for the interval to the next appointment plus extra tablets for a week. They were asked to return the remaining tablets at the time of the next clinic visit. Compliance was assessed as the percentage of pills prescribed which were taken: Compliance (%) =(Number of pills taken)/(Number of pills prescribed)x 100 =(# of tabs prescribed-#of tabs returned)/(# of tabs prescribed)x100
3. 3. MEMS devices – – Medication Event Monitoring System – Standard pill containers with microprocessors to record timing and frequency of bottle openings – Major limitation – opening of the bottle is recorded as an event whether or not patient actually took the drug – At every visit, patient had a MEMS reading, data showed as a calendar plot with information regarding no. of bottle openings each day and exact time when the bottle was opened – Compliance – assessed as ratio of no. of opening to no. of doses prescribed

Direct methods –

1. Drug Analysis – – Specific and sensitive methods of analysis to detect potent agents in body fluids – Bioavailability (F) and clearance (CL) – assumed to remain constant, average steady state concentration (CPSS) for a dose (D) administered at dosage interval (T) is expressed as – • CPSS = (FD)/(CL*T) – Dose input rate is calculated as – • FD/T = CPSS*CL
2. 2. Urine markers – – Urine marker – Riboflavin : added to dosage regimen and its presence in the urine is noted for more accurate assessment of compliance

Q.16). Give the reasons for non-compliance.

Reason for patient noncompliance

1. **Poor standards of labeling –**
   • Labels – must be clear and specific (no ambiguity)
   • Instructions such as "take as required" or "use as directed" are not specific
   • Poorly written labels with bad handwriting – major source of medication errors
2. **Inappropriate packing –**
   • Elderly patients – difficulty in opening container, specially if size is too small or cap is difficult to twist
   • Blister pack – too rigid Glass bottle – fragile Thus difficulty in handling

3. **Complex Therapeutic Regimen**
   Difficult to memorize and thus unintentional noncompliance
4. **Nature of Medication –**
   Unpleasant taste, colour or odour – noncompliance within patients (particularly children)
   • Extremely small tablets – difficult to handle or identify Large tablets – difficult to swallow
   • Occurance of irritating side effects – precipitate in noncompliance
5. **Deliberate deviation –**
   Some patients believe that once they begin to feel better, treatment may be stopped
   • Mental frailty – may forget to take occasional dose
   • Forgetfulness – complete omission of doses or duplication of doses : more common with socially isolated geriatric patients
   • Lack of proper physician – pharmacist – patient rapport

Q.17) Classify hospitals on the basis of ownership.

On the basis of ownership hospitals classified as 1) Public 2) Private

1) Public hospitals are owned by Government.

a) Central Government Hospitals

- Military hospital
- Railway hospital
- All India Institute of Medical sciences, New Delhi.

-JIPMER

b) State Government Hospitals

- J.J. Hospital- Mumbai
- Sassoon hospital-Pune
- Ghati hospital- Aurangabad
- ESIS Hospital- Mulund

-Victoria hospital- Bengaluru
-Stanley hospital- Chennai
-Civil hospital- Jalgaon

c) Local-Self Government Hospitals

- BMC Hospital-Sion,Mumbai
- KEM Hospital- Parel, Mumbai
- Cooper hospital- Vile Parle, Mumbai

-Bhagwati hospital-Mumbai.

2) Hospitals owned by Private:

a) Private Trust hospital

- Bombay hospital-Marine lines , Mumbai
- Jaslok hospital- Mumbai
- Rajasthan hospital- Ahmedabad

-Jindal hospital- Bengalaru

b) Hospital owned by Religious Trust/bodies

- Hindu Mission Hospital- Chennai
- Al-Ameen Hospital- Bengalaru
- Christian Medical College Hospital – Vellore
-Minakshi Mission Hospital- Madurai.

c) Private Company Hospitals

-Fortis Hospital-Bengalaru
- Apollo Hospital- Chennai
-Medinova Hospital- Gujarat
-HMT Hospital- Hyderabad.

g) Private Clinics/Nursing Homes

Such clinics are owned by an individual doctor or a group of doctors in towns or big cities and serve for 24 hrs.

Q.18) Define Adverse Drug Reaction. Classify ADR with examples.

Adverse drug reactions (ADR) – "Any response to a drug which is noxious and unintended, and which occurs at doses used in man for prophylaxis, diagnosis or therapy".

Classification of ADRs:

A) Predictable ADRs:

1. Excessive Pharmacological Effect.
2. Secondary Pharmacological Effects.
3. Rebound response on discontinuation.

B)Unpredictable ADRs:

1. Allergic drug reaction and Anaphylaxis.
2. Idiosyncrasy.
3. Genetically determined Toxicities.

Examples:

1. Excessive Pharmacological effect :

It is common experience of patient receiving CNS depressants, cardioactive, hypotensive and hypoglycemic agents. If excessive dose is given, all patients are at risk of developing this reaction. Certain patients are more susceptible to this reaction even when average dose is prescribed.

a) Patient with Kidney disease who have lost more than 70% of their kidney function

b) Patients with hypoalbuminemia due to failure of albumin production by liver or excessive loss of albumin as in nephrotic syndrome.

c) Patients age – Neonates, infants and elderly patient.

2. Secondary Pharmacological Effects

It is mainly observed in patients, who consumes OTC drugs or go for self-medication .e.g. Drugs like Antihistamine used mainly as anti-allergic particularly for common cold and cough , but it may produce drowsiness in large repeated doses for repeated doses on self-medication

Q.19) Give any six functions of hospital.

Functions of Hospital:

The main functions of the hospital are:

1. Patient care: It includes services for diagnosis, prophylaxis and treatment of diseases to the sick or injured patients. It is a centre of community health and contributes a great deal to preventive and social medicine.

2. **Public health:** The hospitals are required to support all the activities carried out by various public health and voluntary agencies such as immunization programme, blood donation camps, social and economics rehabilitation, health education etc. by providing facilities and advice.

3. Medical research: Research is an important activity in the hospital that helps in developing the new methods of treatment and improving the hospital services. Some of the common areas of research in the hospital are development of new techniques in surgery, laboratory diagnostic procedures, evaluation of investigational drugs in diseases.

4. Educational training: - This facility, particularly for medical students, pharmacist, nursing, medical technologist and allied health professional helps to fulfil their curriculum requirement. Hospital also educates the general public through lectures and demonstrations on the preventive aspects of common and serious diseases. Hospital provides the methods by which the persons can work together in groups with the object of care of patient and community.

5. Patient Counselling: It is a modern concept adopted in big hospitals for the well-being of the patients. During these counselling sessions pharmacist educate people on communicable diseases, epidemics and family welfare etc.

6. **Co-ordination**: It is a link between general public and policy makers.

Q. 20) Enlist different abilities a hospital pharmacist should possess and explain any one ability.

The hospital pharmacist should possess following abilities:

1. Administrative ability
2. Technical ability
3. Manufacturing ability
4. Research ability
5. Teaching/Training ability
6. Ability to Control

1. Administrative ability-Hospital pharmacist should be thoroughly familiar with organization of hospital, with staff and with appropriate channel of communication. Hospital pharmacist should be capable of planning and integrating services, budgeting, inventory control, cost-review, cost-effectiveness, audit, maintenance of records and preparation of reports.

2. Technical ability- Hospital pharmacist must have ability to use his basic knowledge of effect of drug on biological systems, in assessing drug absorption, distribution, metabolism and pathophysiology, therapeutics and patient care techniques.

3. Manufacturing ability-Hospital pharmacist must be able to develop formulations not available commercially. Hospital pharmacist should possess an adequate understanding of the principals involved in formulations and p[reparation of dosage forms.

4. Research ability-Hospital pharmacist must be prepared to participate in clinical research initiated by medical staff and to conduct pharmaceutical research himself. Hospital pharmacist must be able to establish database for drugs being used and patients participating in studies. Hospital pharmacist must have ability to collect appropriate data interpret them and make conclusion from data.

5. Teaching/Training ability- Hospital pharmacist is responsible for training of new personnel and for carrying out continuous educational programme for pharmacist and pharmacy supportive personnel. Hospital pharmacist must be able to develop well planned and co-ordinate training programme and able to deliver lectures.

6. Ability to Control-Hospital pharmacist must be able to develop quality assurance programme for quality services of pharmacy department and products dispensed. Hospital pharmacist must be able to develop control programme for distribution of drugs throughout the hospital.

Q.21) Discuss the role of PTC in drug safety.

Role of PTC in Drug safety –

The PTC plays an effective role in ensuring drug safety on a continuous basis by creating safety awareness in all departments of the hospital. The PTC provides following guidelines to hospital administration.

1. Employment of qualified registered pharmacist with at least B. Pharm degree holder as the chief pharmacist & rest are diploma holders.
2. Takes care that dispensing is done only by the pharmacist.
3. Sufficient number of pharmacists are employed.
4. Proper & adequate storage facilities are provided in pharmacy.
5. Poisonous material & non-poisonous material are stored separately.
6. Pharmacy should have adequate equipments.
7. External preparations are kept separately from internally used preparations.
8. Follow of GMP effectively in the in-house manufacturing unit.
9. Stock & issue of narcotic & psychotropic substances shall conform to the legal requirements.
10. Hospital shall have a drug formulary which is periodically revised & kept up to date.
11. Expired & deteriorated drugs are physically separated.
12. Providing a library & documentation facility.

Q.22) Explain the role of pharmacist in patient counselling.

Role of Pharmacist in patient counselling-

1) Name of the drug and its action- The pharmacist should inform the patient about the name of drug and its common name, if any. He must explain the use of that drug and action on the body.

2) Route of administration- It is important for the pharmacist to inform the patient about the route of administration of drug. Whether the drug is to be taken orally or it is to applied locally or to be used into eye, ear or nose or inserted rectally or vaginally. The pharmacist should ensure that the patient understands how to use ophthalmic preparations, and suppositories.

3) Time of administration- The pharmacist should instruct the patient when to take the medication e.g. some drugs should be taken on empty stomach i.e. about 1 hour before meal or 2-3 hours after meal to ensure adequate absorption of drug. The patient should be provided for the medication calendar.

4) Duration of therapy- The pharmacist should encourage the patient to continue taking the medicine for the prescribed duration of the treatment. He should explain that thecourse of treatment must be completed to achieve best results.

5) Storage of drugs- The pharmacist should inform the patient regarding storage of drugs; those are labelled on the container. The patient should be advised to store the drugs in a separate cabinet where children will not reach.

6) Side effects of drugs- The patient should be informed about the known side effects of the drugs. This knowledge will help the patient to follow treatment without any fear and thereby improve the compliance of patient. e.g. change in colour of urine, stool; drowsiness,

7) Contraindications (Restrictions) - The patient should be informed well that he should avoid certain drugs and foods during the therapy. E.g. Restriction of Tyramine containing food in patients on MAO inhibitor therapy

8) Allergic reactions- Before dispensing the drugs like penicillin or sulphonamide, the pharmacist should ask the patient about his allergic reactions in the past. It helps in avoid in further complications of treatment.

9) Removal of drug from package- The patient is not familiar with the packing of the product, as the pharmacist. Hence, the pharmacist should demonstrate the method of removal of drug from the package to the patient so that he can handle it properly.

10) Refill information- The pharmacist should inform the patient verbally, whether the prescription is refillable, or not. If it is, then for how many times it should be refilled and length of time during which it may be refilled. If it is not refillable, he should be instructed such, so that he may contact the physician after completion of treatment.

Q.23) Explain how purchase order is prepared?

Purchase order is prepared in 2 steps-

Step 1- Purchase requisition:

Once the specifications are drawn, a purchase requisition is prepared. The requisition carries the description of items needed, their packaging, their price, their quantity. It may also mention the quantity right now in hand and the quantity required for future period. The original requisition is sent to the administrative head of the concerned department. Once approved by administrative head, it is sent to the purchasing officer. One copy is retained by the pharmacist. Several copies of purchase order can be prepared.

Step2- Purchase order:

After the receipt of purchase requisition, the purchase officer/pharmacist prepares a detailed purchase order in a printed form. The items are systematically order by spelling out the specifications, prices and quantities of ordered.

Then 7 copies of purchase order are prepared.

1st copy—Sent to supplier by post or hand delivery for supply.

2nd copy--Sent to accounts department where it will be retained for accounting.

3rdcopy—Retained by purchasing officer for his departments file.
4th copy—sent to the department from where 'request form' is received.
5th & 6th copy—Completion of 5th copy is done if articles are received and sent to account departments and 6th copy is utilized only when goods are back ordered.
7th copy---Is history copy is kept by purchase officer to ascertain rates and for other things in future use.
When the supplies are obtained they are carefully checked with purchase order. If it is according to the given order, the supplies are retained; if not even in part that part or whole lot is returned to supplier immediately with goods. Returned note and a credit note are obtained from the supplier. The supplies received are entered on the Purchase Record Register and complete inventory is prepared. This supply is then ready for dispensing to inpatients or outpatients.

Q.24) Define clinical pharmacy. Give different roles of clinical pharmacist.(1 markdefinition,
Definition of Clinical pharmacy – Clinical pharmacy is a new-born discipline that carries traditional hospital pharmacist from his product oriented approach to more healthier patient oriented approach, so as to ensure maximum well-being of the patient while on drug therapy.
OR
It is the branch of pharmacy which is concerned with various aspects of patient care & deals not only with dispensing of drug but also advising the patients on safe & rational use of drugs.
Role of clinical pharmacist—
1. Medication history-It includes past and present of prescription and non – prescription drug, dietary supplements, dietary habits, drug and estimate of patient compliance with the drug therapy.
2. Monitoring drug therapy- It includes evaluation of patient pharmacokinetics and pharmacodynamics parameters, lab findings, medical problems and communicating relevant findings to physician.
3. Participation in ward rounds- The clinical pharmacist with physicians participates in ward rounds, observe individual patient and decide the drug therapy.
4. Drug information- The clinical pharmacist establish drug information centre. The drug info is available at this centre and utilized suitably. This data is sent to physician as per their requirements.
5. Patient counselling- it involves providing information to the patient about drug therapy and illness. The pharmacist acts as resource for information about health promotion and disease prevention.
6. Participation in new drug investigation- Clinical pharmacist along with physician participates in investigation of new drugs. Data of this investigation is compiled, analyzed and maintained at drug information centre.
7. ADR management- Along with physicians, clinical pharmacist is actively involved in reporting and management of ADR.

8. Educational Programme- Clinical pharmacist organizes educational programs for Nursing and education related to safe and effective use of drugs.

9. Tailoring drug therapy- Clinical pharmacist after the diagnosis of physician formulates drug therapy to clinical need of patient.

Q.25) Write three administrative patterns of central sterile service department.

1- Department as a part of Nursing services-

The majority of items to be dispensed are used by the nurses for the patients care. She should therefore be work as head of this department.

2- Department under a pharmacist-

Pharmacist by taking training is competent to handle the functions of this department.i.epurchase, storage and distribution of supplies and also the preparation of sterile solution.

3- Department under dual control of pharmacist as well as nurse-

Some functions of the department like cleaning, packaging and distribution of medical supplies and equipments should be placed in charge of nurse whereas manufacturing of sterile solutions should be placed in charge of pharmacist.

Q.26) Comment on various sources of drug information.

Sources of drug information-

1.Primary sources –

Information obtained from basic researches and developments which are published for first time .e.g. Peer reviewed journals-International Journal of Pharmaceutics, Indian Journal of Pharmacology, Journal of Pharmacy and Pharmacology.

2.Secondary sources –

Information in the form of abstracts, journals, periodicals, references and official books is called secondary sources.

i) Abstract Services: Chemical Abstract Service, Pharmaceutical Abstract Service.

ii) Text books –Text book of Hospital Pharmacy, Clinical Toxicology.

iii) Reference books- Remington's Pharmaceutical Sciences, Merck Index

iv) Pharmacopoeias – The Indian Pharmacopoeia, British Pharmacopoeia

v) Formularies – National Formulary of India, British National Formulary.

3) Tertiary Sources -

It includes dictionaries, encyclopaedias, and desk references.

The Chemist and Druggist directory

Indian Pharmaceutical Guide- which gives the manufacturers or suppliers catalogues and price list.

Medical register and Directory of Pharmaceutical Chemists.

Statistical Table and Mathematical table to provide scientific data

Websites: Drugscontrol.org, who.int, usfda.org

Q.27) Enlist methods of drug distribution in hospital. Give advantages and disadvantages

of floor stock system.

Methods of drug distribution in hospital-

I) Outpatient services

II) **Inpatient services-** It includes

i) Floor Stock System

ii) Unit Dose Dispensing System

iii) Individual Prescription Order System

iv) Combination of Floor Stock and Individual Prescription Order System

Advantages of floor stock system-

1. The drugs are easily available at the wards and nursing units.
2. Elimination of drug returns.
3. Reduction in number of drug transcription orders at pharmacy.
4. Reduction in the number of pharmacists required.

Disadvantages of floor stock system-

1. Chances of medication error may increase.
2. Increased drug inventory at wards and nursing units.
3. Greater opportunity for spoilage of the drug as they are stored in large quantity.
4. Increased hazards associated with drug deterioration.

Q.28) Explain food drug interactions with examples.

Food affects the absorption of the drug. It may be attributed to

1) Dilution of the drug

2) Adsorption or complexation of drug

3) The alteration of gastric emptying.

Examples:

1) Food reduces the absorption of aspirin, isoniazid, tetracycline, benzylpenicillin, amoxicillin, Ampicillin, levodopa and Rifampicin

2) Food increases the absorption of hydralazine, Nitrofurantoin, lithium citrate, riboflavin, carbamazepine, metoprolol, propanolol, and spironolactone.

3) Iron absorption is reduced if food has been taken within the previous two hours. On the other hand, nausea is more likely if iron is taken on empty stomach so iron tablets are often given with food.

4) Nitrofurantoin is given with food to avoid GIT irritation.

5) Meals containing high fat increase the absorption of fat soluble drug Griseofulvin. Fat containing drug increases degree of ionization of Griseofulvin, so increases its absorption.

6) The diuretic effect of tea takes place rapidly if given before meals but diuresis is delayed if it is given after food.

7) The absorption of nitrazepam, glibenclamide, metronidazole, oxazepam, theopylline is unchanged by food.

8) Monoamine oxidase (MAO) is an enzyme which breaks down catecholamines such as or epinephrine. When the enzyme is inhibited, there are increased levels of nor epinephrine in adrenergic neurons. Thus, MAO inhibitors are used as antihypertensive. Certain food like cheese, chocolate, alcoholic beverages, liver, yeast extract contain tyramine. Tyramine is metabolized by MAO. When the patients being treated by MAO inhibitors also take tyramine containing food, tyramine reaches the systemic circulation causing severe hypertension.

9) Milk reduces absorption of tetracycline by forming an insoluble complex

Q.29) Define patient compliance? Discuss factors that influence patient compliance.

Patient compliance- A faithful adherence by a patient to prescriber's instructions is called as patient compliance.

Factors that influence patient compliance-

1. Inappropriate packaging: Sometimes design or size of container makes it difficult to remove the medicament. Many elderly patients, arthritis patients have difficulty with unit dose pack or foil wrapping while removing medicament.

2. Poor understanding: Poorly handwritten labels are difficult to read or follow for the patient/pharmacist. Many prescriptions contain directions which are inadequate like take when required or use as directed that may produce confusion.

3. Multiple drug therapy: Greater the number of drugs patient is taking, the higher is the risk of non-compliance.

4. Asymptomatic nature of patient: In case of asymptomatic patient, it is difficult to convince a patient by explaining the value of drug therapy and this results in noncompliance.

5. Measurement of medication: Many times there is confusion to the patient in measuring liquid preparations or number of tablets.

6. Cost of medication: Because of high cost of drug, poor patients are unable to purchase such drugs.

7. Frequency of medication: Higher the frequency of the medicines, the greater is risk of non-compliance. Many times regular schedule of dosage form cannot be followed due to work routine.

8. Duration of therapy: Usually long duration treatment leads to patient non-compliance.

9. Illness: The nature of patient's illness may contribute to non-compliance like chronic hypertension, mental illness.

10. Age: Paediatric and geriatric patients contribute to non-compliance.

Q.30) Explain the role of computers in purchase and inventory control in hospitals.

Purchasing & inventory control in Hospitals –

By using computers it is done by-

1. Periodic inventory control method- In this method, quantities of drugs available in stock are manually checked. These are then compared with the minimum stock level & maximum stock level maintained on the computer. When the drug level reaches the minimum stock level purchase orders are placed by using computer.

2. Perpetual inventory control method - In this method computer maintains running balance of all the drugs in stock. All the drugs are entered in database when new stock is received by pharmacy. Computer adds this to the initial stock & reflects current available stock. The quantities of drugs leaving the pharmacy are entered in the computer. Computer subtracts this from the initial stock & reflects current available stock. Whenever the drug level reaches the minimum stock level purchase orders are placed by using computer.

Thus, the computer can list out minimum order quantity of each drug. In this way computer can help in inventory control-
- To detect the items those have reached minimum order level.
- To prepare the list of drugs to be ordered and their quantities.
- To prepare the purchase order and avoid duplicate orders.
- Keeping the inventory records for accounting aspects, audit inspections and legal requirements.
- For automatic updating of price
- For evaluation of demand.
- To detect infrequently purchased items for possible return of elimination from pharmacy's drug supply.

Q.31) Classify pharmacodynamics drug interactions with examples.
Classification:
1) Interaction enhancing effect:-e.g. Synergistic effect of Trimethoprim and sulphamethoxazole. MAOI and sympathomimetic drugs which increases activity.
2) Interaction inhibiting the effect:-
E.g Acetylcholine and atropine by competitive antagonism oppose the action of each other. Alcohol and amphetamines have opposite effects on CNS.
3) Alteration of electrolyte levels: Drugs which cause alterations in fluid and electrolyte balance may modify the responses of tissues to drugs. e.g. Diuretics losing potassium, may cause hypokalaemia, in turn making the heart more sensitive to digitalis.
4) Drug interactions at same receptors: Drugs that act at the same receptor site, if prescribed together, may produce additive effect or antagonize one another; e.g. respiratory depression and other central effects of morphine are antagonized by nalorphine.
5) Drug interactions at different receptors: Drugs may interact on the same target organ, but at different receptor sites. E.g. Adrenaline activates adenylcyclase system and causes an increase in cyclic 3-5 AMP (Adenosine MonoPhosphate) which then acts as the mediator in a number of beta effects of adrenaline for relaxation of bronchial smooth muscles. Theophylline produces the same effect, an increase in cyclic 3-5 AMP, by inhibiting phosphodiesterase, and also causes bronchial smooth muscle relaxation. Thus, drugs that inhibit different enzymes may show synergistic effect.

Q.32) Explain the factors influencing make or buy decision in hospital. What are the different methods of estimation of demand?
Following factors affect make or buy decision in hospital manufacturing:
1. Quality 2.Quantity 3.Cost and 4.Service.
1) QUALITY
The quality of outside purchases & the quality that could be possibly achieved when manufactured within the hospital are compared. If there are no wide variations between these two, it is not an important consideration. If there is a wide variation, it becomes a crucial factor. If a better quality results from in-house manufacturing, the matter should be probed further.

2) QUANTITY

Generally, those items whose orders are too small to purchase it from an outside supplier are manufactured within the hospital.Similarly, items which are required every day for use in hospitals, in large quantities, are generally decided to be manufacture. Break-even analysis and EOQ give the hospital the quantity of production.

3) COST

Here we compare the costs of buying from outside with the cost of in-house manufacturing. The cost of manufacturing the items within the hospital is estimated by drawing up a cost-sheet. Cost and quantity together considered for making the decision.

4) SERVICE:

Generally, a supply is more assured when a hospital makes an item then when it buys it. Assured supply is often a valid reason for manufacturing. Interruption in supplies may affect the major clinical services of the hospital. Unfair practices of outsider make a hospital opt for making rather than buying.

There are three methods of estimation of demand-

1) Judgmental Method-

This is a method which depends upon the judgment of clinical and pharmacy staff where they express an opinion based on experiences about name and quantity of product that will be required majorly in the hospital.

2) Experience of Past -

The experience and reviewing records of consumption of drugs in the past helps in deciding the requirement of drugs in future.

3) Causal Method-

In this method by assessing medical record of the hospital one can estimate the demand for specific drug based on specific criteria. e.g. - i) Antibiotic drugs –No of patients admitted every month for whom the specific antibiotic is used.

ii) Insulin- No of diabetic patients admitted in the hospital.

iii) Demand of whole blood- Is estimated on the basis of no of patients admitted in emergency wards.

Q.33) Define Hospital formulary? Write the guiding principles while using Hospital Formulary.

Hospital formulary- Hospital formulary is revised compilation of pharmaceutical preparations and ancillary drugs which reflects current clinical judgment of medical staff of the hospital.

Guiding principles for preparation of Hospital Formulary: (any 6 points)

The following principles will serve as guide to all those utilizing the formulary system:

1. The medical staff of the hospital shall appoint P and T Committee and outline its scope, purpose, organization and function.
2. The formulary system will be sponsored by medical staff based upon recommendations of P and T Committee.
3. The medical staff shall adopt the written policies and procedures of the formulary system.

4. Drugs should be included in the formulary by their nonproprietary names and should be prescribed by the same name.
5. Limiting the number of drugs available from pharmacy can produce substantial patient care and financial benefits. These benefits can be greatly increased by using generic equivalents. Generic equivalent- The drugs containing identical active compounds. .E.g Two brands of tetracycline.
Therapeutic equivalent- The drugs differing in composition but having very similar pharmacological or therapeutic effects. E.g: two different antacid products.
6. The management of the hospital shall inform all the medical and nursing staff about the existence of the formulary system, procedures of the operation of the system and any changes in those preparations. Copies of formulary must be readily available at all times.
7. Provision shall be made for the use of drugs not included in the formulary, by the medical staff.
8. The pharmacist shall be responsible for specification as to quality, quantity, and source of supply of all the drugs used in the diagnosis and treatment of patients

Q.34) What are the objectives of hospital pharmacy?
1. To professionalize the functioning of pharmaceutical services in a hospital.
2. To ensure the availability of the right medication at the right time, in the right dose, at the minimum possible cost.
3. To teach the hospital pharmacist about the philosophy and ethics of hospital pharmacy and guide them to take responsibility of professional practice.
4. To strengthen the management skills of hospital pharmacist working as the head of the department
5. To strengthen the scientific and professional aspects of practice of hospital pharmacy such as his consulting, teaching role and research activities.
6. To utilize the resources of hospital pharmacy for the development of profession.
7. To attract the greater number of pharmacist to work in the hospital.
8. To promote the payment of good salaries to pharmacist.
9. To establish drug information services
10. To participate in research projects carried out in hospital.
11. To implement decisions of Pharmacy and Therapeutics Committee.

Q.35) Give any two reasons for patient noncompliance.
1.In appropriate packaging : Some time design or size of container make difficulty to remove the medicament .Many elderly patient ,arthritis patient have difficulty with unit dose pack or foil wrapping while removing medicament
2. Poor labelling: Poorly hand written label are difficult to read or follow for the patient/pharmacist. Many prescriptions contain direction which are inadequate like take when required or use as directed that may produce confusion.
3. Multiple drug therapy: Greater the number of drugs patients is taking the higher is the risk of non compliance.
4. Asymptomatic nature of patient: In case of asymptomatic patient, it is difficult to convenience a patient by explaining the value of drug therapy results in non compliance.

5. Measurement of medication: Many times there is confusion to the patient in measuring liquid preparations or number of tablets.
6. Cost of medication: Because of high cost of drugs, poor patients are not purchase such drug.
7. Frequency of medication: Regular schedule of dosage intake cannot be followed due to work load.
8. Duration of therapy: Long duration treatment lead to patient noncompliance.
9. Illness: The nature of patient's illness may contribute to non-compliance like chronic hypertension, mental illness.

Q.36) Classify Hospital on the basis of its bed size.
i) Large Hospitals- Bed capacity 1000 and above
e.g.- J.J.Hospital Mumbai
ii) Medium Hospitals- Bed capacity 500-1000
e.g.- Bombay hospital
iii) Small hospitals- Bed capacity 100-500
e.g.- Breach candy hospital Mumbai
iv) Very small hospital- Bed capacity below 100
e.g.- Any private hospital

Q.37) Give the functions of PTC.
1) To advise the medical staff and hospital administration in matters related to the use of drugs
2) To establish and develop suitable educational schemes to improve the professional staff on the matters related to the use of drugs.
3) To develop and compile formulary of drugs and prescription accepted for use in hospital. It also minimizes the duplication of the same type of drugs or products.
4) To study problems related to the distribution and administration of drugs used in hospital.
5) To review adverse drug interaction occurring in hospital.
6) To initiate and promote studies on drug use and review the results of such studies.
7) To recommend about the drugs to be stocked in hospital patient care areas.
8) To advise the pharmacy in the implementation of effective drug distribution and control Procedures

Q.38) Define clinical pharmacy. What is the scope of clinical pharmacy? and 2 marks for any 4 points)
Definition of Clinical pharmacy – Clinical pharmacy is a new-born discipline that carries traditional hospital pharmacist from his product oriented approach to more healthier patient oriented approach, so as to ensure maximum well-being of the patient while on drug therapy.
OR

It is the branch of pharmacy which is concerned with various aspects of patient care & deals not only with dispensing of drug but also advising the patients on safe & rational use of drugs.

Scope of clinical pharmacy— (any 4 points)

1. Medication history- it includes past and present of prescription and non – prescription drug, dietary supplements, dietary habits, drug and estimate of patient compliance with the drug therapy.

2. Monitoring drug therapy- it includes evaluation of patient pharmacokinetics and pharmacodynamics parameters, lab. Findings, medical problems and communicating relevant findings to physician.

3. Participation in ward rounds- The clinical pharmacist with physicians should participate in ward rounds, observe individual patient and decide the drug therapy.

4. Drug information- The clinical pharmacist establish drug information center. The drug info. Is available at this centre and utilized suitably. This data is send to physician as per their requirements.

5. Patient counselling- it involves providing information to the patient about drug therapy and illness. The pharmacist acts as resource for information about health promotion and disease prevention.

6. Participation in new drug investigation- clinical pharmacist along with physician participates in investigation of new drugs. Data of this investigation is complied, analyzed and maintained at drug information centre.

7. ADR management- Along with physician clinical pharmacist's activity is involved in reporting of management of ADR.

8. Educational Programme- clinical pharmacist organized educational programs for nursing and education related to safe and effective use of drugs.

9. Tailoring drug therapy- the clinical pharmacist after the diagnosis of physician formulates drug therapy as per clinical need of individual patient.

Q.39) Discuss four important factors governing make or buy decision.

Four important factors are:

1) **QUALITY**-The quality of outside purchases & the quality that could be possibly achieved when manufactured within the hospital are compared. If there are no wide variations between these two, it is not an important consideration .if there is a wide variation, it becomes crucial factor. If a better quality results from in-house manufacturing, the matter should be probed further. Why do the outsiders fail to come up to the desired quality level? Also, is the hospital competent to produce the desired quality?

Does it have the necessary infrastructure? Most of the times, as in case of large volume fluids, the hospital favors in-house manufacturing as it has a legitimate apprehension that an outsider may compromise with the quality of his supplies.

2) **QUANTITY**-Generally, those items whose orders are too small to purchase it from an outside supplier are manufactured within the hospital. Similarly, items which are required every day for use in hospitals, in large quantities, are generally decided to be

manufacture. Break-even analysis gives the hospital the break-even quantity of production. Break-even is at a point where there are no profits and no losses.

3) **COST-**Here we compare the costs of buying from outside with the cost of in-house manufacturing. The cost of manufacturing the items within the hospital is estimated by drawing up a cost-sheet. It is important to allocate over-heads correctly. Cost and quantity together considered for making the decision.

4**) SERVICE:** Generally, a supply is more assured when a hospital makes an item then when it buys it. Assured supply is often a valid reason for manufacturing. Interruption in supplies may affect the major clinical series of the hospital. Unfair practices of outsider make a hospital opt for making rather than buying.

Q.40) Explain about types of drug distribution systems?

They are four systems in general use for dispensing drugs for inpatients. They may be classified as follows;

i. Individual prescription order system.

ii. Complete floor stock system

a) Charge floor stock drugs

- Envelope method

b) Non-charge floor stock drugs

- Drug basket method
- Mobile dispensing unit

iii. Combination of individual & floor stock system

iv. Unit dose dispensing system

a) Centralized unit-dose dispensing (CUDD)

b) De-centralized unit dose dispensing (DUDD) [2]

i. Individual prescription order system:

• It is a type of prescription system where the physician writes the prescription for individual patient who obtains the drug prescribed from any medical store or hospital dispensary by paying own charges.

• This system is mainly used in small or private hospitals because of its economic consideration and reduced manpower requirements.

Advantages:

• All medication orders are directly reviewed by pharmacists.

• It provides the interaction of pharmacist-doctor, nurse and the patient.

• It provides clear control of inventory.

Disadvantages:

• There may be possible delay in obtaining the required medications for administration to the patient.

• Increase in the cost to the patient.

ii. Complete floor stock system

• Drugs are stored at the nursing station and are administered by a nurse according to the chart order of the physician. This system is most often used in private hospitals in India.

• The drugs are stored in the pharmacy stores, supplied to the wards/rooms on order and kept under the supervision of registered nurse at nursing station.

Advantages:
• The drugs are readily available for administration.
• Minimum return of drugs.
• Reduced in-patient prescription orders.
• Reduction in number of pharmacy personnel required.
• Easy and prompt delivery of the required drug.
Disadvantages:
• Increase in chance of medication errors.
• Increase in drug inventory.
• Increase chances of drug deterioration due to lack of proper storage facilities and due to unnoticed drug degradation.
• Increased workload on nurses.
iii. Combination of individual & floor stock system
- Falling into this category are those hospitals which use the prescription order system as their primary means of dispensing and also utilize a limit floor stock [1].
- This combination system is most commonly used in hospitals today.
- Selection of charge floor stock drugs: The drugs should be placed under the category of 'charge' drugs depending on pharmacy and therapeutic committee (PTC).The committee will concerned with the availability of therapeutically effective drugs and their immediate use for diagnosis or symptomatic treatment.
- Selection of Non-charge floor stock drugs: A list of non-charge floor stock is prepared on the basis of following criteria:
- The cost of preparation
- The frequency of use
- The quantity use
- The hospital budget

iv. Unit dose dispensing system:
- Unit dose packages are defined as those medications which are ordered, packaged, handled and administered and charged in the multiples of single dose units containing a predetermined amount of drug or supply sufficient for one regular dose, application or use.
- The pharmacist is held responsible for unit dose dispensing system.
- Example: Single dose disposable syringes of medications and single unit foil or cellophane wrapped capsules and tablets.
- Advantage of unit dose dispensing:
- Better financial control.
- It prevents the loss of partially used medications.
- It does not require storage facilities at the nursing station.
- It eliminates labeling errors
- There is a accurate medication charge

• Two methods of dispensing unit doses are:

a. Centralised unit-dose dose dispensing (CUDD):

• All in-patient drugs are dispensed in unit doses and all the drugs are stored in central area of the pharmacy and dispensed at the time the dose is due to be given to the patient.

• Drugs are transferred from the pharmacy to the indoor patient by medication cards.

b. Decentralized unit dose dispensing: (DUDD)

This operates through small satellite pharmacies located on each floor of the hospital.

Procedure:

- Patient profile card containing full date, disease, and diagnosis is prepared.
- Prescription is sent directly to the pharmacist who is then entered in the patient profile card.
- Pharmacist checks medication order.
- Patient profile card and prescription order is filled by pharmacy technicians.
- The nurses administer the drugs and make the entry in their records

Advantages:

- Easy for the administration staff.
- Accounting becomes easier in certain cases.
- Better stability of the products

Ex-Eno-fruit salt in sachets.

Disadvantages:

- High cost.
- Consumes more time and doubtful.
- Occupy more space for storing.
- Ledger posting and inventory control problem

Q. 41) Explain the term therapeutic drug monitoring?

- Therapeutic drug monitoring (TDM) refers to the measurement of drug concentrations in

biological fluids with the purpose of optimizing a patient's drug therapy. During administration of a dosage regimen, the concentration should be maintained within the therapeutic window. TDM is an important tool utilized, to individualize dosage regimen by maintaining plasma or blood drug concentrations within the therapeutic range.

• In general TDM is not used if the response to drug therapy can be directly and easily measured.

• The main goal of TDM is to ensure that a given drug dosage produce Maximum therapeutic benefit and minimum toxic effect.

- Drug must have an appropriate concentration at site of action that produces benefits

Q. 42) Give the need of TDM?

NEED FOR THERAPEUTIC DRUG MONITORING:

- TDM can be an important tool in selected situation. Some criteria of drug in TDM are given below

• Drug with narrow therapeutic index.

• Drug should exhibit non-linear pharmacokinetics.
• Should have a beneficial concentration response relationship between the blood drug conc. and pharmacological effects with respect to both efficacy and toxicity.
• There should be no easily measurable physiological parameter.

- TDM is used in two major situations

• To assist the optimization of drug therapy, including minimizing the risk of drug toxicity.
• To identify a drug or substance this may be contributing to the presentation of a medical emergency.

- There are some common clinical situations where therapeutic monitoring of drugs may be useful
- To confirm adequate serum concentrations where clinical response is inadequate
- TDM can be used to assess the appropriateness of dosing regimen to maintain the minimum concentration required to exhibit efficacy
- To avoid drug toxicity: maintaining a drug within the therapeutic range can help to minimize the risk of toxicity
- To individualize dosing of some drug with an unpredictable dose-response curve
- To assess medication compliance
- To help predict a patients dose requirements.
- To minimize the time period needed for dosage adjustment.
- To identify poisons and to assess the severity of poisoning on an emergency basis in a poisoned patient.
- To assist dose adjustment in various disease states where individual variations in drug ADME is important.

Q.43) Give the Causes Of Medication Non-Adherence

- Non-adherence with medication is a complex and multidimensional health care problem.
- The causes may be related to the patient, treatment, and/or health care provider. The patients may not believe the treatment is necessary complex treatment plans may increase the risk of nonadherence and there may be insufficient communication between patient and provider. As a consequence of nonadherence, substantial numbers of patients do not benefit optimally from medication, resulting in increased morbidity and mortality as well as increased societal costs.
- The elderly are a patient group that is vulnerable to negative health outcomes due to lack of adherence. Because older patients often use a variety of drugs for a number of chronic diseases, the consequences of nonadherence may be more serious, but nonadherence may be less easily detected and resolved than in younger age groups.
- Factors that may predict nonadherence include forgetfulness, illiteracy, inability to understand the purpose of treatment, not perceiving the treatment as necessary, a lack of trust in the treatment, and a lack of knowledge about the effects of treatment. In addition, psychiatric problems, including depression, cognitive limitations, missing visits, and a

poor relationship with the health care provider have also been found to contribute to nonadherence. Some of these factors are associated with intentional nonadherence, while others are more likely to be correlated with unintentional nonadherence.

- The number of co-morbid conditions and presence of cognitive, vision and/or hearing impairment may predispose the patient to nonadherence. Similarly, medications themselves may contribute to nonadherence secondary to adverse effects or costs.

Especially worrisome is nonadherence to 'less forgiving' drugs that, when missed may lead to an adverse event (e.g. withdrawal symptoms) or disease exacerbation.

- Non-adherence was associated with higher health care costs for both in- and outpatient settings. Patients need educated regarding non-adherence and increased costs.
- Non-adherence also incurred more costs for outpatient services and office visits.
- Several interventions may contribute to improved adherence.

ASSIGNMENT 1				
Question	**Details**	**Unit no. as per syllabus**	**CO mapped**	**Bloom's Taxonomy Level**
1	Define Hospital. Classify it on the basis of clinical parameter.	1	CO1	2
2	Explain food-drug interactions with examples.	1	CO2	2,3
ASSIGNMENT 2				
1	Define clinical pharmacy. Give different roles of clinical pharmacist.	4	CO3	2
2	Discuss the role of PTC in drug safety.	3	CO3	2,3

CLASS TEST-1					
Question	**Details**	**Marks**	**Unit no. as per syllabus**	**CO mapped**	**Bloom's Taxonomy Level**
1	Give any six functions of hospital.	5	1	CO 1	2
2	Define Adverse Drug Reaction. Classify ADR with examples.	5	1	CO 2	2,3
CLASS TEST-2					
1	Define Hospital formulary. Write about the guiding principles while using a hospital formulary.	5	2	CO 3	2,3
2	Write A Note On TDM.	5	2	CO 3	2

SUBJECT IV

BP 704T NOVEL DRUG DELIVERY SYSTEM

THEORY

SCHEME

BP704T Novel Drug Delivery System-Theory

SCHEME FOR TEACHING

Course of study for semester VI

Course Code	Course Name	No. of Hours per week			Credit Points
		Theory	Practical	Tutorial	
BP704T	NDDS	03	0	01	04

SCHEME FOR INTERNAL AND END SEMESTER EXAMINATIONS

Course code	Name of the course	Internal Assessment				End Semester Exams		Total Marks
		Continuous Assessment	Sessional Exams		Total	Marks	Duration	
			Marks	Duration				
BP704T	NDDS	10	15	01 hrs	25	75	03 hrs	100

SYLLABUS

BP704T Novel Drug Delivery System-Theory

Course Content

UNIT-I **10 Hours**

Controlled drug delivery systems: Introduction, terminology/definitions and rationale, advantages, disadvantages, selection of drug candidates. Approaches to design controlled release formulations based on diffusion, dissolution and ion exchange principles. Physicochemical and biological properties of drugs relevant to controlled release formulations

Polymers: Introduction, classification, properties, advantages and application of polymers in formulation of controlled release drug delivery systems

UNIT-II **10Hours**

Microencapsulation: Definition, advantages and disadvantages, microspheres /microcapsules, microparticles, methods of microencapsulation, applications

Mucosal Drug Delivery system: Introduction, Principles of bioadhesion /mucoadhesion, concepts, advantages and disadvantages, transmucosal permeability and formulation considerations of buccal delivery systems

Implantable Drug Delivery Systems: Introduction, advantages and disadvantages, concept of implants and osmotic pump

UNIT-III **10 Hours**

Transdermal Drug Delivery Systems: Introduction, Permeation through skin, factors affecting permeation, permeation enhancers, basic components of TDDS, formulation approaches

Gastroretentive drug delivery systems: Introduction, advantages, disadvantages, approaches for GRDDS – Floating, high density systems, inflatable and gastroadhesive systems and their applications

Nasopulmonary drug delivery system: Introduction to Nasal and Pulmonary routes of drug delivery, Formulation of Inhalers (dry powder and metered dose), nasal sprays, nebulizers

UNIT-IV **08Hours**

Targeted drug Delivery: Concepts and approaches advantages and disadvantages, introduction to liposomes, niosomes, nanoparticles, monoclonal antibodies and their applications

UNIT-V **07 Hours**

Ocular Drug Delivery Systems: Introduction, intra ocular barriers and methods to overcome –Preliminary study, ocular formulations and ocuserts

Intrauterine Drug Delivery Systems: Introduction, advantages and disadvantages, development of intra uterine devices (IUDs) and applications

BOOKS:

Recommended Books: (Latest Editions)

1. Y W. Chien, Novel Drug Delivery Systems, 2nd edition, revised and expanded, Marcel Dekker, Inc., New York, 1992.
2. Robinson, J. R., Lee V. H. L, Controlled Drug Delivery Systems, Marcel Dekker, Inc., New York, 1992.
3. Encyclopedia of Controlled Delivery. Edith Mathiowitz, Published by Wiley Interscience Publication, John Wiley and Sons, Inc, New York. Chichester/Weinheim
4. N.K. Jain, Controlled and Novel Drug Delivery, CBS Publishers & Distributors, New Delhi, First edition 1997 (reprint in 2001).
5. S.P. Vyas and R.K. Khar, Controlled Drug Delivery -concepts and advances, Vallabh Prakashan, New Delhi, First edition 2002.

Journals

1. Indian Journal of Pharmaceutical Sciences (IPA)
2. Indian Drugs (IDMA)
3. Journal of Controlled Release (Elsevier Sciences)
4. Drug Development and Industrial Pharmacy (Marcel & Decker)
5. International Journal of Pharmaceutics (Elsevier Sciences)

LESSION PLAN

BP704T Novel Drug Delivery System-Theory

Name of the faculty: Mrs. Archana S. Kadam

Lect. No.	Topics / Sub- Topics	Course Outcome/s Addressed	BL Level	Reference (Text Book, Website)
0	Orientation Program			
1	**Microencapsulation:** Introduction	CO3	1	N.K. Jain, Controlled and Novel Drug Delivery, Y W. Chien, Novel Drug Delivery Systems, Robinson, J. R., Lee V. H. L, Controlled Drug Delivery Systems
2	Concept of microencapsulation, merits and demerits.	CO3	1	
3	Types of Microencapsulation: Physical encapsulation processes	CO3	1, 2	
1 T				
4	Types of Microencapsulation: Physical encapsulation processes	CO3	1, 2	
5	Types of Microencapsulation: chemical encapsulation processes	CO3	1, 2	
6	Types of Microencapsulation: chemical encapsulation processes	CO3	1, 2	
2 T				
7	Types of Microencapsulation: chemical encapsulation processes	CO3	1, 2	
8	Types of Microencapsulation: mechanical encapsulation processes	CO3	1, 2	
9	Types of Microencapsulation: mechanical encapsulation processes	CO3	1, 2	
3 T				

10	Application of microencapsulation.	CO3	1, 2	
11	**Nasopulmonary drug delivery system:** Introduction to Nasal and Pulmonary routes of drug delivery	CO3	1	N.K. Jain, Controlled and Novel Drug Delivery, Y W. Chien, Novel Drug Delivery Systems, Robinson, J. R., Lee V. H. L, Controlled Drug Delivery Systems
12	Formulation of Inhalers (dry powder and metered dose), nasal sprays, nebulizers	CO3	1	
4 T				
13	Recent advances, objectives of therapeutic aerosols	CO3	1	
14	Fundamentals and principle of design, drug substances	CO3	1	
15	Important physicochemical properties of aerosol system solutions	CO3	1	
5 T				
16	Suspensions and emulsions	CO3	1	
17	Formulation design and stability	CO3	1, 3	
18	Typical formulations from, metered dose, intranasal and topical applications	CO3	1, 2	
6 T				
19	Factors influencing drug deposition, manufacturing techniques.	CO3	1, 3	
20	Product evaluation including safety considerations	CO3	1, 3	
21	**Controlled Drug Release :** Definitions of controlled release, sustained release time release drug delivery Systems.	CO1	1, 3	
7 T				

22	Pre requisites of drug candidates.	CO1	1, 3	
23	Various approaches and Classification.	CO1	1, 3	
24	Dose calculation for controlled release & sustained release. Robinson Eriksen equation.	CO1	1, 3	
8 T				
25	Mucosal drug delivery system	CO3	1, 3	N.K. Jain, Controlled and Novel Drug Delivery, Y W. Chien, Novel Drug Delivery Systems, Robinson, J. R., Lee V. H. L, Controlled Drug Delivery Systems
26	Transdermal drug delivery system(TDDS)	CO3	1, 2	
27	Transdermal drug delivery system(TDDS)	CO3	1, 2	
9 T				
28	Parenteral implants	CO3	1	
29	Parenteral implants	CO3	1	
30	Ophthalmic inserts	CO3	1	
10 T				
31	Intrauterine drug delivery system (IUDs)	CO3	1	
32	Liposomes	CO3	1	
33	Liposomes	CO3	1	
11 T				
34	Gastro retentive drug delivery system	CO3	1	
35	Gastro retentive drug delivery system	CO3	1	
36	Osmotic drug delivery system	CO3	1	
12 T				
37	Colon targeted drug delivery system	CO3	1	
38	Externally modulated devices and delivery; iontophoresis	CO3	1	

	and sonophoresis.			
39	Introduction to nanoparticulate drug delivery system	CO3	1	
13 T				
40	**Polymers**- Introduction to polymers, classification (biodegradable /nonbiodegradable),	CO2	1	N.K. Jain, Controlled and Novel Drug Delivery
41	Environment responsive polymers.	CO2	1	
42	Parameters affecting selection of polymers for modified release systems, application and examples.	CO2	1	
14 T				
43	Evaluation techniques.	CO2	1	N.K. Jain, Controlled and Novel Drug Delivery, Y W. Chien, Novel Drug Delivery Systems, Robinson, J. R., Lee V. H. L, Controlled Drug Delivery Systems
44	monoclonal antibodies	CO3	1	
45	monoclonal antibodies	CO3	1	
15 T				

Note: 1.Home Assignment will be given after completion of each unit.

2. Class Test I & II will be conduct as per the schedule of Academic Calendar.

COURSE DELIVERY, OBJECTIVES, OUTCOMES

BP704T Novel Drug Delivery System-Theory

Course Delivery:

The course will be delivered through lectures, class room interaction, and presentations.

Course Objectives:

Upon the completion of the course student shall be able to

1. Understand various approaches for development of novel drug delivery systems.
2. Understand the criteria for selection of drugs and polymers for the development of Novel drug delivery systems, their formulation and evaluation.
3. Describe the Fundamental Concept of Modified Drug Release and Prerequisites of drug candidates, along with various approaches and classification
4. Describe Polymers with respect to introduction to polymers, classification, types, selection, application and examples.
5. Describe. Introduction, formulation, merits, demerits, application and evaluation of Novel Drug Delivery Systems
6. Explain Therapeutic Aerosols along with typical formulations from, metered dose, intranasal and topical applications,
7. Explain concept of microencapsulation, merits, demerits and application, Types of Microencapsulation and Evaluation of microcapsules

Course Outcomes (COs):

After successful completion of course student will able to

Upon the completion students are able to **CO-PO**

CO1	Understand **[L2:Understanding]** and describe the basic concept, design **[L6:Creating]** and types of controlled drug delivery system.
CO2	Understand **[L2:Understanding]** and describe the selection, types and application of polymers.
CO3	Understand **[L2:Understanding]** and study the concept behind, formulation and evaluation **[L5:Evaluating]** of novel drug delivery system like particulate drug carrier, pulmonary drug delivery system, nasopulmonary DDS, TDDS, mucoadhesive DDS and microencapsulation etc.

Mapping of Course Outcome (CO) with Program Outcome (PO) and Program Specific Outcome (PSO)

1: Slight (Low) 2: Moderate (Medium) 3: Substantial (High)

If there is no correlation, put "-"

CO	PO1	PO2	PO3	PO4	PO5	PO6	PO7	PO8	PO9	PO10	PO11	PSO1	PSO2	PSO3	PSO4
CO1	3	3	3	3	-	-	-	-	3	-	3	3	3	2	3
CO2	3	2	3	3	-	-	-	-	-	-	3	3	3	2	3
CO3	3	3	3	3	-	-	-	-	-	-	3	3	3	2	3
Average	3	2.5	3	3	-	-	-	-	3	-	3	3	3	2	3

Justification of CO-PO Mapping

CO1 with PO1	CO1 is aligned with PO1 because CO1 gives the Highly basic knowledge of the pharmacy.
CO1 with PO2	CO1 is aligned with PO2 because it is relevant with the formulation and evaluation of modified release DDS
CO1 with PO3	CO1 is aligned with PO3 because it deals with the formulation of modified release DDS related problems and its solution
CO1 with PO4	CO1 is aligned with PO4 because it deals with formulation and evaluation of modified release DDS and it uses modern techniques and tools for conducting pharma based studies
CO1 with PO9	CO1 is aligned with PO9 because it is related to treatment of disease and has local and global impact of pharmacy on individuals, organizations, and society.
CO1 with PO11	CO1 is aligned with PO11 because it correlate the pharmaceutical principals of modified release DDS, demonstrate the knowledge and apply it at work place for continuous professional development.
CO2 with PO1	CO2 is aligned with PO1 because it deals with the basic pharmacy knowledge of polymers used in formulation of different DDS
CO2 with PO2	CO2 is aligned with PO2 because it moderately deals with formulation and evaluation of polymer based DDS using time and resource management
CO2 with PO3	CO2 is aligned with PO3 because it deals with the formulation of polymer related problems and its solution
CO2 with PO4	CO2 is aligned with PO4 as it deals with use of modern tools and techniques for formulation and evaluation of polymers.
CO 2with PO11	CO2 is aligned with PO11 because it deals with implementation of

	knowledge of polymers for pharma process and developing novel DDS for better therapeutic effect
CO3 with PO1	CO3 is aligned with PO1 because it gives the basic knowledge of the pharmacy and various novel drug delivery systems.
CO3 with PO2	CO3 is aligned with PO2 because it deals with design and evaluation of novel drug delivery systems to meet desired pharmacological action
CO3 with PO3	CO3 is aligned with PO3 because it deals analyzing and solving problem related development of NDDS
CO3 with PO4	CO3 is aligned PO4 as it is related to use of modern tools and methods for formulation, evaluation of novel drug delivery systems.
CO 3 with PO11	CO3 is aligned with PO11 because it deals with implementation of knowledge of novel drug delivery systems in the formulation of drug delivery system
Justification of CO-PSO Mapping	
CO1 with PSO1	CO1 is aligned with PSO1 because it deals with the technical knowledge of subject
CO1 with PSO2	CO1 is aligned with PSO2 because it deals with application of methods and modern tools for formulation and evaluation of Modified release DDS
CO1 with PSO3	CO1 is aligned with PSO3 because it deals with evaluation of Modified release DDS.
CO1 with PSO4	CO1 is aligned with PSO4 because it deals with the knowledge of process of formulation of Modified release DDS to meet desired need
CO2 with PSO1	CO2 is aligned with PSO1 because it deal with the theoretical knowledge about the polymers
CO2 with PSO2	CO2 is aligned with PSO2 because it deals with use of modern tools for analyzing formulation and evaluation of polymers
CO2 with PSO3	CO2 is aligned with PSO3 because it involve analyzing and evaluating polymers
CO2 with PSO4	CO2 is aligned with PSO4 because it deals health and safety related to use of polymers for drug delivery system
CO3 with PSO1	CO3 is aligned with PSO1 because it deals with the development of technical knowledge of NDDS
CO3 with PSO2	CO3 is aligned with PSO2 because it deals with new techniques of NDDS
CO3 with PSO3	CO3 is aligned with PSO3 because it deals with the evaluation of NDDS
CO3 with PSO4	CO3 is aligned with PSO4 because it deals with understanding the process of formulation of NDDS

QUESTION BANK

BP704T Novel Drug Delivery System-Theory

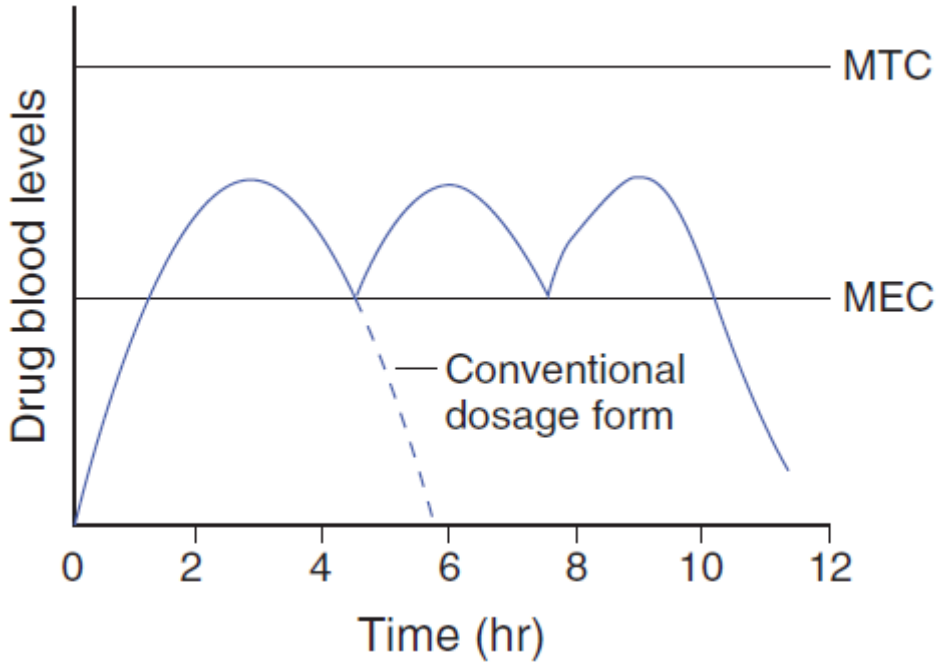
Q. No	Questions	CO mapped	Bloom level
	Controlled Drug Release		
Q.1	Define and discuss concept of Controlled release, sustained release time release drug delivery Systems	CO1	2,3,4
Q.2	Pre requisites of drug candidates-Note	CO1	2
Q.3	Note on Robinson Eriksen equation	CO1	2,3
Q.4	Discuss in brief Classification of Controlled release drug delivery Systems	CO1	3, 4
	Polymers		
Q.5	Discuss Classification of polymer	CO2	1,2
Q.6	Explain parameters affecting selection of polymers for modified release systems	CO2	3
Q.7	Note on Evaluation techniques of polymers	CO2	3
	Novel Drug Delivery Systems		
Q.8	Note on Mucosal drug delivery system	CO3	2,3,4
Q.9	Note on Transdermal drug delivery system	CO3	2,3,4
Q.10	Note on Parenteral implants	CO3	2,3,4
Q.11	Note on Ophthalmic inserts	CO3	2,3,4
Q.12	Note on Intrauterine drug delivery system (IUDs)	CO3	2,3,4
Q.13	Note on Liposomes	CO3	2,3,4
Q.14	Note on Probiotics andPrebiotic	CO3	2,3,4
Q.15	Note on Grastro retentive drug delivery system	CO3	2,3,4
Q. 16	Note on monoclonal antibodies	CO3	2,3
Q. 17	Note on Nasal formulations	CO3	2,3,4
	Microencapsulation		
Q.18	Write a note on merits, demerits and application of microencapsulation	CO3	2,3,4

MODEL ANSWERS

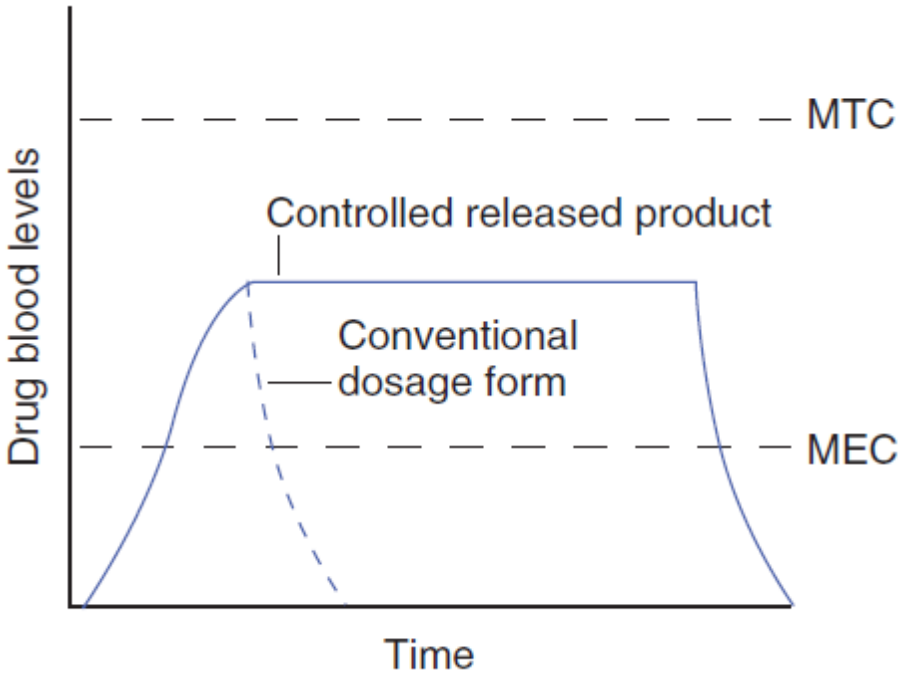
BP704T Novel Drug Delivery System-Theory

Q.1 Define and discuss concept of Controlled release, sustained release time release drug delivery Systems.

Some drugs are inherently long lasting and require only once-a-day oral dosing to sustain adequate drug blood levels and the desired therapeutic effect. These drugs are formulated in the conventional manner in immediate release dosage forms. However, many other drugs are not inherently long lasting and require multiple daily dosing to achieve the desired therapeutic results. Multiple daily dosing is inconvenient for the patient and can result in missed doses, made up doses, and noncompliance with the regimen. When conventional immediate-release dosage forms are taken on schedule and more than once daily, they cause sequential therapeutic blood level peaks and valleys (troughs) associated with the taking of each dose.



However, when doses are not administered on schedule, the resulting peaks and valleys reflect less than optimum drug therapy. For example, if doses are administered too frequently, minimum toxic concentrations of drug may be reached, with toxic side effects resulting. If doses are missed, periods of sub therapeutic drug blood levels or those below the minimum effective concentration may result, with no benefit to the patient. Extended-release tablets and capsules are commonly taken only once or twice daily, compared with counterpart conventional forms that may have to be taken three or four times daily to achieve the same therapeutic effect. Typically, extended-release products provide an immediate release of drug that promptly produces the desired therapeutic effect, followed by gradual release of additional amounts of drug to maintain this effect over a predetermined period.



The sustained plasma drug levels provided by extended-release products oftentimes eliminate the need for night dosing, which benefits not only the patient but the caregiver as well. For non oral rate controlled drug delivery systems, the drug release pattern ranges in duration from 24 hours for most transdermal patches to 3 months for the estradiol vaginal ring insert.
Some advantages of extended-release systems are given in Table.

ADVANTAGE	EXPLANATION
Less fluctuation in drug blood levels	Controlling rate of release eliminates peaks and valleys of blood levels
Frequency reduction in dosing	Extended-release products frequently deliver more than a single dose, hence may be taken less often than conventional forms
Enhanced convenience and compliance	With less frequency of dosing, a patient is less apt to neglect taking a dose; also greater convenience with day and night administration
Reduction in adverse side effects	Because of fewer blood level peaks outside therapeutic range and into toxic range, adverse side effects are less frequent
Reduction in overall health care costs	Although initial cost of extended-release dosage forms may be greater than for conventional forms, overall cost of treatment may be less because of enhanced therapeutic benefit, fewer side effects, reduced time for health care personnel to dispense and administer drugs and monitor patients

Some disadvantages are the loss of flexibility in adjusting the drug dose and/or dosage regimen and a risk of sudden and total drug release, or dose dumping, due to a failure of technology.

MODIFIED RELEASE

In recent years, *modified release* has come into general use to describe dosage forms having drug release features based on time, course, and/ or location that are designed to accomplish therapeutic or convenience objectives not offered by conventional or immediate-release forms.

EXTENDED RELEASE

The U.S. Food and Drug Administration (FDA) defines an extended-release dosage form as one that allows a reduction in dosing frequency from that necessitated by a conventional dosage form, such as a solution or an immediate-release dosage form.

DELAYED RELEASE

A delayed-release dosage form is designed to release the drug at a time other than promptly

after administration. The delay may be time based or based on the influence of environmental conditions, like gastrointestinal pH.

REPEAT ACTION

Repeat-action forms usually contain two single doses of medication, one for immediate release and the second for delayed release. Two-layer tablets, for example, may be prepared with one layer of drug for immediate release with the second layer designed to release drug later as either a second dose or in an extended-release manner.

TARGETED RELEASE

Targeted release describes drug release directed toward isolating or concentrating a drug in a body region, tissue, or site for absorption or for drug action.

Q.2 Pre requisites of drug candidates-Note

Not all drugs are suited for formulation into extended-release products, and not all medical conditions require treatment with such a product. The drug and the therapeutic indication must be considered jointly in determining whether or not to develop an extended-release dosage form.

PARAMETERS FOR DRUG TO BE FORMULATED IN SUSTAINED RELEASE DOSAGE FORM:

Physicochemical parameters for drug selection.

1. Molecular weight/size < 1000 Daltons.
2. Solubility > 0.1 mg/ml for pH 1 to pH 7.8.
3. Apparent partition coefficient High.
4. Absorption mechanism Diffusion.
5. General absorbability from all GI segments.
6. Release should not be influenced by pH and enzymes.

Pharmacokinetic parameters for drug selection

1. Elimination half-life preferably between 2 to 8 hrs
2. Total clearance should not be dose dependent
3. Elimination rate constant required for design
4. Apparent volume of distribution (Vd) The larger Vd and MEC, the larger will be the required dose size
5. Absolute bioavailability should be 75% or more
6. Intrinsic absorption rate must be greater than release rate
7. Therapeutic concentration Css The lower Css and smaller Vd, the loss among of drug required.
8. Toxic concentration Apart the values of MTC and MEC, safer the dosage form. Also suitable for drugs with very short half-life.

Table 1. Physicochemical parameters for drug selection

Parameters	**Criteria**
Molecular size	Less than 600 Daltons
Aqueous solubility	More than 0.1mg/ml
Partition coefficient Ko/w	1-2
Dissociation constant pka	Acidic drugs, pka>2.5 Basic drugs, pka<11.0

Parameters	Criteria
Absorption mechanism	Passive
Stability in GI milieu	Stable at both gastric and intestinal pH
Ionization at physiological pH	Not more than 95%

Table 2. Pharmacokinetic parameters for drug selection

Parameters	Comment
Elimination half life	Between 2-6 hrs
Absolute bioavailability	> 75% or more
Absorption rate constant (Ka)	High
Metabolism Rate	Not too High
Total clearance	Should not depend on dose
Therapeutic concentration (Css)	Lower Css and small Vd

FACTORS AFFECTING THE ORAL SUSTAIN RELEASE DOSAGE FORM DESIGN

A) Pharmacokinetics and pharmacodynamics factor:

1. Biological half-life

Drug with biological half-life of 2-8 hours are considered suitable candidate for sustain release dosage form, since this can reduce dosing frequency. However this is limited in that drugs with very short biological half lives may require excessive large amounts of drug in each dosage unit to maintain sustained effects, forcing the dosage form itself to become limitingly large.

2. Absorption

Rate of absorption of a sustained formulating depends upon release rate constant of the drug from the dosage form, and for the drugs that are absorbed by active transport the absorption is limited to intestine.

3. Distribution

The distribution of drugs into tissues can be important factor in the overall drug elimination kinetics. Since it not only lowers the concentration of circulating drug but it also can be rate limiting in its equilibrium with blood and extra vascular tissue, consequently apparent volume of distribution assumes different values depending n the time course of drug disposition. Thus for design of sustain release products, one must have information of disposition of drug.

4. Metabolism

The metabolic conversion to a drug is to be considered before converting into another form. Since as long as the location, rate, and extent of metabolism are known a successful sustain release product can be developed.

B) Drug properties relevant to sustain release formulation:

1. Dose size

A dose size of 500-1000mg is considered maximal for a conventional dosage form. This also holds true for sustain release dosage forms. Since dose size consideration serves to be a parameter for the safety involved in administration of large amounts with narrow therapeutic range.

2. Ionization, pka and aqueous solubility

Most drugs are weak acids or bases and in order for a drug to get absorbed, it must dissolve in the aqueous phase surrounding the site of administration and then partition into the absorbing membrane.

3. Partition coefficient

Bioavailability of a drug is largely influenced by the partition coefficient, as the biological membrane lipophilic in nature transport of drug across the membrane largely depends upon the partition coefficient of the drug. Drugs having low partition coefficient are considered as poor candidate for the sustain release formulation as it will be localized in the aqueous phase eg: Barbituric acid and vice a versa.

4. Drug stability

When drugs are orally administered, they come across acid-base hydrolysis and enzymatic degradation. In this case, if the drug is unstable in stomach, drug release system which provides medication over extended period of time is preferred, whereas in contrast the drug unstable in intestine will face problem of less bioavailability

Q.3 Note on Robinson Eriksen equation

The total dose of drug for a sustained release formulation was calculated by following four equations using pharmacokinetic data from a design of one compartment model with simultaneous release of loading dose and a zero order release maintenance dose, as described by Robison and Eriksen

$$k_0 = D_i k_e \quad (1)$$

$$D_m = k_0 T \quad (2)$$

$$D_i = D_i - k_0 T_p \quad (3)$$

$$D_t = D_i + D_m \quad (4)$$

.

Q.4 Discuss in brief Classification of Controlled release drug delivery Systems

Sustained Release Dosage Form

Sustained release dosage form is defined as well characterized and reproducible dosage form, which is designed to control drug release profile at a specified rate to achieve desired drug concentration either in blood plasma or at target site.

This system will provide actual therapeutic control that would be temporal (time related), spatial (site related) or both.

Advantages of sustained drug delivery system:

• Reduced see-saw fluctuations.
• Total amount of dose decreases.
• Improved patient compliance.
• Increased safety of drugs.

Disadvantages of sustained drug delivery system:

• Chances of dose dumping.
• Dose retrieval is difficult.
• High cost of formulation.
• Need for additional patient education.
• Reduced potential for accurate dose adjustment **(Figure 1)**.

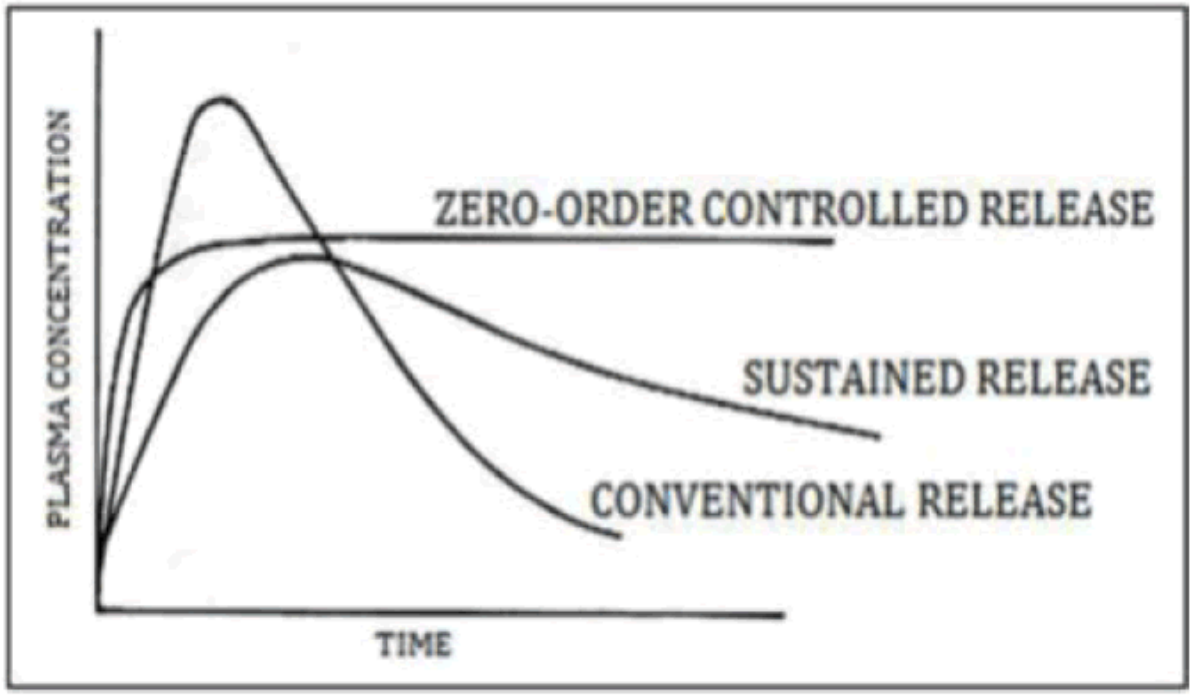


Figure 1. Plasma drug concentration vs. time profile for oral conventional dosing and single oral dose of sustained and controlled release formulation

Figure 1: Plasma drug concentration vs. time profile for oral conventional dosing and single oral dose of sustained and controlled release formulation

The performance of a drug presented as a controlled/sustained release system depends upon its:

• Release from the formulation.
• Movement within the body during its passage to the site of action.

Formulation Strategies for Oral Sustained Release System

Diffusion Sustained Release
Dissolution Sustained Release
pH Dependent System
Altered Density System
Osmotic Pump System
Ion Exchange System

Types of diffusion sustained system:

• Swellable matrix.
• Reservoir/Laminate matrix.
Types of dissolution sustained system:
• Matrix/Monolith Dissolution System.
• Encapsulation/Coating/Reservoir System.
Types of altered density system:
• High Density System.
• Low Density System.
• Muco Adhesive System

Diffusion sustained system: These systems are those where the rate controlling step is not the dissolution rate of the drug but diffusion of the dissolved drug molecule. Depending upon the mechanism such system can be classified as:

Porous membrane controlled system: In these type of system the rate controlling element is a water insoluble non swellable polymer like ethyl cellulose, polymethaacrylate etc. which controls the drug release through the micro pores present in their membrane or matrix structure **(Figure 2)**.

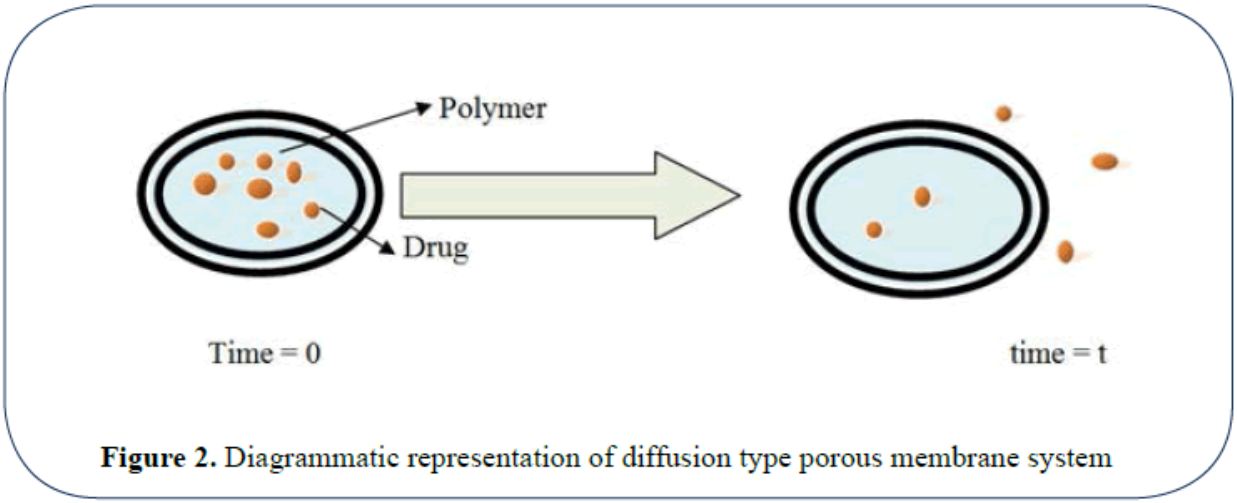


Figure 2. Diagrammatic representation of diffusion type porous membrane system

Figure 2: Diagrammatic representation of diffusion type porous membrane system

Advantages
• Can provide zero order drug release.

Disadvantages
• High cost per dosage unit.
• In case of dose dumping toxicity can take place.

Porous matrix controlled system: In these type of system the rate controlling element is a water swellable material (hydrophilic polymers and gums) like alginates, xanthan gum, locust bean gum, HPMC etc. or a non swellable water insoluble polymer like ethyl cellulose **(Figure 3)**.

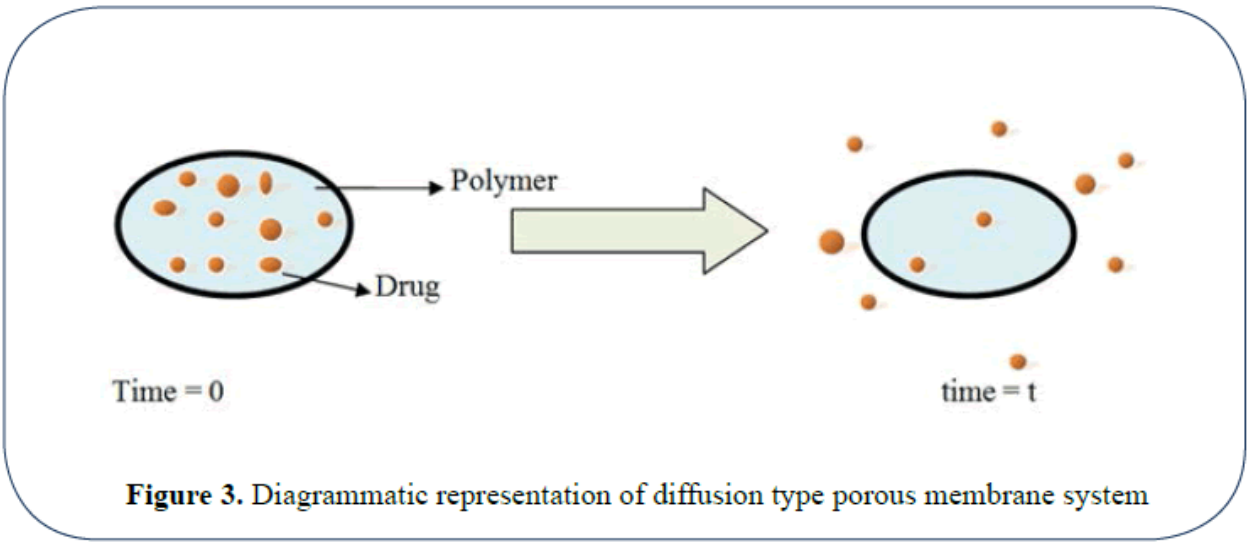


Figure 3. Diagrammatic representation of diffusion type porous membrane system

Figure 3: Diagrammatic representation of diffusion type porous membrane system

Advantages

• Cost effective.
• Easy to fabricate.
• Drug could be protected from hydrolysis or other changes in GIT, so enhanced stability.
• Compounds with high molecular weight could be formulated.

Disadvantages

• Release rate is affected by presence of food.
• Matrix must be removed after the release of drug.

Dissolution sustained system

The drugs with slow solubility are suitable candidates for this system and for the drugs having high solubility the dissolution is decreased by conversion into a suitable salt or derivative.

Drug present in this system may be of two types:

• Drugs with inherently slow dissolution rate. e.g. griseofulvin, digoxin, nifedipine etc.
• Drugs that transforms into a slow dissolving form on coming in contact with GI fluids. e.g. Ferrous sulphate.
• Drugs having high aqueous solubility and dissolution rate.

These systems can further be categorized as:

Coating dissolution system: In this type of system the drug particles are coated with polymers like cellulose, polymethacrylates, PEGs etc. The resulting pellets are compressed as tablets. The dissolution rate of the coat depends upon thickness and solubility of coat **(Figure 4)**.

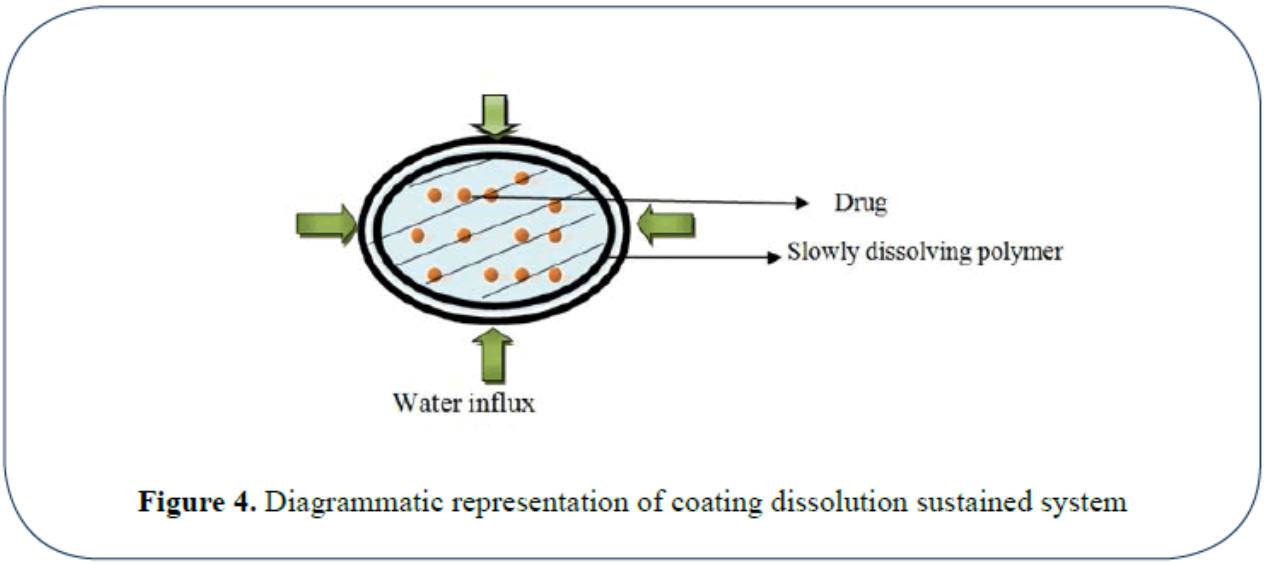


Figure 4. Diagrammatic representation of coating dissolution sustained system

Figure 4: Diagrammatic representation of coating dissolution sustained system

Soluble matrix system: These systems are also known as monoliths as the drug is homogenously dispersed in a rate controlling medium. Waxes like bee wax, carnauba wax etc. are used for controlling the dissolution rate.

The rate of dissolution is controlled by either of following mechanisms:

• Altering the rate of fluid penetration into tablet by altering the porosity of tablet.

• Decreasing the wettability of tablet.

• Slow dissolution rate of polymer **(Figure 5)**.

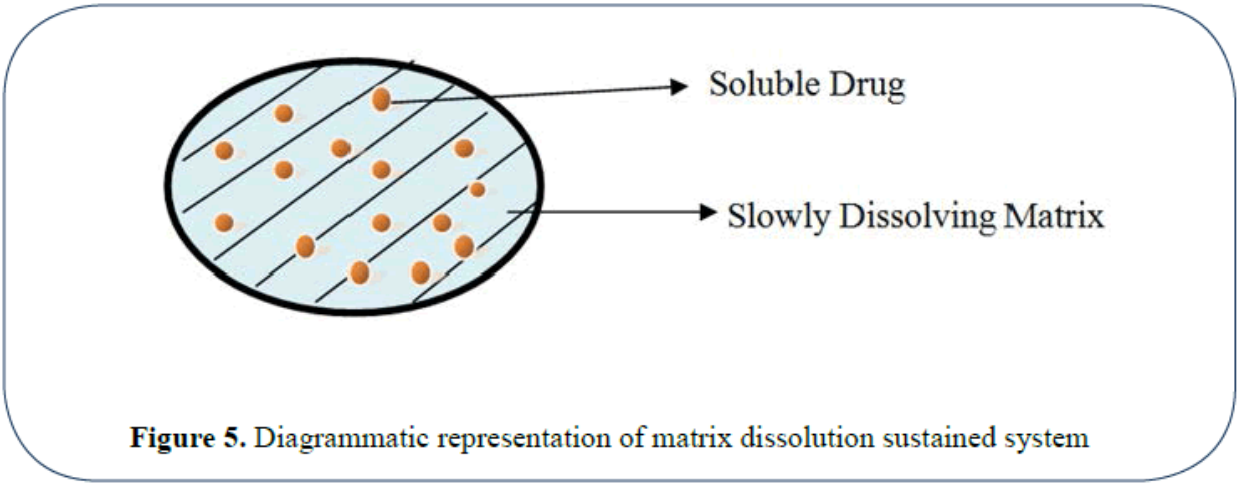


Figure 5. Diagrammatic representation of matrix dissolution sustained system

Figure 5: Diagrammatic representation of matrix dissolution sustained system

Ion exchange resins: Based upon the principle that GIT has a relatively constant level of ions, this type of system has developed for controlling the rate of delivery of ionisable or ionic drugs. Such a system can be prepared by incubating the drug resin solution or by passing the drug solution through a column containing exchange resin. A cationic drug is complexed with a resin containing SO_3^- group and for anionic drug resin containing $N(CH_3)_3$ group is used. In the GIT hydronium and chloride ions diffuses into the sustained release tablet and interact with drug resin complex to trigger the release of drug.

+Types of ion exchange resins:

Cationic exchange resin: Contains acidic functional group.

Anion exchange resin: Contains basic functional group.

These systems prevent dose dumping as they have better drug retaining properties. So, chances of toxicity are reduced. Moreover, the polymeric and ionic property of ion exchange resin makes the drug release more uniform than that of simple matrices.

Method using osmotic pump: Osmotic systems are based on the principle of osmosis. Such systems release the drugs at a constant zero order rate. These systems are popularly known as OROS.

The system consist of a drug core and an osmotically active substance (osmogen) like mannitol surrounded by a semipermeable membrane coating with an orifice of 0.4 mm made by laser beam to facilitate drug exit. When exposed to GI Fluids, water flows though semipermeable membrane, under the influence of osmotic force of osmogen the drug release is facilitated via orifice.

These systems could be of two types:

In type-A system drug solution along with osmogen is surrounded by a semi permeable membrane.

In type-B system, the drug solution is present in a semi permeable membrane surrounded by the electrolytes **(Figure 6)**.

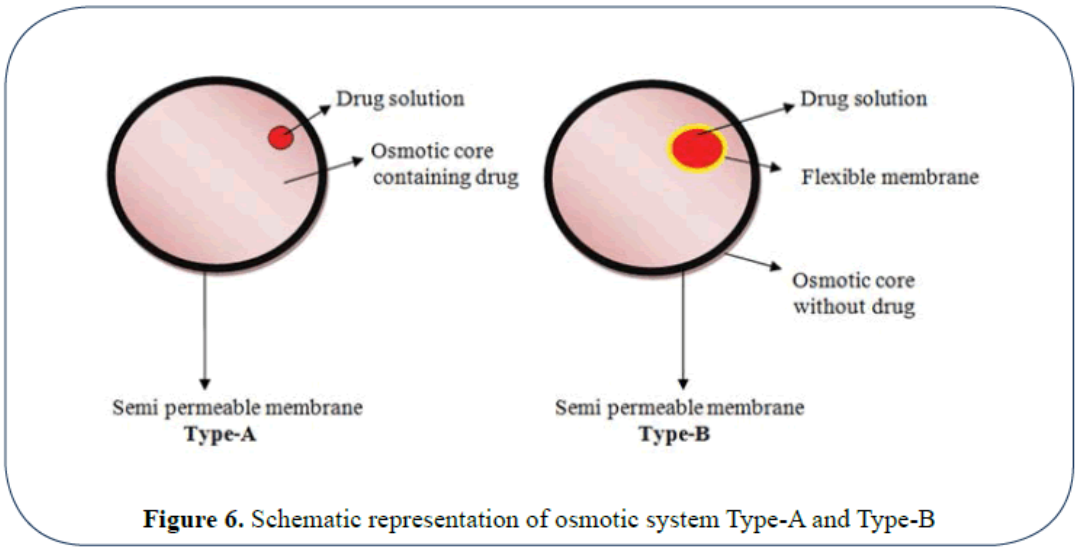


Figure 6. Schematic representation of osmotic system Type-A and Type-B

Figure 6: Schematic representation of osmotic system Type-A and Type-B

pH independent formulations: These systems are designed for acid-labile drugs or drugs irritating GIT mucosa and targeting their delivery to the intestinal tract. It is fabricated by coating the core of tablet with a combination of intestinal fluid insoluble polymer (ethyl cellulose) and intestinal fluid soluble polymer (HPMCP). The coating membrane resists the dissolution of drug in stomach at acidic pH. After gastric emptying the system travels to small intestine. At a pH above 5 the intestine soluble component dissolves; thereby producing a porous membrane that controls the release of drug from the core of the tablet.

Altered density formulations: The transit time of GI contents is usually less than 24 hours. This is major limiting factor in design of sustained release formulation. If the residence time of drug in stomach or intestine is prolonged the frequency of dosing can further be reduced. This could be achieved by altering the density of drug particles, using mucoadhesive polymers or by altering the size of dosage form.

Altered density formulation can further be classified as:

i) High density approach

The density of GI fluids is about 1.4 g/ cc so the drug particles having density greater than this value usually 1.6 g/cc can be used for this purpose. These systems have prolonged residence time and not affected by presence of food. Iron oxide and barium sulfate can be used for this purpose.

ii) Low density approach

These pellets have density lower than that of GI fluids. So, such tablets tend to float on gastric juice for an extended time period thereby slowing down the drug release. Such system can be formulated by granulating a drug with 20- 80% of hydrogel like HPMC, HPC and HEC. On contact with GI fluids, tablets swells and form a diffusible gel barrier that lowers the density of the system lower than 1; thereby allowing it to float.

Matrix Tablet

Matrix tablet is defined as "Oral solid dosage form in which active pharmaceutical ingredient is uniformly dispersed throughout polymeric matrices (hydrophilic or hydrophobic) which retards the drug release rate.

This approach is widely used for formulating the sustained release tablets. The mechanism involved in the drug release is either dissolution controlled or diffusion controlled.

Advantages of matrix system:

• Easy to manufacture.
• Cost effective.
• Improved patient compliance.
• Sustained release formulations avoid the high blood concentration.
• Reduce drug toxicity by slowing down drug absorption.
• Enhanced drug stability in GI milieu.
• Minimize the local and systemic side effects.
• No see-saw fluctuations in plasma drug concentration profile.
• Less amount of drug is required.
• Temporal effects can be provided. e.g. morning relief of arthritis through bed time dosing.

Disadvantages of matrix tablets:

• Matrix needs to be removed after drug release.
• Costly in comparison to conventional dosage form.
• Presence of food and gut transition time can affect the release rate.

Classification of Matrix Tablets

A) On the basis of retardant material used matrix can be divided into 5 types:

Hydrophobic matrices (plastic matrices):

In this technique hydrophobic inert polymer are used as release retarding matrix material. The drug is mixed with the hydrophobic inert polymer (e.g. polyethylene, poly vinyl chloride, ethyl cellulose) and then compressed into tablet. The drug is entrapped between the network channels of polymer particles thereby sustaining the release of drug.

Lipid matrices:

Lipid material is used as release retardant (e.g. carnauba wax in combination with stearyl alcohol). Mechanism involved in drug release includes both pore diffusion and matrix erosion.

Hydrophilic matrices:

In this type of system a variety of hydrophilic polymers can be used, such systems are also known as swellable matrices. These polymers are more preferred than former ones as they are cost effective and a desirable drug profile can be easily obtained.

Classification of hydrophilic polymer matrices:

• **Cellulose derivatives:** Methyl cellulose 400 and 4000cPs; Hydroxy ethyl cellulose, Hydroxy propyl methyl cellulose (HPMC) 25, 100, 4000 and 15000cPs and Sodium carboxy methyl cellulose.

• **Non cellulose natural and semi-synthetic polymers:** Agar-Agar; alginates; carob gum; molasses; polysaccharides of galactose and mannose; chitosan and modified starches.

• **Polymer of acrylic acid:** carbopol-934.

Biodegradable polymers:

These consist of biodegradable polymers that are degraded either by enzymatic or non enzymatic process into by products which are excreted out from the body e.g. Polyanhydrides, proteins, polysaccharides.

Mineral matrices: Species of sea weeds like alginic acid are used as release retardants **(Tables 3 and 4)**.

Table 3. Classification of matrix tablets on the basis of porosity of matrix

S No.	Type	Pore size	Mechanism involved
1	Macro Porous System	0.1-1µm	Diffusion through pore of matrix
2	Micro Porous System	50-200Å	Diffusion through pore of matrix
3	Non Porous System	----------	Diffusion through network meshes

Table 4. Polymers used in matrix tablet

S No.	Polymer Class	Example
1	Hydrogels	Cross-linked polyvinyl alcohol (PVA), Cross-linked polyvinyl pyrrolidone(PVP), Polyethylene oxide (PEO)
2	Soluble polymers	Polyvinylpyrrolidone (PVP), Hydroxypropyl methyl cellulose (HPMC)
3	Biodegradable polymers	Polylactic acid (PLA), Polyglycolic acid (PGA)
4	Mucoadhesive polymers	Polyacrylic acid, Tragacanth, Methyl cellulose, Pectin
5	Non-Biodegradable Polymers	Cellulose acetate (CA), Ethyl cellulose (EC)
6	Natural gums	Guar gum, Karaya gum, Locust bean gum

Mechanism of drug release: The mechanism involved in drug release includes either diffusion or dissolution. On exposure with aqueous solution hydration of matrix takes place as a result it swells to block up existing pores, dissolution of the contents takes place. Due to gel formation a viscous solution is formed which give rise to a positive pressure which opposes the liquid entry and causes the disintegration of matrix.

The swelling of the matrix and consequent drug release by diffusion from the matrix and erosion of the matrix is as shown in **(Figures 7 and 8)**.

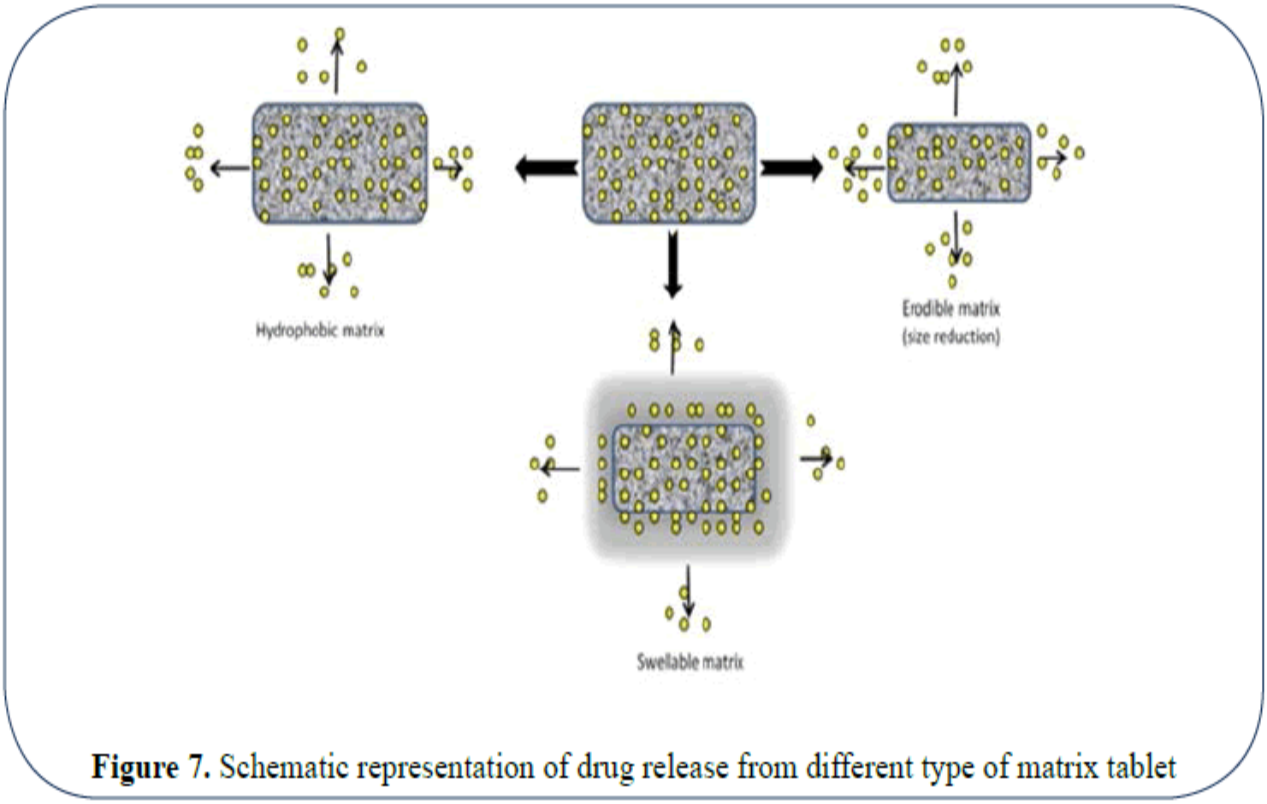


Figure 7. Schematic representation of drug release from different type of matrix tablet

Figure 7: Schematic representation of drug release from different type of matrix tablet

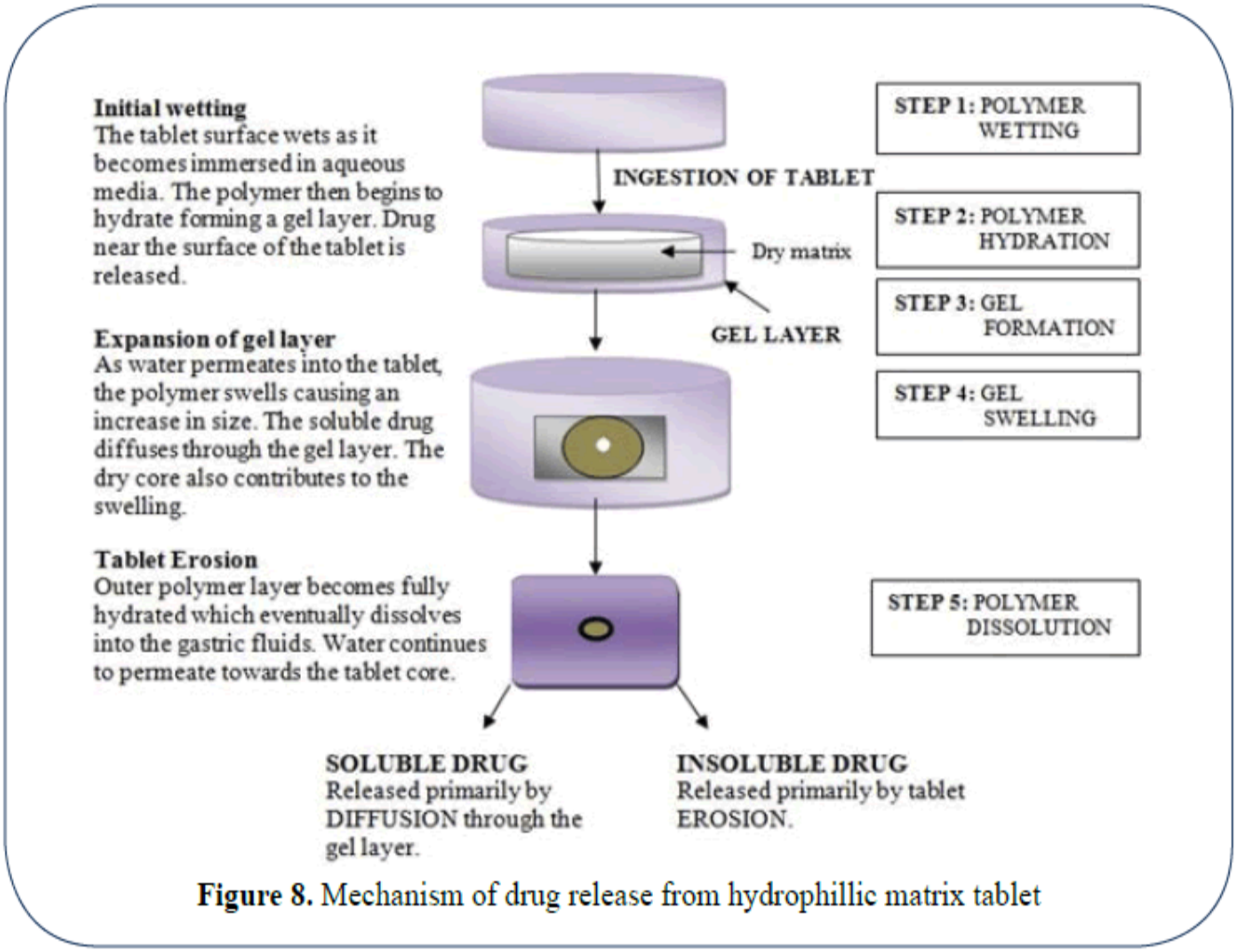


Figure 8. Mechanism of drug release from hydrophillic matrix tablet

Figure 8: Mechanism of drug release from hydrophillic matrix tablet

Evaluation of Oral Sustained Release Tablets

Thickness of tablet: Thickness of tablet is evaluated by using micrometer screw gauge. Test is carried out randomly on twenty tablets and average values are calculated.

Hardness of tablet: Hardness of tablet of each batch is evaluated by monsantto hardness tester and average values are calculated.

Uniformity of weight: 20 tablets are selected randomly and weighed individually and collectively; average weight is calculated **(Table 5)**.

Table 5. Average weight of tablet showing permissible percentage deviation

S No.	Average weight of tablet deviation	Percentage
1	80 mg or less	10
2	More than 80 mg or less than 250 mg	7.5
3	250 mg or more	5

% of weight variation=(Individual Weight- Average weight/Average Weight) × 100

Uniformity of content: This test is done to make sure that every tablet should contain the same amount of active ingredient with little or no variation within a batch. For content uniformity test 30 tablets are selected and 10 are assayed individually. At least 9 must assay between ±15% of the declared potency and should not exceed ±25%

Friability: 20 tablets are weighed and placed in friabilator. The chamber is rotated for 4 minutes at a speed of 25 r.p.m. the tablets are removed from the chamber and weighed again. Loss in weight indicates friability. The tablets to be considered of good quality if loss in weight is less than 0.8%

In vitro dissolution studies: The test is carried out to measure the amount of time required for certain percentage of drug to go into the solution under the specific test conditions. Rotating paddle type and rotating basket type apparatus can be used as per pharmacopoeial standards or as mentioned in monograph of particular drug.

The test is passed if for each of the five tablets, the amount of active ingredient in solution is not less than 70% of the stated amount or as specified in the monograph of the API in pharmacopoeia.

Q. 5 Discuss Classification of polymer

Polymer type:

Silicon derivatives have been used in the past for fabrication of controlled release matrix systems, but now water soluble or biodegradable polymers are used. Polymers that are sufficiently polar can interact with an aqueous medium and generate sufficient energy to disperse polymer chains from glassy state. Although many polymers have been widely used in drug deliver, hydro-polymers such as cellulose ether perhaps the most often used. Water-insoluble polymers such as ethyl cellulose have been reported to have utility in controlled release matrix systems. Some important parameters, which need consideration during the selection of polymer include viscosity, hydration rate and glass transition temperature.

Excipients:

The physicochemical properties of excipients present in the system should be well controlled to provide reproducible performance. Studies of possible interactions between excipients in the solid dosage forms are necessary because these interactions can affect the drug release and bioavailability. The presence of hydrophobic diluents can result in a more resistant gel layer which reduces the infiltration of aqueous medium and drug diffusion. The addition of soluble fillers enhances the dissolution of soluble drugs, while insoluble fillers affect the diffusion rate. Incorporation of surfactants may result in an increase in drug release rate through improved wetting or solubilization. Binding agents used during the granulation process coat the drug particles and also change the rheology of the gel layer, leading to retardation in release rates .However , the degree of retardation is determined by the swelling and hydrating capacities of the binding agent, amount of binder added and the method of addition .Other excipients such as plasticizers, may enhance drug release rates, due to the increased dissolution rate of plasticized polymer, while generally used lubricants will retard drug release rates because of their hydrophobic nature.

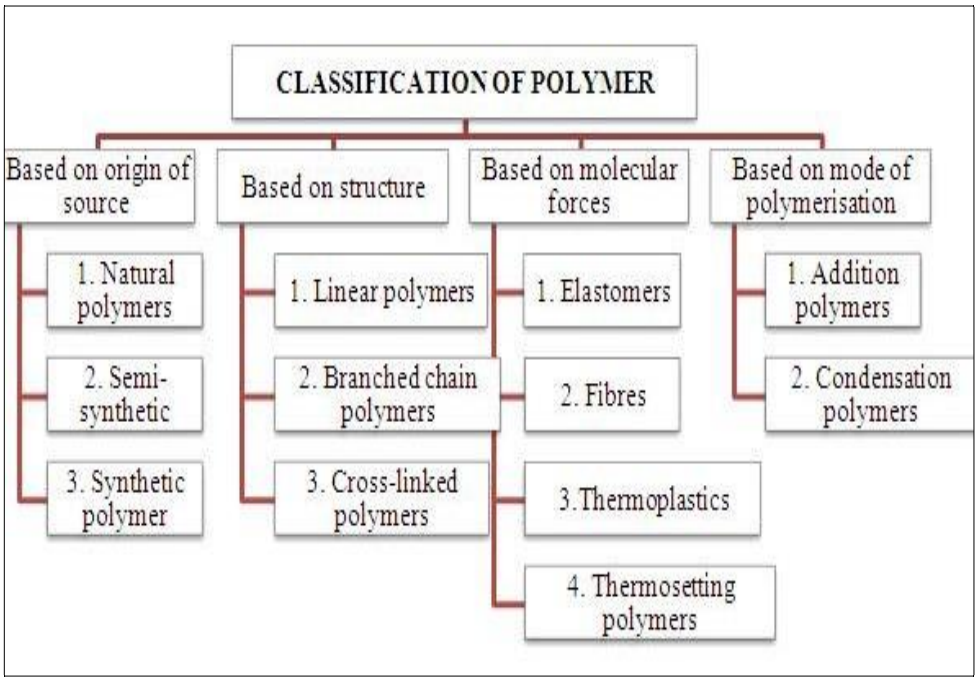
THE POLYMERS:

Polymers in the technology of prolonged release drug formulations macro-molecules have also found the application in the technology of prolonged release drug formulations. They are mainly intended to ensure the constant concentration of the therapeutic agent in the certain time (e.g.8-24 hours), in the patient body. The group of these drugs, therefore, can eliminate the drug multiple dosing during a day and reduce total daily dose of it. The prolonged drug forms are usually applied in the therapy of cardiac and alimentary tract diseases, coronory vessels, diabetics, psychiatric disorders. The absorption of the therapeutic agent using prolonged release

drug forms can be reduced by coating, incorporation, complexation or bonding on the ionites.

Polymer Classification

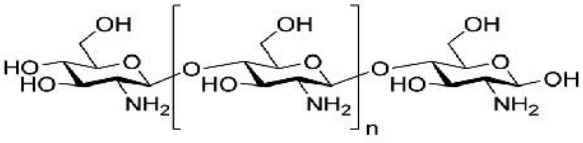
The polymers are classified in to various types based on different categories. They are



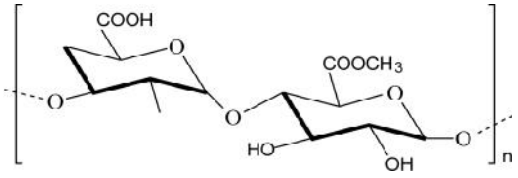
Examples of polymers based on origin are

1) Natural polymers:

Ex: Chitosan, pectin, alginate, gelatin, albumin, collagen, cyclo dextrin.



(a)

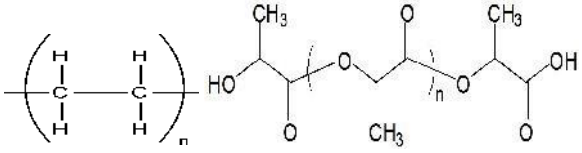


(b)

Fig : Chemical structure of (a) chitosan and (b) pectin

2) Synthetic polymers:

Ex: Polyethylene, polylactic acid, polypropylene, polyglycolic acid, polyhydroxybuterate, polyanhydride, polyacrylamide.

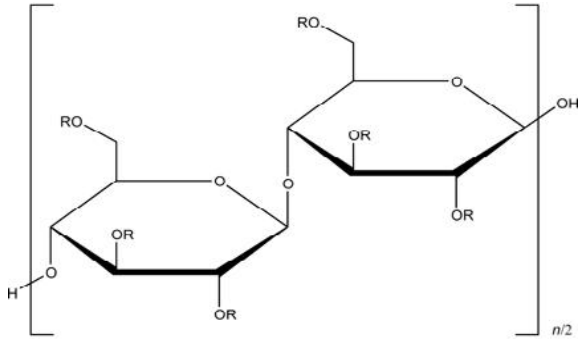


(a) (b)

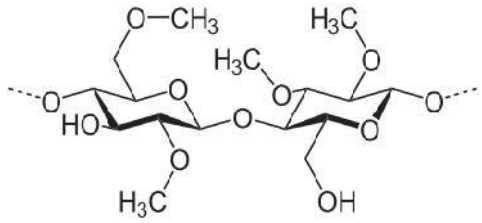
Fig : Chemical structure of (a) polyethylene and (b) polylactic acid

3) Semi synthetic polymers:

Ex: Hydroxyl propyl cellulose, methyl cellulose, hydroxyl propyl methyl cellulose, hydroxyl ethyl cellulose,sodium CMC(carboxy methyl cellulose).



(a)



(b)

Fig : Chemical structure of (a) Hydroxyl propyl cellulose and (b) methyl cellulose

Based On Degradation Polymers Are Classified In To Various Types,

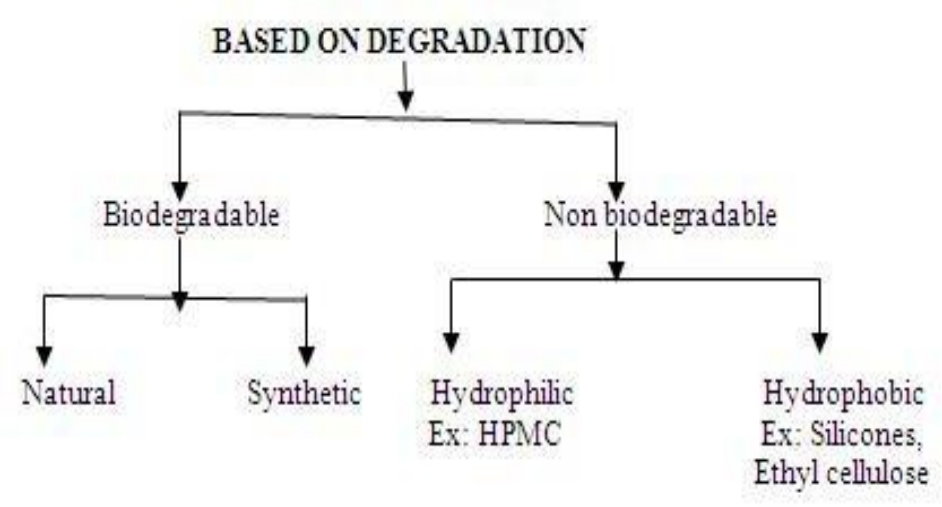


Fig 8: Classification of polymer based on degradation

Biodegradable macromolecules are definitely more preferred from the toxicological point of view. In the technology of prolonged release drug formulation, natural polymers and their modified derivative (e.g. starch, cellulose) as well as synthetic polymers are used e.g., polyacrylamides, polyacrylates and polyethyleneglycol.

An appropriate selection of the polymer matrix is necessary in order to develop a successful drug delivery system.

A major disadvantage with non-degradable polymer is that a surgery is required to harvest these polymers out of the body once they are depleted of the drug. Hence, non-degradable polymers can be used only if removal of the implant is easy.

Degradable polymers do not require surgical removal and hence are preferred for drug delivery applications. They degrade to smaller absorbable molecules, it is important to make sure that the monomers are non toxic in nature. The most commonly used polymers for this application are Polylactide (PLA) and Poly Lactide co Glycolide (PLGA). These polymers have been used in biomedical applications for more than 20 years and are known to be biodegradable, biocompatible and non toxic.

Q. 6 Explain parameters affecting selection of polymers for modified release systems

Factors Affecting Biodegradation of Polymers

- Chemical structure.
- Chemical composition.

- Distribution of repeat units in multimers.
- Presents of ionic groups.
- Presence of unexpected units or chain defects.
- Configuration structure.
- Molecular weight.
- Molecular-weight distribution.
- Morphology (amorphous/semicrystalline, microstructures, residual stresses).
- Presence of low-molecular-weight compounds.
- Processing conditions.
- Annealing.
- Sterilization process.
- Storage history.
- Shape.
- Site of implantation.
- Adsorbed and absorbed compounds (water, lipids, ions, etc.).
- Physicochemical factors (ion exchange, ionic strength, pH).
- Physical factors (shape and size changes, variations of diffusion coefficients, mechanical stresses, stress- and solvent-induced cracking, etc.).
- Mechanism of hydrolysis (enzymes versus water).

Q. 7 Note on Evaluation techniques of polymers

1 Physicochemical stability and acid/alkali solubility tests

(1) Particle size of the test substance Pulverize the test substance into grains as small as possible. 60-80 mesh is recommended.

(2) pH range of the test liquid Adjust the pH to 4.0, 7.0, 9.0 and 1.2, as adopted in 111 "Hydrolysis as a Function of pH" in The OECD (Organization for Economic Co-operation and Development) Guidelines for the Testing of Chemicals (OECD Council Decision [C(81)30 Final Appendix 1]).

(3) Testing temperature 40±2°C.

(4) Light Indoor light.

(5) Air Stir the test liquid to facilitate its contact with air.

(6) Testing period Two weeks, except for the testing period for pH 1.2, which is 24 hours, considering the retention time in digestive organs.

(7) Test concentration of the test substance Set the concentration within the range of 102 -104 mg/l in accordance with the properties of the test substance (1,000 mg/l is recommended).

(8) Number of repetitions n=2

(9) Analysis Analyze as many of the following parameters as possible at the beginning and end of the test to detect any chemical change. Dissolved oxygen concentration (DOC), weight, molecular weight and infrared absorption spectrum etc.

2 Solubility in water and organic solvents

(1) Test solvents

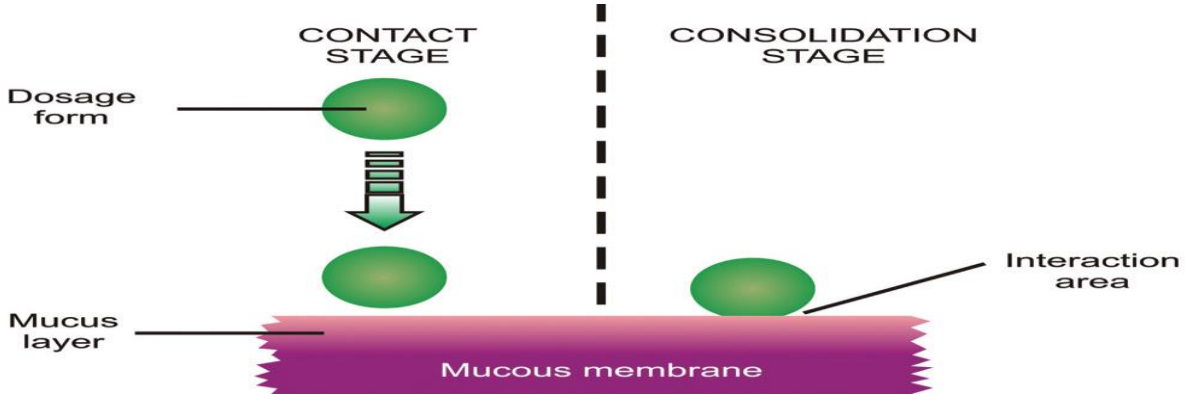
(i) As indices for lipophilicity n-octanol, n-heptane.

(ii) As general solvents Toluene, 1,2-dichloroethane, Isopropyl alcohol, THF (Tetrahydrofuran), MIBK (Methyl isobutylketon), DMF (Dimethyl formamide).
(iii) Water
(2) Testing conditions
(i) Temperature Stir at 35-40°C and subsequently cool to 25±2°C to achieve equilibrium.
(ii) Testing period Twenty-four hours.
(iii) Test concentrations of the test substance Test at two concentrations, i.e., 200 mg/l and 2,000 mg/l. (iv) Particle size of the test substance Pulverize the test substance into grains as small as possible. 60- 80 mesh is recommended.
(v) Number of repetitions Two repetitions.
(vi) Stirring constantly stir or shake the test liquid to facilitate contact between the test substance and the solvent.
(vii) Analysis Perform a gravimetric analysis. For water, also perform a total organic carbon (TOC) analysis. Perform as many instrumental analyses as possible for other organic solvents depend on the properties of the test substance.
(3) Evaluation of solubility as a general rule, confirm the insolubility of the test substance in nine solvents. If the test substance has been confirmed to be soluble in one of the nine solvents, the remaining eight solvents do not necessarily need to be tested. However, it is recommended that solubility data on at least one solvent from each of the categories 2 (1)(i) to (iii) are submitted.
3 Molecular Weight Distribution Measurement As a general rule, if the test substance has been confirmed to be soluble in 2(3), perform molecular weight distribution measurement by gel permeation chromatography (GPC) paying attention to the following points:
(1) Molecular weight calculation method Choose from the following methods depends on the nature of the test substance.
(i) Primary reference standard (Polyethylene glycol, polystyrene).
(ii) Secondary reference standard (1-2 substances with known molecular weight or weight average molecular weight).
(iii) Method based on extended-chain length.
(iv) Method based on hydrodynamic volume.
(2) Stability The base line should be straight.
(3) Detector response sensitivity preferably, the response sensitivity shows no dependence on molecular weight (correct the measurement if it shows dependence).
(4) Separation preferably, the peak of the polymer does not overlap the peaks of other substances (additives, impurities in solvents, etc.).
(5) How to draw a baseline in the low-molecular-weight region preferably, take the average of the two charts with stable baselines.

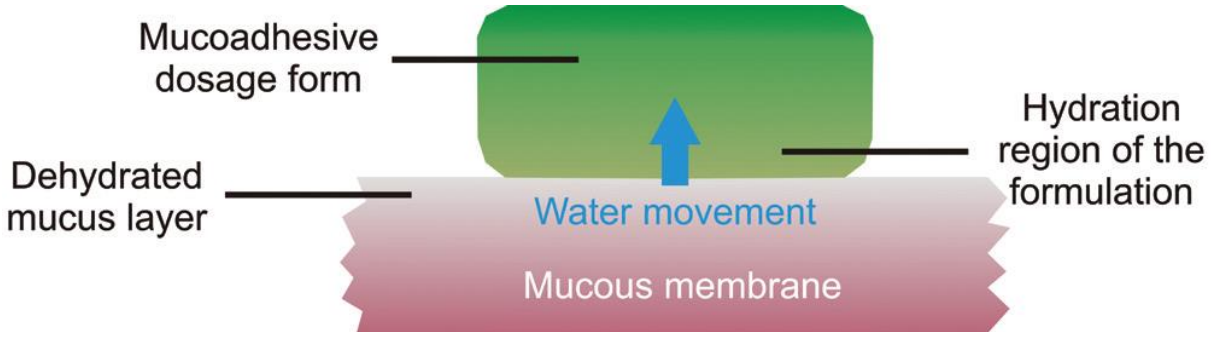
Q. 8 Note on Mucosal drug delivery system
MECHANISMS OF MUCOADHESION
The mechanism of adhesion of certain macromolecules to the surface of a mucous tissue is not well understood yet. The mucoadhesive must spread over the substrate to initiate close contact and increase surface contact, promoting the diffusion of its chains within the mucus. Attraction and repulsion forces arise and, for a mucoadhesive to be successful, the attraction forces must

dominate. Each step can be facilitated by the nature of the dosage form and how it is administered. For example, a partially hydrated polymer can be adsorbed by the substrate because of the attraction by the surface water.

Thus, the mechanism of mucoadhesion is generally divided in two steps, the contact stage and the consolidation stage (Figure 1). The first stage is characterized by the contact between the mucoadhesive and the mucous membrane, with spreading and swelling of the formulation, initiating its deep contact with the mucus layer. In some cases, such as for ocular or vaginal formulations, the delivery system is mechanically attached over the membrane. In other cases, the deposition is promoted by the aerodynamics of the organ to which the system is administered, such as for the nasal route. On the other hand, in the gastrointestinal tract direct formulation attachment over the mucous membrane is not feasible. Peristaltic motions can contribute to this contact, but there is little evidence in the literature showing appropriate adhesion. Additionally, an undesirable adhesion in the esophagus can occur. In these cases, mucoadhesion can be explained by peristalsis, the motion of organic fluids in the organ cavity, or by Brownian motion. If the particle approaches the mucous surface, it will come into contact with repulsive forces (osmotic pressure, electrostatic repulsion, etc.) and attractive forces (van der Waals forces and electrostatic attraction). Therefore, the particle must overcome this repulsive barrier.



In the consolidation step (Figure 1), the mucoadhesive materials are activated by the presence of moisture. Moisture plasticizes the system, allowing the mucoadhesive molecules to break free and to link up by weak van der Waals and hydrogen bonds. Essentially, there are two theories explaining the consolidation step: the diffusion theory and the dehydration theory. According to diffusion theory, the mucoadhesive molecules and the glycoproteins of the mucus mutually interact by means of interpenetration of their chains and the building of secondary bonds. For this to take place the mucoadhesive device has features favoring both chemical and mechanical interactions. For example, molecules with hydrogen bonds building groups (–OH, –COOH), with an anionic surface charge, high molecular weight, flexible chains and surface-active properties, which induct its spread throughout the mucus layer, can present mucoadhesive properties.



According to dehydration theory, materials that are able to readily gelify in an aqueous environment, when placed in contact with the mucus can cause its dehydration due to the difference of osmotic pressure. The difference in concentration gradient draws the water into the formulation until the osmotic balance is reached. This process leads to the mixture of formulation and mucus and can thus increase contact time with the mucous membrane. Therefore, it is the water motion that leads to the consolidation of the adhesive bond, and not the interpenetration of macromolecular chains. However, the dehydration theory is not applicable for solid formulations or highly hydrated forms.

MUCOADHESION THEORIES

Although the chemical and physical basis of mucoadhesion are not yet well understood, there are six classical theories adapted from studies on the performance of several materials and polymer-polymer adhesion which explain the phenomenon.

Electronic theory

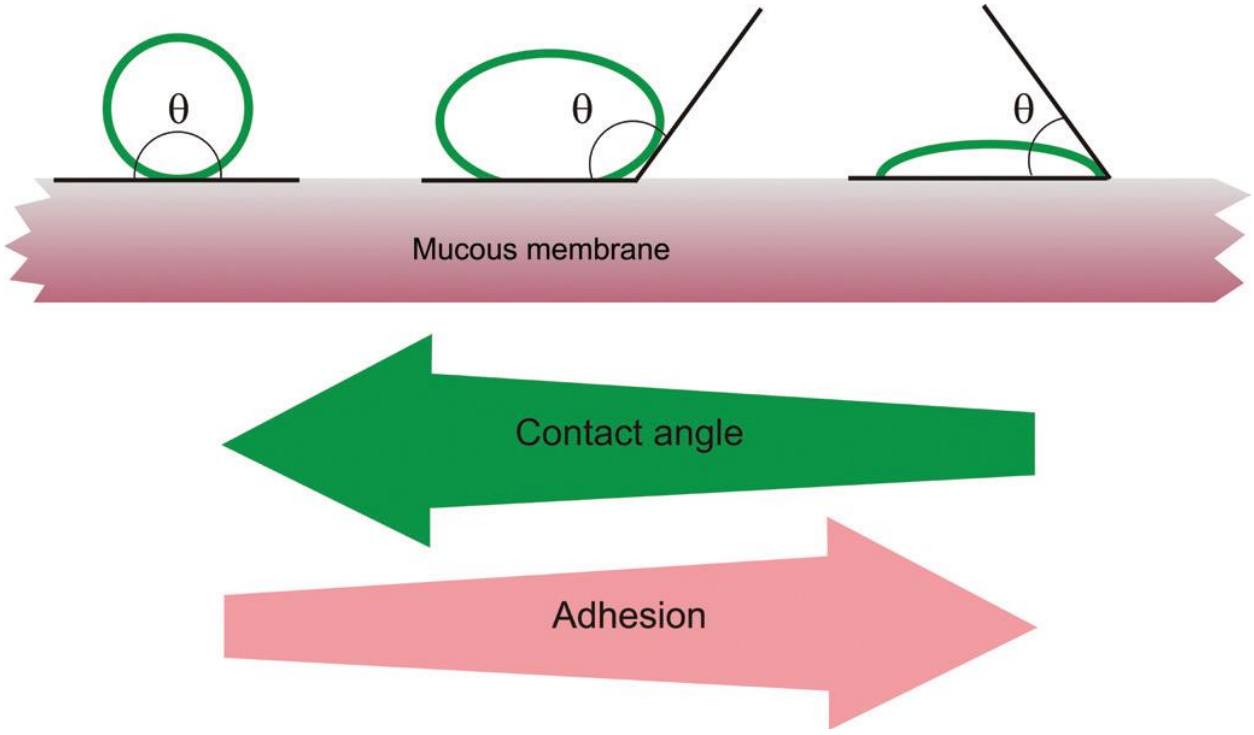
Electronic theory is based on the premise that both mucoadhesive and biological materials possess opposing electrical charges. Thus, when both materials come into contact, they transfer electrons leading to the building of a double electronic layer at the interface, where the attractive forces within this electronic double layer determines the mucoadhesive strength.

Adsorption theory

According to the adsorption theory, the mucoadhesive device adheres to the mucus by secondary chemical interactions, such as in van der Waals and hydrogen bonds, electrostatic attraction or hydrophobic interactions. For example, hydrogen bonds are the prevalent interfacial forces in polymers containing carboxyl groups. Such forces have been considered the most important in the adhesive interaction phenomenon because, although they are individually weak, a great number of interactions can result in an intense global adhesion.

Wetting theory

The wetting theory applies to liquid systems which present affinity to the surface in order to spread over it. This affinity can be found by using measuring techniques such as the contact angle. The general rule states that the lower the contact angle then the greater the affinity (Figure 3). The contact angle should be equal or close to zero to provide adequate spreadability.



The spreadability coefficient, *SAB*, can be calculated from the difference between the surface energies *γB* and *γA* and the interfacial energy *γAB*, as indicated in equation (1).

$$S_{AB} = \gamma_B - \gamma_A - \gamma_{AB} \qquad (1)$$

The greater the individual surface energy of mucus and device in relation to the interfacial energy, the greater the adhesion work, *WA*, i.e. the greater the energy needed to separate the two phases.

$$W_A = \gamma_A + \gamma_B - \gamma_{AB} \qquad (2)$$

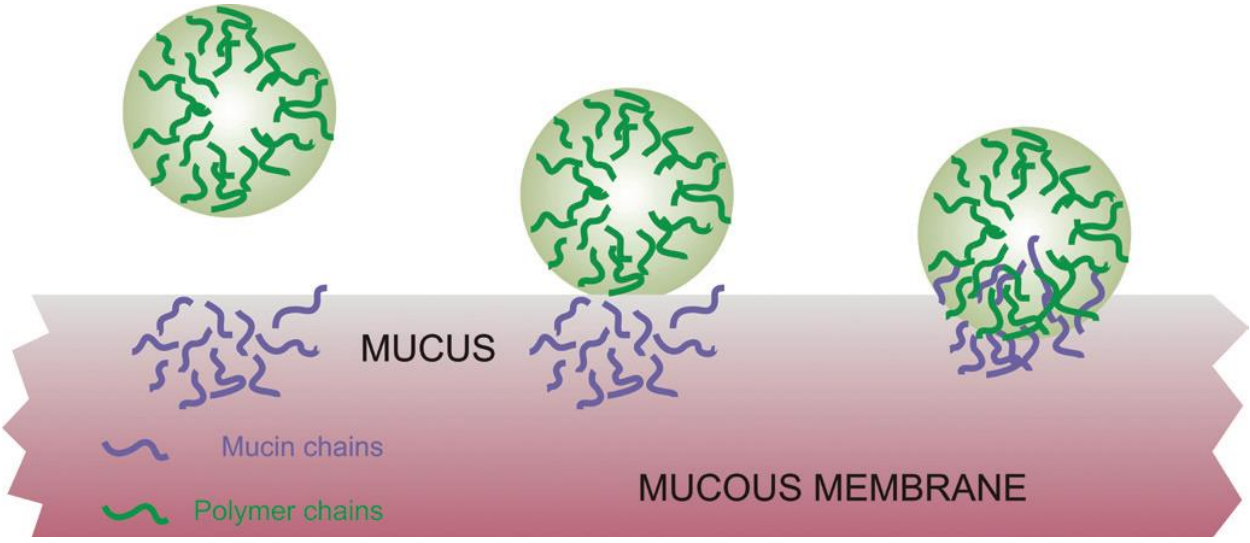
Diffusion theory

Diffusion theory describes the interpenetration of both polymer and mucin chains to a sufficient depth to create a semi-permanent adhesive bond (Figure 4). It is believed that the adhesion force increases with the degree of penetration of the polymer chains. This penetration rate depends on the diffusion coefficient, flexibility and nature of the mucoadhesive chains, mobility and contact time. According to the literature, the depth of interpenetration required to produce an efficient bioadhesive bond lies in the range 0.2-0.5 μm. This interpenetration depth of polymer and mucin chains can be estimated by equation 3:

$$l = (tD_b)^{1/2} \qquad (3)$$

where *t* is the contact time, and *Db* is the diffusion coefficient of the mucoadhesive material in the mucus. The adhesion strength for a polymer is reached when the depth of penetration is approximately equivalent to the polymer chain size.

In order for diffusion to occur, it is important that the components involved have good mutual solubility, that is, both the bioadhesive and the mucus have similar chemical structures. The greater the structural similarity, the better the mucoadhesive bond.



Fracture theory

This is perhaps the most-used theory in studies on the mechanical measurement of mucoadhesion. It analyses the force required to separate two surfaces after adhesion is established. This force, *sm*, is frequently calculated in tests of resistance to rupture by the ratio of the maximal detachment force, *Fm*, and the total surface area, *A0*, involved in the adhesive interaction (equation 4):

$$s_m = \frac{F_m}{A_0} \qquad (4)$$

In a single component uniform system, the fracture force, *sj*, which is equivalent to the maximal rupture tensile strength, *sm*, is proportional to the fracture energy (*gc*), for Young's module (*E*) and to the critical breaking length (*c*) for the fracture site, as described in equation 5: (5)

$$s_f \sim \left(\frac{g_c E}{c} \right)^{1/2} \quad (5)$$

Fracture energy (*gc*) can be obtained from the reversible adhesion work, *Wr* (energy required to produce new fractured surfaces), and the irreversible adhesion work, *Wi* (work of plastic deformation provoked by the removal of a proof tip until the disruption of the adhesive bond), and both values are expressed as units of fracture surface (*Af*).

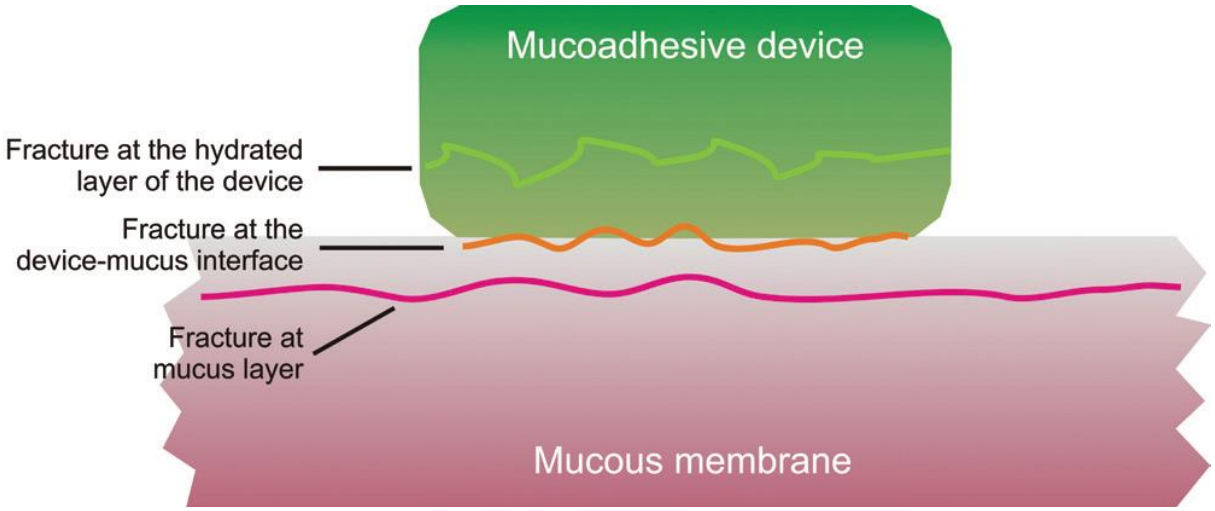
$$g_c = W_r + W_i \quad (6)$$

The elastic module of the system (*E*) is related to the stress (*s*) and to the shear (*e*) by Hooke's law:

$$E = \left[\frac{\sigma}{\varepsilon} \right]_{\varepsilon \to 0} = \left[\frac{F / A_0}{\Delta l / l_0} \right]_{\Delta l \to o} \quad (7)$$

In equation 7, the stress is the ratio between force (*F*) and area (*A0*), and shear is given by the ratio between the variation of system thickness (D*l*) and the original thickness (*l0*).

A criticism of this analysis is that the system under investigation must have known physical dimensions and should be constituted by a single and uniform material. In virtue of this, the relationship obtained cannot be applied to analyze the fracture site of a multiple component bioadhesive. In this case, the equation should be expanded to accommodate elastic dimensions and modules for each component. Besides, it must be considered that a failure of adhesion will occur at the bioadhesive interface. However, it has been demonstrated that the rupture rarely occurs at the surface, but near it or at the weakest point, which can be the interface itself, the mucus layer or the hydrated region of the mucus, as illustrated in Figure 5.



Since the fracture theory is concerned only with the force required to separate the parts, it does not take into account the interpenetration or diffusion of polymer chains. Consequently, it is appropriate for use in the calculations for rigid or semi-rigid bioadhesive materials, in which the polymer chains do not penetrate into the mucus layer.

Mechanical theory

Mechanical theory considers adhesion to be due to the filling of the irregularities on a rough surface by a mucoadhesive liquid. Moreover, such roughness increases the interfacial area available to interactions thereby aiding dissipating energy and can be considered the most important phenomenon of the process.

It is unlikely that the mucoadhesion process is the same for all cases and therefore it cannot be described by a single theory. In fact, all theories are relevant to identify the important process variables.

The mechanisms governing mucoadhesion are also determined by the intrinsic properties of the formulation and by the environment in which it is applied. Intrinsic factors of the polymer are related to its molecular weight, concentration and chain flexibility. For linear polymers, mucoadhesion increases with molecular weight, but the same relationship does not hold for non-linear polymers. It has been shown that more concentrated mucoadhesive dispersions are retained on the mucous membrane for longer periods, as in the case of systems formed by *in situ* gelification. After application, such systems spread easily, since they present rheological properties of a liquid, but gelify as they come into contact the absorption site, thus preventing their rapid removal. Chain flexibility is critical to consolidate the interpenetration between formulation and mucus.

Environment-related factors include pH, initial contact time, swelling and physiological variations. The pH can influence the formation of ionizable groups in polymers as well as the formation of charges on the mucus

Q.9 Note on Transdermal drug delivery system

A transdermal patch or skin patch is a medicated adhesive patch that is placed on the skin to deliver a specific dose of medication through the skin and into the bloodstream.

Advantages of transdermal patches

The advantages of transdermal delivery are obvious even delivery of a therapeutic level of drug is painless, the patient does not need to inject himself, there are no bulky delivery devices to manage or dangerous needles to dispose of, and there are few or no gastrointestinal effects from the drug itself. Peak plasma levels of the drug are reduced, leading to decreased side effects. In addition, transdermal delivery is useful for those drugs that have a high first pass effect through the liver, have poor oral uptake, need frequent administration, or that interact with stomach acid. The first pass effect results in the destruction of a significant amount of the drug.

Drugs absorbed through the skin, however, enter the general circulation directly avoiding the liver, with less total drug absorption occurring

 Topical patches are a painless, noninvasive way to deliver substances directly into the body.

 Topical patches are a better way to deliver substances that are broken down by the stomach acids, not well-absorbed from the gut, or extensively degraded by the liver.

 Topical patches over a controlled, steady delivery of medication over long periods of time.

 Topical patches have fewer side effects than oral medications or supplements.

 Topical patches are easier to use and remember.

 Topical patches over an alternative to people who cannot, or prefer not to take medications or supplements orally.

 Topical patches are cost-effective.

 People prefer topical patches.

Limitation

 TDDS cannot deliver ionic drugs.

 TDDS cannot achieve high drug levels in blood/plasma.

 It cannot develop for drugs of large molecular size.

 TDDS cannot deliver drugs in a pulsatile fashion.

 TDDS cannot develop if drug or formulation causes irritation to skin

RATIONALE FOR TRANSDERMAL DRUG DELIVERY

Given that the skin offers such an excellent barrier to molecular transport, the rationale for this delivery strategy needs to be carefully identified. Clearly, there are several instances in which the most convenient of drug intake methods (the oral route) is not feasible and when alternative routes must be sought.

Although intravenous introduction of the medicament avoids many of these shortfalls (such as gastrointestinal and hepatic metabolism), its invasive and apprehensive nature (particularly for chronic administration) has encouraged the search for alternative strategies, and few anatomical orifices have not been investigated for their potential as optional drug delivery routes. Nevertheless, the transdermal mode offers several distinct advantages: (1) the skin presents a

relatively large and readily accessible surface area (1–2 m2) for absorption; and (2) the application of a patch-like device to the skin surface is a non-invasive (and thus a patient compliant) procedure that allows continuous intervention (i.e., system repositioning, removal or replacement).

Further benefits of TDDSs have emerged over the past few years as technologies have evolved. These include the potential for sustained release (useful for drugs with short biological half-lives requiring frequent oral or parenteral administration) and controlled input kinetics, which are particularly indispensable for drugs with narrow therapeutic indices. Of course, the implementation of TDD technology must be therapeutically "justified": drugs with high oral bioavailability and infrequent dosing regimens that are well accepted by patients do not warrant such measures. Similarly, transdermal administration is not a means to achieve rapid bolus-type drug inputs; rather, it is usually designed to offer slow, sustained drug delivery over substantial periods of time and, as such, tolerance-inducing drugs or those (e.g., hormones) requiring chronopharmacological management are, at least to date, not suitable. Nevertheless, there remains a large pool of drugs for which TDD is desirable but presently unfeasible. The nature of the SC is, in essence, the key to this problem. The excellent diffusional resistance offered by the membrane means that the daily drug dose that can be systemically delivered through a reasonable "patch-sized" area remains in the 10 mg range. This limitation imposes the first criterion for a successful transdermal candidate: transdermal drugs must be pharmacologically potent, requiring therapeutic blood concentrations in the ng/ml range, or less. The second criterion is that SC is very selective with respect to the type of molecule that can be transported across this outer covering, and not all molecules that pass the "potency" test will have the necessary physicochemical properties.

FACTORS AFFECTING TRANSDERMAL DRUG DELIVERY

Skin condition

The intact skin itself acts as a barrier, but many agents like acids and alkali cross the barrier cells and penetrate through the skin. Many solvents open the complex dense structure of the horny layer: solvents like methanol and chloroform remove the lipid fraction, forming artificial shunts through which drug molecules can pass easily.

Skin age

It is seen that the skin of adults and young ones is more permeable than that of the older ones. But there is no dramatic difference. Children show toxic effects because of the greater surface area per unit body weight. Thus, potent steroids, boric acid and hexachlorophene have produced severe side-effects.

Physicochemical factors

Hydration of skin

Generally, when water saturates the skin, it swells tissues, softens wrinkles on the skin and its permeability increases for the drug molecules that penetrate through the skin.

Temperature and pH of the skin

The penetration rate varies if the temperature varies and the diffusion coefficient decreases as the temperature falls; however adequate clothing on the body prevents wide fluctuations in temperature and penetration rates. According to pH, only unionized molecules pass readily across the lipid membrane, and weak acids and bases dissociate to different degrees according to their pH and pKa or pKb values. Thus, the concentration of unionized drug in applied phase will determine the effective membrane gradient, which is directly related to its pH.

Environmental factors

Sunlight

Because of to sunlight, the walls of blood vessels become thinner, leading to bruising, with only minor trauma in the sun-exposed areas. Also, pigmentation, the most noticeable sun-induced pigment change, is a freckle or solar lentigo.

Cold season

The cold season often results in itchy and dry skin. The skin responds by increasing oil production to compensate for the weather's drying effects. A good moisturizer will help ease symptoms of dry skin. Also, drinking lots of water can keep your skin hydrated and looking radiant.

Air pollution

Dust can clog pores and increase bacteria on the face and the surface of skin, both of which lead to acne or spots, which affects drug delivery through the skin. Invisible chemical pollutants in the air can interfere with the skin's natural protection system, breaking down the skin's natural oils that normally trap moisture in the skin and keep it supple.

BASIC COMPONENTS OF TDDS

- Polymer matrix/drug reservoir
- Membrane
- Drug
- Permeation enhancers
- Pressure-sensitive adhesives (PSA)
- Backing laminates
- Release liner
- Other excipients like plasticizers and solvents

Polymer matrix/drug reservoir

Polymers are the backbone of TDDS, which control the release of the drug from the device. A polymer matrix can be prepared by dispersion of drug in a liquid or solid state synthetic polymer base. Polymers used in TDDS should have biocompatibility and chemical compatibility with the drug and other components of the system, such as penetration enhancers and PSAs. Additionally, they should provide consistent and effective delivery of a drug throughout the product's intended shelf-life, and should be safe.

The following criteria should be preferred in selecting the polymer to be used in the transdermal system:

(i) Molecular weight, glass transition temperature and chemical functionality of the polymer should be such that the specific drug diffuses properly and gets released through it.
(ii) The polymer should be stable, nonreactive with the drug, easily manufactured and fabricated into the desired product, and should be inexpensive.
(iii) The polymer and its degradation products must be nontoxic or nonantagonistic to the host.
(iv)The mechanical properties of the polymer should not deteriorate excessively when large amounts of active ingredients are incorporated into it.
The polymers utilized for TDDS are presented in Table 2.

Membrane

A membrane may be sealed to the backing to form a pocket to enclose the drug-containing matrix or used as a single layer in the patch construction. The diffusion properties of the membrane are used to control availability of the drug and/or excipients to the skin. For example, ethylene vinyl acetate, silicone rubber, polyurethrane, etc. are used as a rate-controlling membrane.

Drug

For successfully developing a TDDS, the drug should be chosen with great care. Transdermal patches offer many advantages to drugs that undergo extensive first-pass metabolism, drugs with narrow therapeutic window or drugs with a short half-life, which cause noncompliance due to frequent dosing. Some of the desirable properties of a drug and factors to be considered for transdermal delivery are shown in Tables 3 and 4.
There are some examples of drugs that are suitable for TDDS, like Nicardipine hydrochloride, Captopril, Atenolol, Metoprolol tartarate, Clonidine, Indapamide, Propranolol hydrochloride, Carvedilol, Verapamil hydrochloride and Niterdipine, etc.

Permeation enhancers

One long-standing approach for improving TDD uses penetration enhancers (also called sorption promoters or accelerants), which increase the permeability of the SC so as to attain higher therapeutic levels of the drug candidate.
Penetration enhancers interact with structural components of the SC thus modifying the barrier functions, leading to increased permeability. Three pathways are suggested for drug penetration through the skin: polar, nonpolar and polar/nonpolar. The enhancers act by altering one of these pathways. The key to altering the polar pathway is to cause protein conformational change or solvent swelling.
The key to altering the nonpolar pathway is to alter the rigidity of the lipid structure and fluidize the crystalline pathway (this substantially increases diffusion). The fatty acid enhancers increase the fluidity of the lipid portion of the SC. Some enhancers (binary vehicles) act on both polar and nonpolar pathways by altering the multilaminate pathway for penetrants. The methods employed for modifying the barrier properties of the SC to enhance the drug penetration (and absorption) through the skin can be categorized as (1) chemical and (2) physical methods of enhancement.

Table 1 : Polymers used in TDDS

Natural polymers	Synthetic elastomers	Synthetic polymers
Cellulose derivatives, zein, gelatin, waxes, proteins and their derivatives, natural rubber, starch, chitosan, etc.	Polybutadiene, hydrin rubber, polysiloxane silicone rubber, nitrile, acrylonitrile, butyl rubber rubber, styrene–butadiene rubber, neoprene, etc.	Polyvinylalcohol, polyvinylchloride, polyethylene, polypropylene, polyacrylate, polyurea, polyvinyl pyrrolidone, polymethyl methacrylate, epoxy, ethyl cellulose, hydroxy propyl cellulose, polyamide, etc.

Table 2: Ideal properties of drugs for TDDS

Parameters	Properties
Dose	Should be low (less than 20 mg/day)
Half-life	10 or less (h)
Molecular weight	<400 Da
Partition coefficient	Log P (octanol–water) between 1.0 and 4.0
Skin permeability coefficient	$>0.5 \times 10^{-3}$ cm/h
Liophilicity	10 < Ko/w < 1000
Oral bioavailability	Low
Therapeutic index	Low
Melting point	<200°C
pH	Between 5.0 and –9.0

Table 3: Factors to be considered for transdermal dose calculation

Physiochemical	Pharmacokinetic	Biological
Solubility	Half-life	Skin toxicity
Crystallinity	Volume of distribution	Site of application
Molecular weight	Total body clearance	Allergic reaction
Polarity	Therapeutic plasma concentration	Skin metabolism
Melting point	Bioavailability factor	Skin permeability

Chemical enhancers

Chemicals that promote the penetration of topically applied drugs are commonly referred to as accelerants, absorption promoters or penetration enhancers. Chemical enhancers act by:

- Increasing (and optimizing) the thermodynamic activity of the drug when functioning as a co-solvent
- Increasing the partition coefficient of the drug to promote its release from the vehicle into the skin
- Conditioning the SC to promote drug diffusion
- Promoting penetration and establishing drug reservoir in the SC.

Some of the more desirable properties for penetration enhancers acting within the skin have been given as:

- They should be nontoxic, nonirritating and nonallergenic

They should ideally work rapidly, and the activity and duration of the effect should be both predictable and reproducible
They should have no pharmacological activity within the body, i.e. should not bind to receptor sites
The penetration enhancers should work unidirectionally, i.e. should allow therapeutic agents into the body while preventing the loss of endogenous material from the body
When removed from the skin, barrier properties should return both rapidly and fully
The penetration enhancers should be appropriate for formulation into diverse topical preparations and, thus, should be compatible with both excipients and drugs
They should be cosmetically acceptable with an appropriate skin "feel"

Some of the most widely studied permeation enhancers are sulphoxide (DMSO), fatty acids (oleic acid), alcohol (methanol), glycol (propylene glycol) and surfactant (anionic surfactant), azone (lauracapran), etc.

Physical enhancers

Iontophoresis and ultrasound (also known as phonophoresis or sonophoresis) techniques are examples of physical means of enhancement that have been used for enhancing percutaneous penetration (and absorption) of various therapeutic agents.

PSAs

PSAs are the material that adhere to a substrate, in this case skin, by application of light force and leave no residue when removed. They form interatomic and intermolecular attractive forces at the interface, provided that the intimate contact is formed. To obtain this degree of contact, the material must be able to deform under slight pressure, giving rise to the term "pressure sensitive." Adhesion involves a liquid-like flow, resulting in wetting of the skin surface upon the application of pressure, and, when the pressure is removed, the adhesive sets in that state. A PSA wets and spreads onto the skin when its surface energy is less than that of the skin.

After the initial adhesion, the PSA/skin bond can be built by stronger interactions (e.g., hydrogen bonding), which will depend on skin characteristics and other parameters.Widely used PSA polymers in TDDS are polyisobutylene-based. adhesives, acrylics and silicone-based PSAs, hydrocarbon resin, etc. The PSA can be located around the edge of the TDDS or be laminated as a continuous adhesive layer on the TDDS surface. The PSA should be compatible with the drug and excipients, as their presence can modify the mechanical characteristics of the PSA and the drug delivery rate.

Backing laminates

Backings are chosen for appearance, flexibility and need for occlusion; hence, while designing a backing layer, the consideration of chemical resistance of the material is most important. Excipient compatibility should also be considered because the prolonged contact between the backing layer and the excipients may cause the additives to leach out of the backing layer or may lead to diffusion of excipients, drug or penetration enhancer through the layer. The most comfortable backing will be the one that exhibits lowest modulus or high flexibity, good oxygen

transmission and a high moisture vapor transmission rate. Examples of backing materials are vinyl, polyethylene, polyester films, aluminum and polyolefin films.

Release liner

During storage, the patch is covered by a protective liner that is removed and discarded before the application of the patch to the skin. Because the liner is in intimate contact with the TDDS, the liner should be chemically inert. Typically, a release liner is composed of a base layer that may be nonocclusive (e.g, paper fabric) or occlusive (e.g, polyethylene, polyvinyl chloride) and a release coating layer made up of silicon or Teflon. Other materials used for TDDS release liner are polyester foil and metalized laminates.

Other excipients like plasticizers and solvents

Various solvents such as chloroform, methanol, acetone, isopropanol and dicholoromethane are used to prepare drug reservoir. In addition, plasticizers such as dibutylphthalate, triethyl citrate, polyethylene glycol and propylene glycol are added to provide plasticity to the transdermal patch.

TYPES OF TRANSDERMAL PATCHES

Most commercially available transdermal patches are categorized into the following three types [Figure 3]:

Reservoir system

In this transdermal system, the drug reservoir is embedded between an impervious backing layer and a rate-controlling microporous or non-porous membrane. The drug releases only through the rate-controlling membrane. In the drug reservoir compartment, the drug can be in the form of a solution, suspension or gel, or may be dispersed in a solid polymer matrix. Hypoallergenic adhesive polymer can be applied as a continuous layer between the membrane and the release liner or in a concentric configuration around the membrane.

Matrix system

Drug-in-adhesive system

In this type, the drug reservoir is formed by dispersing the drug in an adhesive polymer and then spreading the medicated adhesive polymer by solvent casting or melting (in the case of hot melt adhesives) on an impervious backing layer. On the top face of the reservoir, unmedicated adhesive polymer layers are applied for protection purpose.

Matrix-dispersion system

The drug is dispersed homogenously in a hydrophilic or lipophilic polymer matrix. This drug-containing polymer disk is then fixed onto an occlusive base plate in a compartment fabricated from a drug-impermeable backing layer. Instead of applying the adhesive on the face of the drug reservoir, it is spread along the circumference to form a strip of adhesive rim.

Microreservoir systems

This TDDS is a combination of a reservoir and a matrix dispersion system. The drug reservoir is formed by first suspending the drug in an aqueous solution of water-soluble polymer and then dispersing the solution homogenously in a lipophilic polymer to form thousands of unleachable,

microscopic spheres of drug reservoirs. The thermodynamically unstable dispersion is stabilized quickly by immediately cross-linking the polymer *in situ*.

EVALUATION OF TRANSDERMAL FILMS

Interaction studies

Excipients are integral components of almost all pharmaceutical dosage forms. The stability of a formulation among other factors depends on the compatibility of the drug with the excipients. The drug and the excipients must be compatible with one another to produce a product that is stable; thus, it is mandatory to detect any possible physical or chemical interaction as it can affect the bioavailability and stability of the drug. If the excipients are new and have not been used in formulations containing the active substance, the compatibility studies play an important role in formulation development. Interaction studies are commonly carried out in thermal analysis, Fourier Transform Infrared spectroscopy, UV and chromatographic techniques by comparing their physicochemical characters, such as assay, melting endotherms, characteristic wave numbers, absorption maxima, etc.

Thickness of the patch

The thickness of the drug-loaded patch is measured in different points by using a digital micrometer, and determines the average thickness and standard deviation for the same to ensure the thickness of the prepared patch.

Weight uniformity

The prepared patches are to be dried at 60°C for 4 h before testing. A specified area of patch is to be cut in different parts of the patch and weighed in a digital balance. The average weight and standard deviation values are to be calculated from the individual weights.

Folding endurance

A strip of the specific area is to be cut evenly and repeatedly folded at the same place till it breaks. The number of times the film can be folded at the same place without breaking gives the value of the folding endurance.

Percentage moisture content

The prepared films are to be weighed individually and are to be kept in a desiccator containing fused calcium chloride at room temperature for 24 h. After 24 h, the films are to be reweighed to determine the percentage moisture content from the below-mentioned formula:

Percentage moisture content = [Initial weight □□Final weight / Final weight] × 100 (1)

Percentage moisture uptake

The weighed films are to be kept in a desiccator at room temperature for 24 h, which contains a saturated solution of potassium chloride in order to maintain 84% RH. After 24 h, the films are to be reweighed to determine the percentage moisture uptake from the below-mentioned formula:

Percentage moisture uptake = [Final weight □□Initial weight / initial weight] × 100 (2)

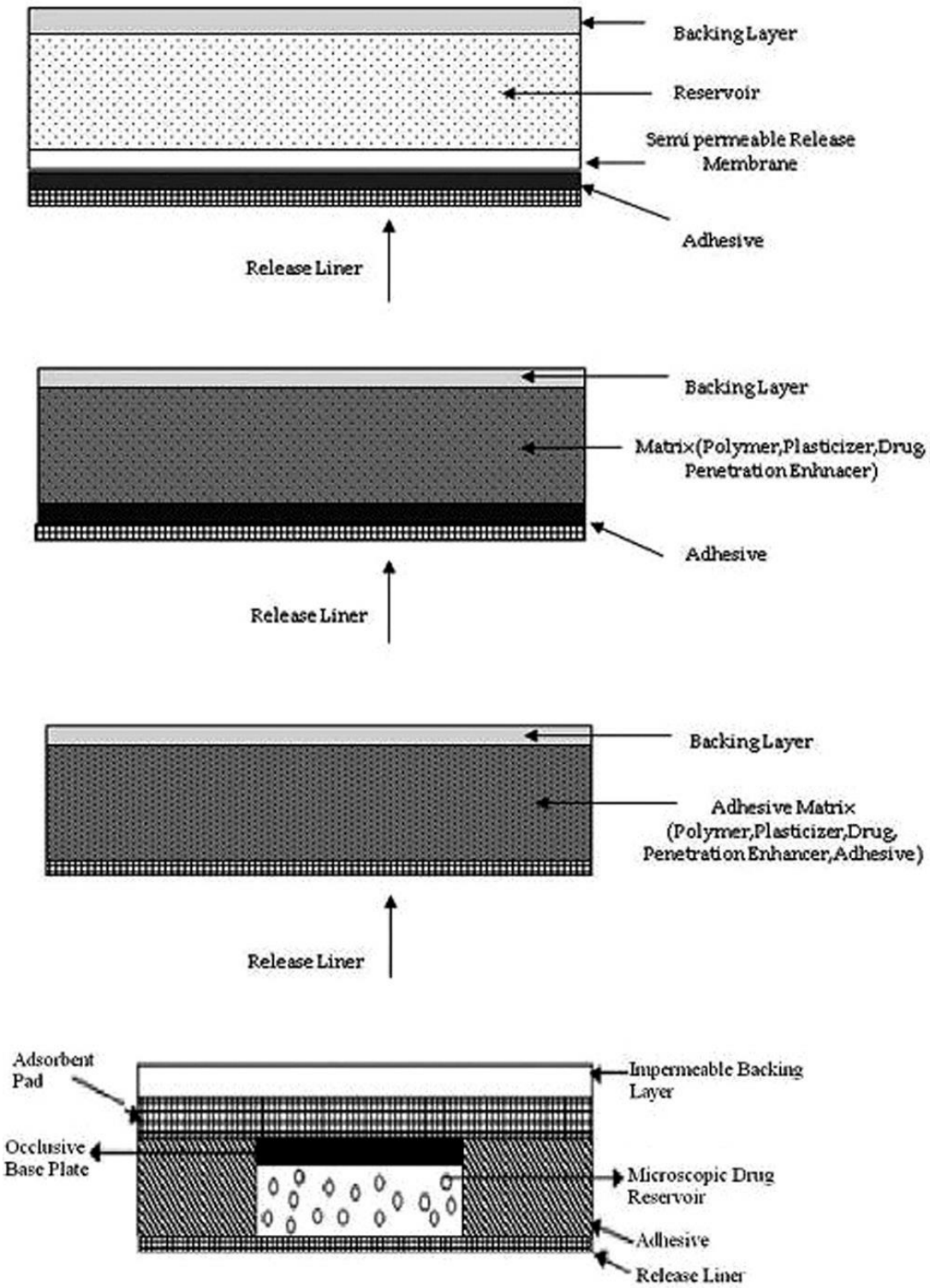


Figure 3: Types of transdermal patches: (a) Reservoir, (b) Matrix, (c) Drug-in-Adhesive, (d) Microreservoir system

Water vapor permeability evaluation

WVP can be determined with the foam dressing method, wherein the air-forced oven is replaced by a natural air circulation oven. The WVP can be determined by the following formula:

WVP = W / A (3)

Where, WVP is expressed in gm/m2 per 24 h, W is the amount of vapor permeated through the patch, expressed in gm/24 h, and A is the surface area of the exposure samples, expressed in m2.

Drug content

A specified area of the patch is to be dissolved in a suitable solvent in a specific volume. Then, the solution is to be filtered through a filter medium and analyze the drug content with the suitable method (UV or HPLC technique). Each value represents an average of three different samples.

Uniformity of the dosage unit test

An accurately weighed portion of the patch is to be cut into small pieces and transferred to a specific volume using a volumetric flask, dissolved in a suitable solvent and sonicate for complete extraction of the drug from the patch and made up to the mark with the same. The resulting solution was allowed to settle for about 1 h and the supernatant was suitably diluted to give the desired concentration with the suitable solvent. The solution was filtered using a 0.2-□m membrane, filtered and analyzed by a suitable analytical technique (UV or HPLC), and the drug content per piece was to be calculated.

Polariscope examination

This test is to be performed to examine the drug crystals from the patch by a polariscope. A specific surface area of the piece is to be kept on the object slide and observed for the drug crystals to distinguish whether the drug is resent as a crystalline form or an amorphous form in the patch.

Shear adhesion test

This test is to be performed for measurement of the cohesive strength of an adhesive polymer. It can be influenced by the molecular weight, the degree of crosslinking and the composition of the polymer and the type and amount of tackifier added. An adhesive-coated tape is applied onto a stainless steel plate; a specified weight is hung from the tape to affect it, pulling in a direction parallel to the plate. Shear adhesion strength is determined by measuring the time it takes to pull the tape off the plate. The longer the time taken for removal, greater is the shear strength.

Peel adhesion test

In this test, the force required to remove an adhesive coating from a test substrate is referred to as peel adhesion.

Molecular weight of the adhesive polymer and the type and amount of additives are the variables that determine the peel adhesion properties. A single tape is applied to a stainless steel plate or a backing membrane of choice and then the tape is pulled from the substrate at a 180º angle, and the force required for tape removal is measured.

Thumb tack test

It is a qualitative test applied for tack property determination of the adhesive. The thumb is simply pressed on the adhesive and the relative tack property is detected.

Flatness test

Three longitudinal strips are to be cut from each film at different portions, like one from the center, one from the left side and another from the right side. The length of each strip was measured and the variation in length because of nonuniformity in flatness was measured by determining the percent constriction, with 0% constriction equivalent to 100% flatness.

Percentage elongation break test

The percentage elongation break is to be determined by noting the length just before the break point. The percentage elongation can be determined from the below-mentioned formula:

Elongation percentage = (L1 □□L2) / L2 × 100 (4)

Where, L1 is the final length of each strip and L2 is the initial length of each strip.

Rolling ball tack test

This test measures the softness of a polymer that relates to talk. In this test, a stainless steel ball of 7/16 inches in diameter is released on an inclined track so that it rolls down and comes in contact with the horizontal, upward facing adhesive. The distance the ball travels along the adhesive provides the measurement of tack, which is expressed in inches.

Quick stick (peel-tack) test

In this test, the tape is pulled away from the substrate at 90º at a speed of 12 inches/min. The peel force required to break the bond between the adhesive and the substrate is measured and recorded as tack value, which is expressed in ounces or grams per inch width.

Probe tack test

In this test, the tip of a clean probe with a defined surface roughness is brought into contact with the adhesive. And, when a bond is formed between the probe and the adhesive, the subsequent removal of the probe mechanically breaks it. The force required to pull the probe away from the adhesive at a fixed rate is recorded as tack, and it is expressed in grams.

***In vitro* drug release studies**

The paddle over disc method (USP apparatus V) can be employed for assessment of the release of the drug from the prepared patches. Dry films of known thickness are to be cut into a definite shape, weighed and fixed over a glass plate with an adhesive. The glass plate was then placed in 500 mL of the dissolution medium or phosphate buffer (pH 7.4), and the apparatus was equilibrated to 32 ± 0.5°C. The paddle was then set at a distance of 2.5 cm from the glass plate and operated at a speed of 50 rpm. Samples (5-mL aliquots) can be withdrawn at appropriate time intervals up to 24 h and analyzed by a UV spectrophotometer or HPLC. The experiment is to be performed in triplicate, and the mean value can be calculated.

***In vitro* skin permeation studies**

An *in vitro* permeation study can be carried out by using diffusion cells. Full-thickness abdominal skin of male Wistar rats weighing 200–250 g was selected. Hair from the abdominal region is to be removed carefully by using a electric clipper; the dermal side of the skin was thoroughly cleaned with distilled water to remove any adhering tissues or blood vessels, equilibrated for 1 h in dissolution medium or phosphate buffer pH 7.4 before starting the experiment and was placed on a magnetic stirrer with a small magnetic needle for uniform

distribution of the diffusant. The temperature of the cell was maintained at 32 ± 0.5°C using a thermostatically controlled heater. The isolated rat skin piece is to be mounted between the compartments of the diffusion cell, with the epidermis facing upward into the donor compartment. Definite volume of sample is to be removed from the receptor compartment at regular intervals, and an equal volume of fresh medium is to be replaced. Samples are to be filtered through the filtering medium, and can be analyzed spectrophotometrically or by using HPLC. Flux can be determined directly as the slope of the curve between the steady state values of the amount of drug permeated (mg/cm2) versus time in hours, and permeability coefficients were deduced by dividing the flux by the initial drug load (mg/cm2).

Skin irritation study

Skin irritation and sensitization testing can be performed on healthy rabbits (average weight 1.2–1.5 kg). The dorsal surface (50 cm2) of the rabbit is to be cleaned and the hair is to be removed from the clean dorsal surface by shaving.

Clean the surface by using rectified spirit and, then, the representative formulations can be applied over the skin.

The patch is to be removed after 24 h and the skin is to be observed and classified into five grades on the basis of the severity of the skin injury.

Stability studies

Stability studies are to be conducted according to the ICH guidelines by storing the TDDS samples at 40 ± 0.5°C and 75 ± 5% RH for 6 months. The samples were withdrawn at 0, 30, 60, 90 and 180 days and analyzed suitably for the drug content.

Q.10 Note on Parenteral implants

PARENTERAL IMPLANTS

Implant is an object or material inserted or grafted into the body for prosthetic, therapeutic, diagnostic, or experimental purposes. Implants are one of the dosage forms used to achieve effective concentrations for a long time. Therefore the base materials for implants are required to be biocompatible. Biodegradable and non-biodegradable polymers are often utilized as a base material. Non biodegradable polymers have to be taken out surgically after completion of the drug release, resulting in pain and a burden on patients. On the other hand, as biodegradable polymers disappear spontaneously from the body during or after drug release, their implants are superior in lowering the burden on patients. In particular, poly-dl-lactic acid (PLA) and poly (dl-lactic acid-co-glycolic acid) copolymer (PLGA) are clinically available as biocompatible and biodegradable polymers, and have been examined extensively and widely. PLGA and PLA show a prolonged drug release for 1 and 3 months, respectively. Other biodegradable polymer like polyanhydride shows a longer drug release about 1 year. Non bio-degradable polymer includes poly vinyl acetate (PVA) etc. Various types of implants are available for the drug delivery system like for delivery into eye, heart, bone, cochlea etc.

Implants classified as-

1. Solid implants-

Solid implants typically exhibit biphasic release kinetics, with initial burst of drug is usually due to the release of drug deposited on the surface of the implant although zero order kinetics may be achieved by. E.g. Coating the implant drug impermeable material Overall drug release may be controlled by varying polymer composition- an increase in the level of lactic acid in a polylactic acid co-glycolic acid copolymer retards drug release and increase in polymer molecular weight also retards drug release and prolongs drug effects.

2. In-Situformingimplants-

Biodegradable injectable *in situ* forming drug delivery systems represent an attractive alternative to microspheres and implants as parenteral depot systems. The controlled release of bioactive macromolecules via (semi-) solid *in situ* forming systems has a number of advantages, such as:

1. Ease of administration,
2. Less complicated fabrication,
3. Less stressful manufacturing conditions for sensitive drug molecules.

From a manufacturing point of view, *in situ* forming depot systems offer the advantage that they are relatively simple to manufacture from polymers adapted for this approach. Compared with microspheres, which have to be washed and isolated after preparation, operating expenses for the production of *in situ* forming applications are marginal, thus lowering investment and manufacturing costs.

Classification of injectable *in situ* forming implants-

In situ cross-linked polymer systems

In situ polymer precipitation

Thermally induced gelling systems

Polymeric controlled release systems-Polymeric release systems can be classified into reservoir and matrix systems. In reservoir systems the drug forms a core surrounded by polymer that forms a diffusion barrier. The drug release is by dissolution into the polymer and then diffusion through the polymer wall. In polymeric matrix systems the drug is dispersed or dissolved in a polymer. The drug release can be diffusion, swelling, and/or erosion controlled. Compared to reservoir systems, matrix systems are easier to be manufactured because they are homogeneous in nature and they are also safer since a mechanical defect of the reservoir device rather than matrix device may cause dose dumping. However, if polymer matrix is non-degradable, the constant release profile is difficult to be achieved with matrix system.

The first polymeric controlled release devices is a reservoir system based on nonbiodegradable polymer silicone rubber.

CONTROLLED DRUG DELIVERY BY DIFFUSION PROCESS

a) Polymer membrane permeation controlled drug delivery device: In this implantable drug delivery device the drug reservoir is encapsulated by a rate controlling polymeric membrane. Different shapes and sizes of implantable drug delivery devices can be fabricated. An example of this type of implantable drug delivery device is the **Norplant** sub dermal implant. Norplant® is a

well-known contraceptive implant approved by U.S. Food and Drug Administration (FDA) in 1990.

b) Polymer matrix diffusion-controlled drug delivery devices: In this implantable controlled-release drug delivery devices the drug reservoir is formed by homogeneous dispersion of solid particle throughout the a lipophilicor hydrophilic polymer matrix .The dispersion of drug solid particle in the polymer matrix can be accomplished by blending drug solid with a viscous liquid polymer at room temperature followed by cross linking of polymer chains or by mixing drug solid with a melted polymer dispersion are then molded or extruded to form a drug delivery device of various shapes and sizes. An example of this type of implantable drug delivery device is the compu dose implant.

c) Membrane-matrix hybrid-type Drug Delivery Devices: This type of implantable controlled release drug delivery devices is hybrid of the polymer membrane permeation controlled drug delivery system and polymer matrix diffusion controlled drug delivery system. It aims to take advantages of the constant drug release kinetics maintained by the membrane permeation-drug delivery system while minimizing the risk of dose dumping from the reservoir compartment of this type of drug delivery system. An example of type of implantable drug delivery device is **Norplant II** sub dermal implant.

d) Micro reservoir partition-controlled drug delivery devices: in this implantable controlled drug delivery device the drug reservoir, which is a suspension of drug crystals in an aqueous solution of water-miscible polymers, forms a homogeneous dispersion of millions of discrete, unreachable, microscopic drug reservoir in a polymer matrix. Different shapes and sizes of drug delivery system by molding or extrusion. Depending upon the physicochemical properties of drug and desired properties of drug rate release, the device can be further coated with a layer of biocompatible polymer to modify the mechanism and rate of drug release. An example of this type implantable drug delivery device is the **Synchro-Mate** implant. It contains drug **norgestomet**.

2. Controlled drug delivery by activation process

A) Osmotic pressure-activated drug delivery device

In this implantable controlled-release drug delivery device osmotic pressure is used as the energy source to activate and modulate the delivery of drugs, the drug reservoir, which is either a solution or a semisolid formulation.

Alzet osmotic pump

The physical or chemical properties of a compound have no influence on the delivery rate of ALZET pumps. The delivery rate of ALZET pumps is controlled by the water permeability of the outer membrane. In short, water from the environment enters the pump through the semipermeable membrane into the osmotic layer, which causes compression of the flexible, impermeable reservoir. The test solution is continuously released through the flow moderator. A flow modulator is a hollow tube with an inner diameter of 500 microns. Solutions and even high molecular weight compounds can effectively flow through the flow moderator of ALZET pumps.

B) Vapor pressure activated drug delivery devices

In this implantable controlled release drug delivery device vapor pressure is used as the power source to activate the controlled delivery of drugs. The drug reservoir, which is a solution formulation, is contained inside an infusate chamber. By a freely movable bellows the infusate chamber is physically separated from the vapor pressure chamber, which contains the vaporizable fluid, such as fluorocarbon. The fluorocarbon vaporizes at body temperature and creates a vapor pressure that pushes the bellows to move upward and forces the drug solution in the infusate chamber to deliver the drug.

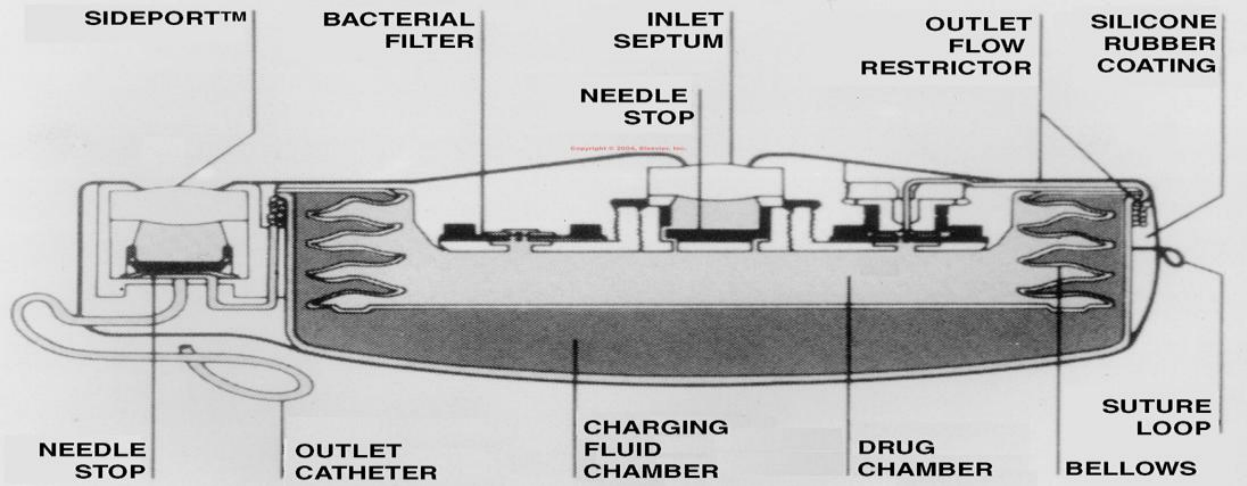


Fig: Infusate chambers

A typical example of drugs that can be given by this type of infusion pump are morphine for patient suffering from intensive pain of terminal cancer, heparin for anticoagulation treatment and insulin for the treatment of diabetes.

C) Magnetically activated drug delivery devices

In this implantable controlled release drug delivery device electromagnetic energy is used as the power source to control the rate of drug delivery. A magnetic wave triggering mechanism is incorporated into the drug delivery device, and drug can be triggered to release at varying rates depending upon the magnitude and the duration of electromagnetic energy applied. This sub dermally implantable, magnetically modulated hemispherical drug delivery device was fabricated by positioning a tiny donut shaped magnet at the center of a medicated polymer matrix that contains a homogenous dispersion of a drug with polymer. The external surface of the hemispherical pellet is further coated with a pure polymer, such as ethylene vinyl acetate copolymer or silicon elastomers, on all sides, expect one cavity at the center of the flat surface, which is left uncoated to permit the drug molecules to be delivered through the cavity. By applying an external magnetic field the drugs are activated by the electromagnetic energy to release from the pellet at a much higher rate of delivery.

D) Hydration activated drug delivery devices

This type of implantable controlled release drug delivery device releases drug molecules upon activation by hydration of the drug delivery device by tissue fluid at the implantation site. To achieve this drug delivery device is often fabricated from a hydrophilic polymer that becomes

swollen upon hydration. Drug molecules are released by diffusing through the polymer matrix. The hydration activated implantable drug delivery device is exemplified by the development of the norgestomet releasing Hydro implant for estrus synchronization in heifers. This was fabricated by polymerizing ethylene glycolmethacrylate (Hydron S) in an alcoholic solution that contains norgestomet, a cross-linking agent (such asethylene dimethacrylate), and an oxidizing catalyst to form a cylindrical water swellable (but insoluble) Hydron implant. The Hydron Implant technology is based upon specialty blends of hydrogel polymers spun cast into small tubes measuring in the order of 1-inch in length and 1/8 inch in diameter.

E) Hydrolysis activated drug delivery devices

This type of implantable controlled release drug delivery device is activated to release drug molecules upon the hydrolysis of the polymer base by tissue fluid at the implantation site. To achieve this drug delivery device is fabricated by depressing a loading dose of solid drug, in micronized form, homogeneously through a polymer matrix made from bioerodible or biodegradable polymer, which is then molded into a pellet or bead-shaped implant. The controlled release of the embedded drug particles is made possible by the combination of polymer erosion by hydrolysis and diffusion through the polymer matrix. The rate of drug release is determined by the rate of biodegradation, polymer composition and molecular weight, drug loading, and drug-polymer interaction. The rate of drug release from this type of drug delivery system is not constant and is highly dependent upon the erosion process of the polymer matrix.

IMPLANTS FOR EYE

Intravitreal injections can enhance ocular drug delivery, but the need for frequent retreatment and potential injection-related side effects limit the utility of this technique. Sustained-release drug delivery systems have been developed to overcome these limitations; such systems can achieve prolonged therapeutic drug concentrations in ocular target tissues while limiting systemic exposure and side effects and improving patient adherence to therapy. Topical drug therapy is the primary form of treatment for front-of-the-eye diseases, such as ocular surface diseases (e.g. conjunctivitis, dry eye), for elevated intraocular pressure, and for anterior uveitis. Anatomical and physiological barriers in the eye, including the corneal epithelium and conjunctival clearance mechanisms, affords protection against the entry of xenobiotic. These barriers also greatly impede the entry of drugs to the posterior segment, making it difficult to achieve therapeutic drug concentrations. Treatment of back-of-the-eye diseases such as diabetic retinopathy, neovascularage-related macular degeneration, and retinal venous occlusive disease is especially challenging with topical therapy given the greater diffusional distance. Systemically administered drugs can be used fortreating front- and back-of-the-eye diseases. However, the accessibility of ocular tissues is greatly limited by the blood-aqueous and blood-retinal barriers. As a result, high systemic doses must be administered, which increases drug exposure in non-ocular tissues and, consequently, the risk of adverse systemic side effects. Therefore Sustained-release intrascleral and Intravitreal drug implants and inserts have been developed for the treatment of ocular diseases.

EXAMPLES OF BIODEGRADABLE OCULAR DRUG DELIVERY SYSTEMS-

1) Lacrisert®
2) Surodex™
3) Ozurdex

NONBIODEGRADABLE OCULAR DRUG DELIVERY SYSTEMS

In nonbiodegradable reservoir-type devices, PVA, a permeable polymer, is typically used as a structural element, while the device's drug-restricting membrane is composed of EVA, a hydrophobic polymer that is relatively impermeable to hydrophilic drugs.

Examples of Non-biodegradable Ocular Drug Delivery Systems

- An Ethylene Vinyl Acetate and Poly(Vinyl) Alcohol Reservoir Device (Vitrasert)
- The Retisert and Medidur Devices-

IMPLANTS FOR HEART-

Percutaneous trans luminal angioplasty (PTCA) is used in the treatment of Coronary Artery Disease. Over the past decade, extensive research has been performed addressing the design of stents, which are commonly used for PTCA. Endoluminal metallic endoprostheses (stents) have reduced procedural complications in PTCA like elastic recoil of the vessel wall, balloon-induced dissection, and reoccurrence of restenosis. To overcome the restenosis issue, stents for local delivery of several drugs were established. First generation drug elutingstents (1GDES) consist of a backbone stent (316 L stainless steel or Nitinol), polymer (biodegradable or non-degradable), and drugs such as Paclitaxel or Sirolimus. This 1 G-DES was designed to reduce in stent neointimal formation and to minimize the appearance of restenosis.

CYPHER STENT-A stent is a permanent implant that remains in your artery. CYPHER® Stent is a small, expandable, slotted metal tube is inserted through a catheter into a coronary artery. There, it acts as a scaffold to help hold the artery open in order to improve blood flow to the heart and relieve the symptoms and dangers associated with artery blockage. The CYPHER® Stent is a drug-eluting stent. The metal of the stent has a soft, plastic coating that contains the anti-rejection-type medicine Sirolimus. Eighty percent (80%) of the Sirolimus is released during the first 30 days. The rest is released by the end of 90 days.

TAXUS STENT-The TAXUS stent uses Translute™ Polymer, a proprietary polymer carrier technology, to control drug release. The durable Translute Polymer protects the drug and maintains coating integrity during preparation, delivery, and stent expansion. The polymer controls the release of paclitaxel, which may allow for consistent drug release and more uniform drug distribution.

Q.11 Note on Ophthalmic inserts

Ophthalmic inserts are sterile preparations with a solid or a semisolid consistency, and whose size and shape are especially designed for ophthalmic application. The inserts are placed in the lower fornix and less frequently, in the upper fornix or on the cornea. Ocular inserts can overcome the disadvantages reported with traditional. Ophthalmic systems like eye drops, suspensions and ointments. The typical pulse entry type drug release behavior observed with eye

drops, suspensions and ointments is replaced by more controlled, sustained and continuous drug delivery using a controlled release ocular drug delivery system. In the recent years, there has been explosion of interest in the polymer based delivery devices, adding further dimension to topical drug delivery thereby promoting the use of polymers such as collagen and fibrin fabricated into erodible inserts for placement in cul-de-sac.

Utilization of the principles of controlled release as embodied by ocular inserts offers an attractive approach to the problem of prolonging precorneal drug residence times. Ocular inserts also offer the potential advantage of improving patient compliance by reducing the dosing frequency.

The main objective of the ophthalmic inserts is to increase the contact time between the preparation and the conjunctival tissue to ensure a sustained release suited to topical or systemic treatment. They are composed of polymeric support with or without drugs, the latter being incorporated as dispersion or a solution in the polymeric support.

Classification of ophthalmic inserts:-

Based upon their solubility behaviour.

(1) Insoluble:- a) Diffusion b) Osmotic and c) Contact lens

(2) Soluble:- a) Based on natural polymers e.g. collagen

b) Based on synthetic or semi synthetic polymers e.g. cellulose derivatives like HPMC, HPC, MC etc

Bioerodible.

a. Insoluble ocuserts.

Only the insoluble types can usually deliver drugs by a variety of methods at controlled, predetermined rate, but need removal from the eye when empty.

b. Soluble ocuserts:

Soluble(S) inserts generally defined as erodible (E), monolithic polymeric devices that undergo gradual dissolution while releasing the drug and do not need removal. True dissolution occurs mainly through polymer swelling, while erosion corresponds to a chemical or enzymatic hydrolytic process. In swelling-controlled devices the active agent is homogeneously dispersed in a glassy polymer, glassy polymers are essentially drug impermeable so no diffusion takes place through the dry matrix. When the insert is placed in the eye water from the tear fluid begins to penetrate the matrix, then swelling and consequently polymer chain relaxation and drug diffusion take place releasing their drug content.

I. Insoluble ocular inserts

Inserts made up of insoluble polymer can be classified into two categories:

A. Reservoir systems; B. Matrix systems.

A. Reservoir systems

Each class of inserts shows different drug release profiles. The reservoir systems can release drug either by diffusion or by an osmotic process. It contains, respectively, a liquid, a gel, a colloid, a semisolid, a solid matrix, or a carrier containing drug. Carriers are made of hydrophobic, hydrophilic, organic, natural or synthetic polymers.

They have been sub-classified into:

1. Diffusional inserts, e.g., 'Ocuserts'; 2. Osmotic inserts.

1. Diffusional insert or Ocuserts

Ocusert system is a novel ocular drug delivery system based on porous membrane. The release of drug from diffusional inserts/Ocusert is based on a diffusional release mechanism. It consists of a central reservoir of drug enclosed in specially designed microporous membrane allowing the drug to diffuse from the reservoir at a precisely determined rate.

As pointed out by Urquhart, the Ocusert pilocarpine ocular therapeutic system, developed by Alza Corporation, is notable for several reasons. This product was the first rate controlled, rate specified pharmaceutical for which the strength is indicated on the label by the rate(s) of drug delivery *in vivo*, rather than by the amount of contained drug. It provides predictable, time-independent concentrations of drug in the target tissues, a feat impossible to achieve with conventional, quantity-specified, pulse entry ophthalmic medications. The near-constant drug concentration in ocular tissues markedly improves the selectivity of action of pilocarpine.

A major advantage is that two disturbing side effects of the drug, miosis and myopia, are significantly reduced, while reduction of intraocular pressure (IOP) in glaucoma patients is fully maintained. Two types of Ocusert are available: the Pilo-20 and Pilo-40. The former delivers the drug at a rate of 20 μg/h for 7 days, and the latter at a rate of 40 μg/h for 7 days. This device, which is certainly well familiar to the readers of this review, has been exhaustively described and discussed in a series of specialized papers. Briefly, it consists of a reservoir containing pilocarpine alginate enclosed above and below by thin EVA (ethylene-vinyl acetate) membranes. The insert is encircled by a retaining ring of the same material, impregnated with titanium dioxide. The dimensions of the elliptical device are (for the 20 μg/h system): major axis- 13.4 mm, minor axis-5.7 mm, thickness-0.3 mm.

The membranes are the same in both systems, but to obtain a higher release rate, the reservoir of the 40 μg/h system contains about 90 mg of di (2-ethylhexyl) phthalate as a flux enhancer.

2. OSMOTIC INSERT

The osmotic inserts are generally composed of a central part surrounded by a peripheral part and are of two types:

Type 1: The central part is composed of a single reservoir of a drug with or without an additional osmotic solute dispersed throughout a polymeric matrix, so that the drug is surrounded by the polymer as discrete small deposits. The second peripheral part of these inserts comprises a covering film made of an insoluble semipermeable polymer. The osmotic pressure against the polymer matrix causes its rupture in the form of apertures. Drug is then released through these apertures from the deposits near the surface of the device.

Type 2: The central part is composed of two distinct compartments. The drug and the osmotic solutes are placed in two separate compartments, the drug reservoir being surrounded by an elastic impermeable membrane and the osmotic solute reservoir by a semi-permeable membrane. The second peripheral part is similar to that of type 1. The tear diffuse into the osmotic compartment inducing an osmotic pressure that stretches the elastic membrane and contracts the

compartment including the drug, so that the active component is forced through the single drug release aperture.

B. Matrix systems

The second category, matrix system, is a particular group of insoluble ophthalmic devices mainly represented by contact lenses. It comprises of covalently cross-linked hydrophilic or hydrophobic polymer that forms a three dimensional network or matrix capable of retaining water, aqueous drug solution or solid components. The hydrophilic or hydrophobic polymer swells by absorbing water. The swelling caused by the osmotic pressure of the polymer segments is opposed by the elastic retroactive forces arising along the chains or crosslinks are stretched until a final swelling (equilibrium) is reached.

1. Contact lenses

Contact lenses are shaped structures and initially used for vision correction. Their use has been extended as potential drug delivery devices by presoaking them in drug solutions. The main advantage of this system is the possibility of correcting vision and releasing drug simultaneously. Subdivision of contact lenses into 5 groups.

a) Rigid
b) Semi-rigid
c) Elastomeric
d) Soft hydrophilic
e) Bio-polymeric

Rigid contact lenses have the disadvantage of being composed of polymers (e.g., poly methyl methacrylic acid) hardly permeable to moisture and oxygen, a problem which has been overcome by using gas permeable polymers such as cellulose acetate butyrate. However, these systems are not suitable for prolonged delivery of drugs to the eye and their rigidity makes them very uncomfortable to wear. For this reason, soft hydrophilic contact lenses were developed for prolonged release of drugs such as pilocarpine, chloramphenicol and tetracycline prednisolone sodium phosphate. The most commonly used polymer in the composition of these types of lenses is hydroxy ethyl methyl metacrylic acid copolymerized with poly (vinyl pyrrolidone) or ethylene glycol dimethacrylic acid (EGDM). Poly (vinyl pyrrolidone) is used for increasing water of hydration, while EGDM is used to decrease the water of hydration. The soft hydrophilic contact lenses are very popular because they are easy to fit and are tolerated better. The drug incorporation into contact lenses depends on whether their structure is hydrophilic or hydrophobic. When contact lens (including 35 to 80% water) is soaked in solution, it absorbs the drug. Drug release depends markedly on the amount of drug, the soaking time of the contact lens and the drug concentration in the soaking solution.

II. Soluble ocular inserts

These soluble inserts offer the advantage of being entirely soluble so that they do not need to be removed from their site of application, thus limiting the intervention to insertion only. They can be broadly divided into two types, the first one being based on natural polymers and the other on synthetic or semi-synthetic polymers.

A. Natural polymers

The first type of soluble inserts is based on natural polymer Natural polymer used to produce soluble ophthalmic inserts is preferably collagen. The therapeutic agent is preferably absorbed by soaking the insert in a solution containing the drug, drying, and re-hydrating it before use on the eye. The amount of drug loaded will depend on the amount of binding agent present, the concentration of the drug solution into which the composite is soaked as well as the duration of the soaking. As the collagen dissolves, the drug is gradually released from the interstics between the collagen molecules.

B. Synthetic and semi-synthetic polymer

The second type of soluble insert is usually based on semi-synthetic polymers (e.g., cellulose derivatives) or on synthetic polymers such as polyvinyl alcohol. A decrease of release rate can be obtained by using Eudragit, a polymer. normally used for enteric coating, as a coating agent of the insert . Saettone *et al* . have observed in rabbits that Eudragit coated inserts containing pilocarpine induced a miotic effect of a longer duration, compared to the corresponding uncoated ones. However, the inherent problems encountered with these soluble inserts are the rapid penetration of the lachrymal fluid into the device, the blurred vision caused by the solubilization of insert components and the risk of expulsion due to the initial dry and glassy consistency of the device. Ethyl cellulose, a hydrophobic polymer, can be used to decrease the deformation of the insert and thus to prevent blurred vision. As for the risk of expulsion, several authors have incorporated carbomer, a strong but well tolerated bio-adhesive polymer.

The soluble inserts offer the additional advantage of being of a generally simple design, of being based on products well adapted for ophthalmic use and easily processed by conventional methods. The main advantage is decreased release rate, but still controlled by diffusion.

III. Bio-erodible ocular inserts

These inserts are formed by bio-erodible polymers (e.g., cross-linked gelatin derivatives, polyester derivatives) which undergo hydrolysis of chemical bonds and hence dissolution. The great advantage of these bio-erodible polymers is the possibility of modulating their erosion rate by modifying their final structure during synthesis and by addition of anionic or cationic surfactants.

A cross-linked gelatin insert was used by Attia *et al* . To increase bioavailability of dexamethasone in the rabbit eye. The dexamethasone levels in the aqueous humor were found to be four-fold greater compared to a dexamethasone suspension. However, erodible systems can have significantly variable erosion rates based on individual patient physiology and lachrimation patterns, while degradation products and residual solvents used during the polymer preparation can cause inflammatory reaction. In the following paragraphs, some important ocular inserts are discussed which are available commercially (SODI) or in advanced states of development (collagen shields, Ocufit, NODS, and Minidisc).

Soluble ophthalmic drug insert

Soluble ophthalmic drug insert (SODI) is a small oval wafer, which was developed by soviet scientists for cosmonauts who could not use eye drops in weightless conditions. SODI is together

with the collagen shields, the first modern revival of the gelatin 'lamellae', which disappeared from pharmacopoeias in the late forties. The SODIs are the result of a vast collaborative effort between eminent Russian chemists and ophthalmologists, and led eventually (in 1976) to the development of a new soluble copolymer of acrylamide, *N* -vinylpyrrolidone and ethyl acrylate (ratio 0.25: 0.25: 0.5), designated ABE. A comparison of medicated eye films prepared with different polymers, showed that ABE produced the highest concentration of drugs in rabbit ocular tissues. After large-scale preclinical and clinical testing, the ABE copolymer was used for the industrial manufacture of the SODI in the form of sterile thin films of oval shape (9 x 4.5 mm, thickness 0.35 mm), weighing 15-16 mg, and color-coded for different drugs (over 20 common ophthalmic drugs, or drug combinations). After introduction into the upper conjunctival sac, a SODI softens in l0-15 s, conforming to the shape of the eyeball. In the next l0-15 min the film turns into a polymer clot, which gradually dissolves within 1 h while releasing the drug. The sensation of an 'extraneous body' in the eye disappears in 5-15 min.

COLLAGEN SHIELDS

Collagen is the structural protein of bones, tendons, ligaments, and skin and comprises more than 25% of the total body protein in mammals. This protein, which is derived from intestinal collagen, has several biomedical applications, the main of which is probably catgut suture. Bloomfield *et al* . are credited for first suggesting, in 1977 and 1978, the use of collagen inserts as tear substitutes and as delivery systems for gentamicin. They compared the levels of gentamicin in tears, cornea, and sclera of the rabbit eye after application of a collagen insert, drops, an ointment or following subconjunctival administration. After 3 h, they found that the collagen insert gave the highest concentration of gentamicin in the tear film and in the tissue. Other treatments using collagen shields impregnated with gentamicin and dexamethasone have been described. In rabbits, aqueous humor levels of dexamethasone and gentamicin achieved with collagen shields were compared to subconjunctival injections. Some drawbacks of these devices, however, need mentioning. To apply the collagen shield, the cornea is anaesthetized while the physician uses a blunt forceps to insert the hydrated or unhydrated shield. Contrary to medicated contact lenses, collagen shields often produce some discomfort and interfere with vision. In rabbits, collagen shields have been found to exacerbate ulcerations of alkali-burned corneas. [A new preparation referred to as collasomes consists of small pieces (1 mm x 2 mm x 0.1 mm) of collagen suspended in a 1% methylcellulose vehicle.

OCUFIT

The Ocufit is a sustained release, rod shaped device made of silicone elastomer, patented in 1992 and currently developed by Escalon Ophthalmics Inc. (Skillman, NJ). It was designed to fit the shape and size of the human conjunctival fornix. Accordingly, it does not exceed 1.9 mm in diameter and 25-30 mm in length, although smaller sizes for children and newborn babies are planned. The superiority of the cylindrical shape can be traced in an earlier paper by Katz and Blackman. They reported the effect of the size and shape of the inserts on tolerance and retention by human volunteers. These workers found that expulsion of rod shaped units was significantly ($P < 0.01$) less frequent than expulsion of oval, flat inserts.

A typical example of a rod-shaped insert is the Lacrisert (Merck and Co., Inc.), a cellulosic device used to treat dry-eye patients.

The insoluble Ocufit reportedly combines two important features, long retention and sustained drug release. When placed in the upper fornix of volunteers, placebo devices were retained for 2 weeks or more in 70% of the cases. Moreover, active disease (bacterial, allergic and adenoviral conjunctivitis, trachoma, episcleritis, anterior uveitis, cornea1 ulcers or scars) did not overtly affect the ability of the patients to retain the inserts. Tetracycline-loaded inserts released *in vitro* 45% of the drug over the 14-day period with an initial burst in the first day followed by a constant rate over the remaining period.

THE MINIDISC OCULAR
THERAPEUTIC SYSTEM

This monolytic polymeric device, originally described by Bawa *et al* . (Bausch and Lomb, Rochester, New York) and referred to as Minidisc ocular therapeutic system (OTS), is shaped like a miniature (diameter 4-5 mm) contact lens, with a convex and a concave face, the latter conforming substantially to the sclera of the eye. The particular size and shape reportedly allow an easy placement of the device under the upper or lower lid without compromising comfort, vision or oxygen permeability. When compared with another standard insert, the Lacrisert, the Minidisc was reported to require less time and less manual dexterity for insertion. Different versions of the device have been evaluated, such as, non-erodible hydrophilic, non-erodible hydrophobic and erodible.

Types	Description
Erodible inserts	The fabrication polymer is hydrophobic but biodegradable. Drug is released through the erosion of the surface of the insert.
Soluble inserts	The fabrication polymer is hydrophilic and water soluble. Drug release characteristics: Diffusion control for soluble drugs Dissolution control for less soluble drugs
Hydrophilic but water insoluble Inserts	The fabrication polymer is hydrophilic but water-insoluble. Drug release characteristics: Diffusion control for soluble drugs Dissolution control for less soluble drugs
Inserts using osmotic system	A polymeric matrix in which the drug is dispersed as discrete small domains. Upon placement in the cul-de-sac, tears are imbibed into the matrix because of an osmotic pressure gradient created by the drug, where upon the drug is dissolved and released.
Membrane-controlled diffusional inserts	The drug core is surrounded by a hydrophobic polymer membrane; this controls the diffusion of the drug from the core to the outside.

Q.12 Note on Intrauterine drug delivery system (IUDs)

The intrauterine device (IUD) is a long-term birth control method. Unlike IUDs that were used in the 1970s, present-day IUDs are small, safe, and highly effective. An Intrauterine Device (IUD) is a small piece of plastic that is inserted by a clinician into the uterus to prevent pregnancy. It is approximately 1½ inches (3cm) in length. There are several different types of IUDs. The most common IUD is T-shaped and coated with copper. This can be left in the uterus for 2-5 years. Another type of IUD contains a hormone (progestin) but it needs to be replaced once a year. Attached to the IUD are two plastic threads or strings that hang down through the cervix into the vagina. The cervix is the opening to the uterus. The threads or strings do not hang outside the body. The IUD can also be used as an emergency method of birth control. If an IUD is inserted within 7 days after unprotected vaginal sex it may prevent a pregnancy. An intrauterine device (IUD) is a small T-shaped plastic device that is placed in the uterus to prevent pregnancy. A plastic string is attached to the end to ensure correct placement and for removal. IUDs are an easily reversible form of birth control , and they can be easily removed. However, an IUD should only be removed by a medical professional. An IUD, or intrauterine device, is a small

contraceptive device made of flexible plastic. It's inserted into the uterus, where it provides highly effective long-term contraception. Two IUDs are currently available in the United States: The Copper T 380A (called ParaGard), which is wrapped in fine copper wire and lasts for ten years before it needs to be replaced. Many providers recommend the progestin IUD for women who suffer from extremely heavy, prolonged, or painful menstruation because it tends to lighten their periods or even suppress them altogether. And because they lose less blood, women using this IUD are less likely to develop iron-deficiency anemia, a condition that can cause fatigue and other symptoms.Some studies have found that women with copper IUDs tend to have a lower risk of endometrial cancer. And some experts suspect they'll find that the progestin IUD has the same effect, since that's the case for progestin-only contraceptives like the minipill and the shot. Intrauterine devices can be used as emergency contraception to prevent pregnancy up to 5 days after unprotected sexual intercourse, or sexual intercourse during which the primary contraception is believed to have failed (e.g. a condom was used, but it broke). Insertion of a copper-T IUD as emergency contraception is more than 99% effective, making it more effective than emergency contraceptive pills. The IUD is the world's most widely used safe and effective method of reversible birth control, currently used by nearly 160 million women. An Intrauterine Device (IUD) is a small object that is inserted through the cervix and placed in the uterus to prevent pregnancy. A small string hangs down from the IUD into the upper part of the vagina. The IUD is not noticeable during intercourse. IUDs can last 1-10 years. They affect the movements of eggs and sperm to prevent fertilization. They also change the lining of the uterus and prevent implantation. IUDs are 99.2-99.9% effective as birth control. They do not protect against sexually transmitted infections, including HIV/AIDS. The IUD is 98% effective in preventing pregnancy.

Types of IUDS

Copper IUDs

The copper IUD is the most commonly used type of IUD. It can be left in the body for up to 10 years. It can be removed at any time if a woman wishes to become pregnant or if she does not want to use it anymore. The arms of this IUD contain some copper, which is slowly released into the uterus. The copper prevents sperm from making their way through the uterus into the tubes and prevents fertilization. If fertilization does occur, the copper prevents the fertilized egg from implanting on the wall of the uterus.

Hormonal IUDs

Hormonal IUDs that contain progesterone must be replaced every 5 years. They can be removed at any time if a woman decides she wishes to become pregnant or if she does not want to use it anymore. Hormones are in the arms of the IUD and are released slowly into the uterus. The Mirena levonorgestrel-releasing intrauterine system (IUS) contains the hormone levonorgestrel (LNg), which is similar to progesterone. The LNg IUS causes cervical mucus to thicken to prevent sperm from entering the cervix and reaching the egg. Only about 1 in 1,000 women who use the LNg IUS experience accidental pregnancy in the first year. The LNg IUS reduces the risk of tubal pregnancies and pelvic inflammatory disease. It also dramatically decreases menstrual

blood loss. It is approved to protect women from pregnancy for up to 5 years when used in the United States and 7 years in Europe and Asia

Risk/ Side effects

During the first few weeks after insertion, you're more likely to develop pelvic inflammatory disease (PID), an infection that can affect the uterus, fallopian tubes, and ovaries, though your overall risk is still low. This infection, most commonly caused by chlamydia or gonorrhea, can lead to scarring that makes it more difficult to get pregnant later and, in rare cases, can even be fatal. The risk of PID is one reason it's important to return to your caregiver or clinic for a follow up visit in the first month after insertion, or sooner if you have any signs of infection. PID can be treated with antibiotics, and the sooner it's caught and treated, the less likely it is to cause long term harm. A very small number of women (about one to eight in 1,000) do become pregnant while using an IUD. For these women, there's a higher than average chance that the pregnancy is ectopic, meaning a fertilized egg has implanted outside of the uterus, typically in one of the fallopian tubes. This is a serious condition that requires immediate treatment. Some women who use the progestin IUD develop what are known as functional ovarian cysts. In most cases these cysts cause no problems and disappear on their own. In rare cases, they require surgery. Finally, the IUD can perforate the uterus while it's being put in, causing bleeding and injury and possibly requiring surgery to retrieve it, but this is quite rare. Women who are pregnant or who have abnormal bleeding or cancer of the cervix or cancer of the uterus should not use IUDs. However, in their discussion of IUDs, the Reproductive Health Technologies Project disagrees with this claim because IUDs are easily reversible.

The IUD is unlikely to cause any serious side effects. For a small number of women, the progestin IUD causes side effects such as acne, headaches, breast tenderness, and depression, which generally get better over time. And your odds of suffering these side effects is much lower than with other progestin-only contraceptives, such as the minipill and the shot, because the amount of progestin in your blood is much lower with the IUD. There are some side effects of the IUD, but not many. Uterine cramps (like menstrual cramps) or low backache when the IUD is inserted, and maybe for a few weeks after insertion. With the levonorgestrel IUS, likely have much lighter periods or none at all. With the copper IUD, you may have increased menstrual flow and cramps, but this usually lessens after the first few months, as your uterus gets used to the IUD. You can relieve any discomfort by over-the-counter medications, such as acetaminophen (Tylenol), ibuprofen (Advil, Motrin, and Nuprin), or naproxen sodium (Aleve). Some women have spotting or bleeding between menstrual periods with the IUD. There is a slightly increased risk of infection, called pelvic inflammatory disease (PID) during the first 6 weeks after the IUD is inserted. After that, the risk for PID is very low. Very rarely, the uterus can be injured when the IUD is inserted.

Effectiveness and mechanism

All second-generation copper-T IUDs have failure rates of less than 1% per year, and cumulative 10-year failure rates of 2-6%. A copper IUD may also be used as emergency contraception. If an

IUD is inserted within five days of unprotected intercourse, a woman's chance of pregnancy is reduced to that of ongoing IUD users. A large World Health Organization trial reported a cumulative 12-year failure rate of 2.2% for the T 380A (ParaGard) (an average failure rate of 0.18% per year over 12 years), equivalent to a cumulative 10-year failure rate of 1.8% following tubal ligation. The frameless GyneFix also has a failure rate of less than 1% per year. Worldwide, older IUD models with lower effectiveness rates are no longer produced. The presence of a device in the uterus prompts the release of leukocytes and prostaglandins by the endometrium. These substances are hostile to both sperm and eggs; the presence of copper increases this spermicidal effect. The current medical consensus is that spermicidal and ovicidal mechanisms are the only way in which IUDs work. Still, a few physicians have suggested they may have a secondary effect of interfering with the development of pre-implanted embryos; this secondary effect is considered more plausible when the IUD is used as contraception. Controversially, the possibility of this secondary effect has led some to consider the IUD an abortifacient. IUD mainly work by changing the intra-uterine environment and making it spermicidal. Nonmedicated IUD cause a sterile inflammatory response by producing a tissue injury of minor degree but sufficient enough to be spermicidal. Copper containing IUD, in addition, release free copper and copper salts that have both a biochemical and morphological impact on the endometrium and also produce alteration in cervical mucus and endometrial secretions. No measurable increase in serum copper is observed.

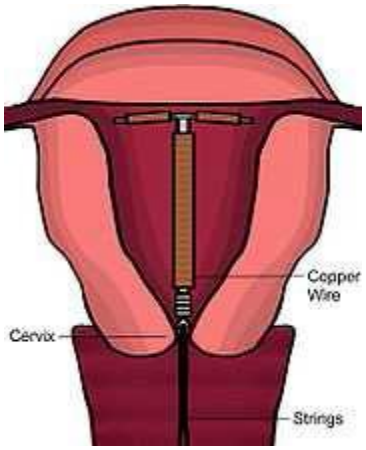


Figure- A diagram showing a copper IUD in place in uterus

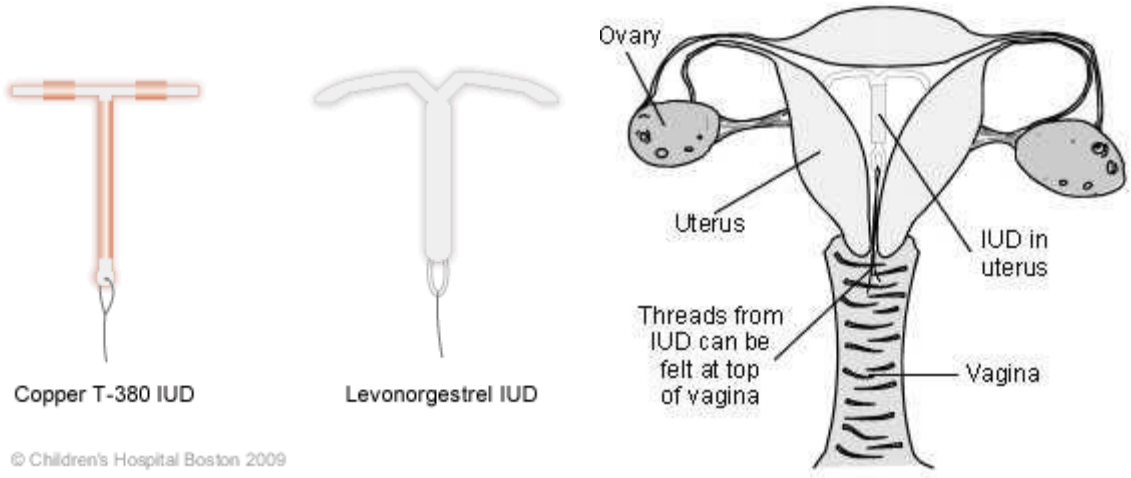


Figure-Intrauterine device used in uterus

Q.13 Note on Liposomes

Liposomes are spherical shaped small vesicles that can be produced from cholesterols, non toxic surfactants, sphingolipids, glycolipids, long chain fatty acids and even membrane proteins. Phospholipids spontaneously form a closed structure when dissolved in water with internal aqueous environment bounded by phospholipids bilayer membranes, this vesicular system is called as liposome. Liposomes are the drug carrier loaded with different variety of molecules such as small drug molecules, proteins, nucleotides and even plasmids. Liposomes were first described in 1961 by British hematologist Dr. Alec D Bangham. Liposomes were discovered when Bangham and R. W. Horne were testing the institute's new electron microscope by adding negative stain to dry phospholipids. The resemblance to the plasma lemma and the microscope pictures served as the first real evidence for the cell membrane being a bilayer lipid structure. Liposome can be formulated and processed to differ in size, composition, charge and lamellarity. Liposomal formulations of various therapeutic drugs have been commercialized.

CLASSIFICATION OF LIPOSOMES

1. Classification Based on Structure

Vesicle Types with their Size and Number of Lipid Layers

Vesicle type	Abbreviation	Diameter Size	No. of Lipid Layers
Unilamellar	UV	All size ranges	One
Small Unilamellar	SUV	20-100nm	One
Medium Unilamellar	MUV	More than 100nm	One
Large Unilamellar	LUV	More than 100nm	One
Giant Unilamellar	GUV	More than 1.0 µm	One
Oligo lamellar	OLV	0.1-1.0 µm	Approx 0.5
Multi lamellar	MLV	More than 0.5 µm	5-25
Multi vesicular	MV	More than 1.0 µm	Multi compartmental structure

2. Based on Method of Preparation

Different Preparation Methods and the Vesicles Formed by these Methods

Preparation Method	Vesicle Type
Single or oligolamellar vesicle made by reverse phase evaporation	REV
Multilamellar vesicle made by reverse phase evaporation method	MLV-REV
Stable pluri lamellar vesicle	SPLV
Frozen and thawed multi lamellar vesicle	FATMLV
Vesicle prepared by extrusion technique	VET
Dehydration- Rehydration method	DRV

3. Based on Composition

Different Liposome with their Compositions

Type	Abbreviation	Composition
Conventional	CL	Neutral or negatively charge phospholipids and cholesterol
Fusogenic	RSVE	Reconstituted sendai virus envelops
pH sensitive	-	Phospholipids such as PER or DOPE with either CHEMS or OA
Cationic	-	Cationic lipid with DOPE
Long circulatory	LCL	Neutral high temp, cholesterol and 5-10% PEG, DSP
Immuno	IL	CL or LCL with attached monoclonal antibody or recognition sequences

4. Based Upon Conventional Liposome

- Natural lecithin mixtures
- Synthetic identical, chain phospholipids
- Liposome with Glycolipids

5. Based Upon Speciality Liposome

- Bipolar fatty acid.
- Antibody directed
- Methyl/ Methylene x- linked
- Lipoprotein coated
- Carbohydrate coated
- Multiple encapsulated

STRUCTURAL COMPONENTS OF LIPOSOMES

The main components of liposomes are

- Phospholipids.
- Cholesterol.

Phospholipids

Phospholipids are the major structural components of biological membranes. The most common phospholipid used in liposomal preparation is phosphatidylcholine (PC). Phosphatidylcholine is an amphipatic molecule containing

- A hydrophilic polar head group, phosphocholine
- A glycerol bridge
- A pair of hydrophobic acyl hydrocarbon chains

Molecules of phosphtaditylcholine are not soluble in water. In aqueous media they align themselves closely in planar bilayer sheets in order to minimize the unfavourable action between the bulk aqueous phase and the long hydrocarbon fatty chain. Then the sheets fold on themselves to form closed sealed vesicles.

There are several phospholipids that can be used for the liposome preparation such as Dilauryl phosphotidyl choline (DLPC), Dimyristoyl phosphotidyl choline (DMPC), Dipalmitoyl phosphotidyl choline (DPPC), Distearoyl phosphotidyl choline (DSPC), Dioleolyl phosphotidyl choline (DOPC), Dilauryl phosphotidyl ethanolamine (DLPE), Dimyristoyl phosphotidyl ethanolamine (DMPE), Distearoyl phosphotidyl ethanolamine (DSPE), Dioleoyl phosphotidyl ethanolamine (DOPE), Dilauryl phosphotidyl glycerol (DLPG), Distearoyl phosphotidyl serine (DSPS).

Cholesterol

The role of cholesterol in formulation of liposomes was given below:

- Incorporation of sterols in liposome bilayer produces major changes in the preparation of these membranes.
- Cholesterol itself does not form a bilayer structure.
- However, cholesterol acts as a fluidity buffer. It makes the membrane less ordered and slightly more permeable below the phase transition and makes the membrane more ordered and stable above the phase transition. It can be incorporated into phospholipid membranes in very high concentration up to 1:1 or even 2:1 molar ratios of cholesterol to phospholipids.

MECHANISM OF VESICLE FORMATION

Lipid vesicles are formed when thin lipid films are hydrated and swelled. The hydrated lipid sheets detach during agitation and form large MLV which prevents the interaction of water with the hydrocarbon core of the bilayer at the edges. Once the particles formed, it is size reduced by sonication or by extrusion.

METHOD OF PREPARATION

I. Passive loading technique

1. Mechanical dispersion

Lipid Hydration Method

This is the common and most widely used method for the preparation of MLV. Round bottomed flask can be used for the preparation. The method involves formation of a thin film by drying the lipid solution and then hydrating the film by adding aqueous buffer and vortexing the dispersion. The hydration step is done at a temperature above the gel liquid crystalline transition temperature of the lipid or above the transition temperature of the highest melting component in the lipid mixture. Depending upon their solubilites the compounds to be encapsulated are added either to aqueous buffer or to organic solvent containing lipids. The disadvantages of the method include low internal volume, less encapsulation efficiency and varying size. The less encapsulation efficiency can be overcome by hydrating the lipids in presence of immiscible organic solvents like petroleum ether, diethyl ether. Then it is emulsified by sonication. MLVs are formed by removing organic layer by passing nitrogen.

Micro emulsification

This method is used for preparing small lipid vesicles in commercial quantities. This can be achieved by microemulsifying lipid compositions using high shearing stress generated from high pressure homogenizer. Microemulsion for biological applications can be produced by adjusting the speed of rotations from 20 to 200.

Sonication

In this method MLVs are sonicated either with a bath type sonicator or probe sonicator. The main drawbacks of this method are very low internal volume/encapsulation efficiency, degradation of phospholipids, exclusion of large molecules, metal contamination from probe tip and presence of MLV along with SUV.

French Pressure Cell Method

The method involves the extrusion of MLV through a small orifice at 20,000 psi at 4°C. The method has several advantages over sonication method. The method is simple, rapid, and reproducible and involves gentle handling of unstable materials. The resulting liposomes are larger than sonicated SUVs. The disadvantages include difficulty in achieving temperature and less working volume (about 50 mL maximum).

Membrane extrusion

In this method, suspension of heterogeneous size liposomes is passed through a polymer filter having a web-like construction providing a tortuous-path capillary pore, network of interconnected, and a membrane thickness of at least about 100 microns. The processed liposomes have a narrow size distribution and selected average size less than about 0.4 microns.

Dried reconstituted vesicles

In this method the preformed liposomes are added to an aqueous solution containing drug or mixed with a lyophilized protein, followed by dehydration of mixture.

Freeze-Thaw Method

In this method the SUVs are rapidly frozen, followed by slow thawing. The sonication disperses aggregated materials to LUV. The fusion of SUV during the processes of freezing and thawing leads to the formation of ULV.

This type of fusion is strongly inhibited by increasing the ionic strength of the medium and by increasing the phospholipid concentration. The entrapment efficiencies of 20 to 30% were obtained by this method.

2. Solvent dispersion

Ethanol Injection Method

A lipid solution of ethanol is rapidly injected to an excess of buffer, which leads to the immediate formation of MLVs. The major drawback of the method is that the particles may be with heterogeneous size distribution (30-110 nm). Another drawback is removal of all ethanol is difficult, which may lead to form azeotrope with water.

Ether Infusion Method

A solution of lipids dissolved in diethyl ether or ether methanol mixture is slowly injected to an aqueous solution of the drug, to be encapsulated at a temperature of 55-65°C under reduced pressure. The liposomes reformed by subsequent removal of ether under vacuum.

The main drawbacks of the method are exposure of drugs and lipids to organic solvents and high temperature which may cause degradation. Further the size may vary from 70 -190 nm.

Double emulsification

In this method, a primary emulsion is prepared by dissolving the drug in an aqueous phase (w1) which is then emulsified in an organic solvent of a polymer to make a primary w1/o emulsion. This primary emulsion is further mixed in an emulsifier-containing aqueous solution (w2) to make a w1/o/ w2 double emulsion. The removal of the solvent leaves microspheres in the aqueous continuous phase, which are collected by filtering/centrifuging.

Reverse-phase evaporation

The lipid mixture is taken in a round bottom flask followed by removal of solvent under reduced pressure by a rotary evaporator. The system is purged with nitrogen and the lipids are re-dissolved in the organic phase. The reverse phase vesicles will form in this phase. The usual solvents used are diethyl ether and isopropyl ether. Aqueous phase which contains drug to be encapsulated is added after the lipids are re-dispersed in this phase. The system is kept under continuous nitrogen and the two phase system is sonicated until the mixture becomes clear one-phase dispersion. The mixture is then placed on the rotary evaporator and the removal of organic solvent is done until a gel is formed followed by removal of non-encapsulated material. The resulting liposomes are called reverse-phase evaporation vesicles.

3. .Detergent removal

Lipids are solubilised by the detergents at their critical micellar concentrations. The micelles become progressively richer in phospholipid as the detergent is removed by dialysis and finally combine to form LUVs. The advantages of detergent dialysis method are outstanding reproducibility and production of liposome populations of homogenous size. The main drawback of the method is the retention of detergent contaminants.

II. Active loading technique

Proliposome

Lipid and drug are coated onto a soluble carrier to form free-flowing granular material in pro-liposome which forms an isotonic liposomal suspension on hydration. The pro-liposome approach may provide an opportunity for cost-effective large scale manufacture of liposomes containing particularly lipophilic drugs.

Lyophilization

The removal of water from products in the frozen state at extremely reduced pressure is called lyophilization (freeze drying). The process is generally used to dry products that are thermolabile which may be destroyed by heat-drying. This technique has a great potential to solve long term stability problems with respect to liposomal stability. Leakage of entrapped materials may take place during the process of freeze- drying and on reconstitution.

SIZING OF LIPOSOMES

Size characteristics of liposome have a major effect on the application they can be used. Physical integrity and stability of lipid bilayers structure influence the therapeutic applications of liposome. Therefore particle size of the liposome must be considered for the liposome production pr.ocedure and it must be predictable and reproducible with particle size distribution within a certain size range. Sequential extrusion, gel chromatography and sonication are the common methods of sizing of liposomes, But ultimately these methods have the following disadvantages:

1. Exclusion of oxygen is difficult which result in per oxidation reaction.
2. Titanium probes shed metal particle resulting in contamination.
3. They can generate aerosols, which exclude them from use with certain agents.

These above problems are mainly related with the probe sonication but these problems can be removed by using the bath sonication.

CHARACTERIZATION OF LIPOSOMES

Liposome should be characterized for visual appearance, turbidity, size distribution, lamellarity, concentration, composition, presence of degradation products, and stability. The behaviour of liposomes in both physical and biological system is governed by these factors; therefore liposomes are characterized for physical attributes and chemical compositions.

A. Biological characterization

- Sterility - Aerobic/anaerobic culture
- Pyrogenicity - Temperature (Rabbit) response
- Animal toxicity - Monitoring survival of animals (rats)

B. Chemical characterization

- Phospholipids concentration - HPLC/Barrlet assay

- Cholesterol concentration - HPLC / cholesterol oxide assay
- Drug concentration - Assay method
- Phospholipids peroxidation - UV observance
- Phospholipids hydrolysis - HPLC/ TLC
- Cholesterol auto-oxidation - HPLC/ TLC
- Anti-oxidant degradation - HPLC/TLC
- PH - PH meter
- Osmolarity - Osmometer

C. Physical Characterization

- Vesicle shape, and surface morphology – SEM / TEM
- Vesicle size and size distribution - Dynamic light scattering, TEM.
- Surface charge - Free flow electrophoresis
- Electrical surface Potential and pH - Zeta potential and pH sensitive probes
- Lamellarity - NMR
- Phase behaviour - DSC, freeze fracture electron microscopy
- Percent capture - Mini column centrifugation, gel exclusion
- Drug release - Diffuse cell / dialysis

1. Visual Appearance

Based on the particle size and composition the appearance of the liposomal suspension may be varying from translucent to milky. The samples are homogeneous if the turbidity has a bluish shade; the presence of a nonliposomal dispersion is by flat, grey colour and is most likely a disperse inverse hexagonal phase or dispersed micro crystallites. An optical microscope can detect liposome of size greater than 0.3 μm as well as contamination with larger particles.

2. Determination of Liposomal Size

Size Distribution

It is usually measured by dynamic light scattering. Liposomes with relatively homogeneous size distribution are reliable for this method. Gel exclusion chromatography is a simple method, in which a truly hydrodynamic radius can be detected. Sephacryl-S100 can separate liposome in size range of 30-300nm. Sepharose -4B and -2B columns can separate SUV from micelles.

3. Determination of lamellarity

The lamellarity of liposomes can be measured by electron microscopy or spectroscopic techniques. The NMR spectrum of liposome is recorded most frequently with and without the addition of a paramagnetic agent that shifts or bleaches the signal of the observed nuclei on the outer surface of liposome.

4. Liposome Stability

Liposome should be physically, chemically, and biologically stable. Physical stability indicates the ratio of lipid to therapeutic agent and steadiness of the size. The chemical stability may be affected by two degradation pathways, oxidative and hydrolytic. Oxidation of phospholipids in liposomes mainly takes place in unsaturated fatty acyl chain-carrying phospholipids.

These chains are oxidised in the absence of particular oxidants. Reduction of oxidation can be achieved by storage at low temperatures and protection from light and oxygen.

5. Entrapped Volume

The entrapped volume of liposome (in µL/ mg phospholipids) can often be deduced from measurements of the total quantity of solute entrapped inside liposome assuring that the concentration of solute in the aqueous medium inside liposomes is the same after separation from unentrapped material. For example, in two phase method of preparation, water can be lost from the internal compartment during the drying down step to remove organic solvent.

6. Surface Charge

Liposomes are usually prepared using charge imparting / constituting lipids and hence it is imparting to study the charge on the vesicle surface. The two methods used in general to assess the charge are free flow electrophoresis and zeta potential measurement.

STABILIZATION OF LIPOSOME

Usually liposomes may create problem in stability during the storage period. In general certain parameters should be considered to achieve successful formulation of stable liposomal drug product:

- Processing with fresh, purified lipids and solvents.
- Avoidance of high temperature and excessive shearing stress.
- Maintenance of low oxygen potential
- Use of antioxidant or metal chelators.
- Formulating at neutral pH.
- Use of lyo-protectant when freeze drying.

ENTRAPMENT OF DRUGS INTO LIPOSOME BILAYERS

Liposomes, because of their biphasic character, can act as carrier for both lipophillic and hydrophillic drugs.

Depending upon their solubility and partitioning characteristics, the drug molecules are located differently in the liposomal environment and exhibit different entrapment and release properties.

APPLICATIONS OF LIPOSOMES

Liposomes have great pharmaceutical applications in oral and transdermal drug delivery systems. Reduction in the toxic effect and enhancement of the effectiveness of drugs are achieved by this drug delivery system. The targeting of liposome to the site of action takes place by the attachment of amino acid fragment that target specific receptors cell. Several modes of drug delivery application have been proposed for the liposomal drug delivery system, few of them are as follows:

1. Enhancement of solubilisation (Amphotericin-B, Paclitaxel)
2. Protection of sensitive drug molecules (Cytosine arabinosa, DNA, RNA, Ribozymes)
3. Enhancement of intracellular uptake (Anticancer, antiviral and antimicrobial drugs)
4. Alteration in pharmacokinetics and bio-distribution (prolonged or SR drugs with short circulatory half life)

Several recent applications of liposomal drug delivery system are as follows

A. Liposome for Respiratory Drug Delivery System

Liposome is widely used in several types of respiratory disorders. Liposomal aerosols can be formulated to achieve sustained release, prevent local irritation, reduced toxicity and improved stability. Whilst preparing liposomes for lung delivery, composition, size, charge, drug/lipid ratio and drug delivery method should be considered. The liquid or dry form is taken for the inhalation during nebulisation. Drug powder liposome is produced by milling or by spray drying.

B. Liposome in Eye Disorders

Liposome has been used widely to treat disorders of eye. The disease of eye includes dryness, keratitis, corneal transplant rejection, endopthelmitis and proliferative vitreo retinopathy. Retinal diseases are important cause of blindness. Liposome is used as vector for genetic transfection and monoclonal antibody directed vehicle.

Applying of focal laser to heat induced release of liposomal drugs and dyes are the recent techniques of the treatment of selective tumour and neo-vascular vessels occlusion, angiography, retinal and choroidal blood vessel stasis.

C. Liposome as Vaccine Adjuvant

Liposome has been established firmly as immunoadjuvant that is potentiating both cell mediated and noncell mediated immunity. Liposomal immuno-adjuvant acts by slow release of encapsulated antigen on intramuscular injection and also by passive accumulation within regional lymph node. The accumulation of liposome to lymphoid is done by the targeting of liposome with the help of phosphotidyl serine. Liposomal vaccine can be prepared by inoculating microbes, soluble antigen and cytokinesis of deoxyribonucleic acid with liposome.

D. Liposomes for Brain Targeting

The biocompatible and biodegradable character of liposomes makes its used in brain drug delivery system. Liposomes with a small diameter (100 nm) and large diameter undergo free diffusion through the BBB. However small unilamellar vesicles (SUVs) coupled to brain drug transport vectors may be transported by receptor mediated or absorptive mediated transcytosis through the BBB. Cationic liposomes undergo absorptive mediated endocytosis into cells whereas the same undergoing absorptive mediated transcytosis through the BBB has not yet been determined. Liposomes coated with the mannose reach brain and assist transport of loaded drug through BBB. The neutropeptides, leuenkephaline and mefenkephalin kyoforphin normally do not cross BBB when given systemically. The anti depressant amitriptylline normally penetrate the BBB, due to versatility of this method.

E. Liposome as Anti-Infective Agents

The diseases like leishmaniasis, candidiasis, aspergelosis, histoplasmosis, erythrococosis, gerardiasis, malaria and tuberculosis can be treated by incorporating and targeting the drug using liposomal carrier.

F. Liposome in cancer therapy

All cancer drugs on long term usage produce stern toxic effects. The liposomal approach causes targeting of drug to tumour with lesser toxic effects. The small and stable liposome is passively targeted to different tumour because they can circulate for longer time. Nowadays many anti-

cancer herbal drugs also formulated into liposomes to provide better targeting with enhanced bioavailability.

Q.14 Note on Probiotics and Prebiotic

The benefits of Probiotics have been recognized and explored for over a century. Probiotic approach can be effective in selectively inhibiting oral pathogens or modulate the microbial composition of dental plaque. Prebiotics are nondigestible dietary supplements.Prebiotics are designed to improve health by stimulating numbers and/or activities of probiotics like Bifidobacteria and Lactobacilli. Prebiotics have been proved to be an aid to complement probiotics in the treatment of oral diseases. Their function is to enhance the growth and activity of beneficial organisms and simultaneously suppress the growth and activity of potentially deleterious bacteria. Synbiotics refer to nutritional supplements combining probiotics and prebiotics that are thought to act together; i.e. synergism. The potential benefits of synbiotic therapy are obvious, however, the great challenge, as is the case with probiotics and prebiotics alone, is to determine the best combination for each disease setting and each individual. Probiotics and prebiotics that are thought to act together; i.e. synergism. It has been suggested that a combination of a probiotic and a prebiotic, i.e. Synbiotics might be more active than either a probiotic or prebiotic alone.

Probiotics

Probiotic is derived from Latin word "pro"-for and Greek word "biotic"- life. The role of fermented milk in human diet was known even in Vedic times. But, the scientific interest in this area boosted after the publication of the book entitled 'The Prolongation of Life' by Ellie Metchinkoff in 1908. He suggested that people should consume fermented milk containing lactobacilli to prolong their lives.

At this time Henry Tissier, a French paediatrician, observed that children with diarrhoea had in their stools a low number of bacteria characterized by a peculiar, Y shaped morphology. These bacteria were, on the contrary, abundant in healthy children. he suggested that these bacteria could be administered to patients with diarrhoea to help restore a healthy gut flora. The works of Metchnikoff and Tissier were the first to make scientific suggestions about the probiotic use of bacteria, even if the word "probitic" was not coined unti 1960.

The term Probiotic was first introduced by Lily and Stillwell (1965). The first probiotic bacteria studied were lactic acid bacteria. Lactobacillae & Bifidobacterium are the main probiotics. Other probiotics are Escherichia, Enterococcus, Bacillus, Saccharomyces, Streptococcus and Propionibacteria. In 1984 Hull identified the first probiotic species, the lactobacillus acidophilus. Later in 1991, Holcombh identified bifidobacterium bifidum. WHO in 1994 described the probiotics as next most important in immune defense system following antibiotic resistance.

Definition of Probitics

Author	Definition
Lilly &	Substances produced by microorganisms that promote the growth of other

Stillwell ,1965	microorganisms
Parker, 1974	Organisms and substances that contribute to intestinal microbial balance
Fuller,1989	A live microbial feed supplement that beneficially affects the host animal by improving its intestinal microbial balance
Havenaar & Huis Int Veld,1992	A viable monoculture or mixed-culture of microorganisms that, when applied to animal or human, beneficially affects the host by improving the properties of the indigenous microflora
Schaafsma,1996	Living microorganisms that, upon ingestion in certain numbers, exert health benefits beyond inherent basic nutrition
Naidu et al, 1999	A microbial dietary adjuvant that beneficially affects the host physiology by modulating mucosal and systemic immunity, as well as by improving nutritional and microbial balance in the intestinal tract.
Schrezemeir & De Vrese,2001	A preparation of, or a product containing, viable, defined microorganisms in sufficient numbers, which alter the microflora (by implantation or colonization) in a compartment of the host and as such exert beneficial health effects in this host
FAO/WHO Report,2001	Live microorganisms that , when administered in adequate amounts, confer a health benefit to the host

Composition of Probiotics

Probiotics, which are regulated as dietary supplements and foods, consist of yeast or bacteria. They are available as capsules, gels, pastes, tablets, packets, liquids, or powders, and are contained in various fermented foods, most commonly yogurt or dairy drinks. Probiotic products may contain a single microorganism or a mixture of several species. Probiotics can be bacteria, moulds, yeast. But most probiotics are bacteria. Among bacteria, lactic acid bacteria are more popular.

Criteria for Probiotics

Fuller in 1989 listed the following as features of a good probiotic. It should be A strain, which is capable of exerting a beneficial effect on the host animal, g. Increased growth or resistance to disease. Non-pathogenic and non-toxic. Present as viable cells, preferably in large numbers. Stable and capable of remaining viable for long periods under storage and field conditions.

Currently Used Probiotics

Bacteria

Lactobacillus: acidophilus, sporogenes, plantarum, rhamnosum, delbrueck, reuteri, fermentum, lactus, cellobiosus, brevis

Bifidobacterium: bifidum, infantis, longum, thermophilum, animalis
Streptococcus: lactis, cremoris, alivarius, intermedius
Leuconostoc
Pediococcus
Propionibacterium
Bacillus
Enterococcus
Faecium
Yeast and moulds
cerevisiae
niger
oryzue
Pintolopesii
Sacharomyces boulardii

Therapeutic Actions of Probiotics

Reduces progression of AIDS.
Enhancement of calcium absorption.
Competition against harmful microorganisms including Candida, preventing colonisation of pathogens through the production of inhibitory substances including acids and hydrogen peroxide and natural antibiotics
Reduction in liver toxicity
Enhancement of peristalsis, digestion, regularity and re-absorption of nutrients, In infants, promotion of healthy digestive tract colonisation
Enhancement and balance of oestrogen levels, prevention of osteoporosis through increased calcium uptake
Enhancement of vitamin status (B, K), digestion of proteins, fats, carbohydrates.
Increased resistance to infectious diseases
Alleviate lactose intolerance
Prevention from gut, diarrhoea, gastritis, vaginal and urogenital infections
Reduction in blood pressure and regulation of hypertension,serum cholesterol concentration
Reduction in allergy, respiratory infections
Resistance to cancer chemotherapy and decreasing risk of colon cancer

Probiotic Products

A culture concentrate added to a beverage or food (such as a fruit juice).
Inoculated into prebiotic fibers.
Inoculants into a milk-based food (dairy products such as milk, milk drink, yoghurt).
As concentrated and dried cells packaged as dietary supplements (non-dairy products).

Different Means of Probiotic Administration for Oral Health Purposes

AUTHOR	VEHICLE	STRAIN	RESULT

Caglar E et al 2005	Straw, tablet	L. reuteri ATCC 55 730	S.mutans level reduction
J.P. Burton et el 2006	Lozenge	S. salivarius	Reduces oral VSC (Volatile sulphur compounds) levels
K. Hatakka et al 2007	Cheese	L. rhamnosus GG; Prorionibacterium JS	Reduced risk of high yeast counts and Hyposalivation
Kang et al 2005	Rinse solution	W. cibaria	Reduction of VSC
Montalto M et al 2004	Capsule, liquid	L. sporogenes, L.bifidum,L.bulgaricus, L. thermophilus, L.acidophilus, L. casei, L. rhamnosus	Increased salivary counts of lactobacilli without significant decrease in S. mutans counts
Yli-Knuuttila H et al 2006	Yogurt drink	L. rhamnosus GG	Temporary oral cavity colonization

Mechanism of Action of Probiotics

Possible Modes of Action of Probiotic

Suppression of viable count by

(a) Production of antibacterial compounds

(b) Competition for nutrients

(c) Competition for adhesion sites

Alteration of microbial metabolism

(a) Increased enzyme activity

(b) Decreased enzyme activity

Stimulation of immunity

(a) Increased antibody levels

(b) Increased macrophage activity

Role of Prebiotics in Dentisry

Most probiotics are in dairy forms containing high calcium, possibly reducing demineralization of teeth. It is possible that these act at bio-film to keep pathogens away and occupy a space that might otherwise be occupied by a pathogen. Probiotics should adhere to dental tissues to establish a cariostatic effect and thus should be a part of the bio-film to fight the cariogenic

bacteria. The duration of their stay locally also is important for beneficial effect. Ideal vehicles of probiotics installation are yogurt, milk and cheese.

Some of the hypothetical mechanism of probiotics action in the oral cavity is by:

Direct interaction in dental plaque

Involvement in binding of oral micro-organisms to proteins

Action on plaque formation and on its complex ecosystem by competing and intervening with bacterial attachments.

Involvement in metabolism of substrate and production ofchemicals that inhibit oral bacteria

Side Effects and Safety Aspects of Probiotics

Probiotics may theoretically be responsible for four types of side effects: systemic infections, deleterious metabolic activities, excessive immune stimulation in susceptible individuals, and gene transfer. Cases of infection due to lactobacilli and bifidobacterium are extremely rare and are estimated to represent 0.05 – 0.4% of cases of infective endocarditis and bacteraemia.

In general gas & bloating is one of the side effects of eating probiotic supplement. Probiotic can heighten & stimulate the immune system .So there is a great chance that people with underlying health issues can catch infections caused by probiotics. Till date no pathogenic or virulence properties have been found for Lactobacilli, Bifidobacterium or Lactococci.

How to assess the safety of probiotic products?

Three approaches can be used to assess the safety:

1) Studies on the intrinsic properties of the strain.

2) Studies on the pharmacokinetics of the strain.

3) Studies searching for interactions between the strain and the host.

Disadvantages of Probiotics:

Liquid preparations like yogurt have some major disadvantages i) short shelf- life, ii) bacteria damaged by pasteurization and/or centrifugation iii) use of additives and preservatives iv) difficult transport and storage because of its bulky nature v) use of normally only one or more strains of bacteria (multiple strains probiotics are more potent vi) damage by stomach acidity vii) refrigeration requirement.

Freeze dried powder probiotics have some disadvantages such as i) bacteria damage by freeze drying ii) short powder shelf life iii) upon absorption of water by powder, bacteria become activated and die iv) poor adherence, colonization and survival in the gut due to damage caused by freeze drying v) Probiotics may become weakened due to addition of stabilizers and preservatives.

Prebiotics

The bacterial population of the human gastrointestinal tract constitutes an enormously complex ecosystem. Most of these organisms are beneficial (e.g. bifidobacterium and lactobacillus) but some are harmful (e.g. Salmonella species, Helicobacter pylori, Clostridium perfringens). Some dietary substances, the so-called prebiotics can favor the growth of these beneficial bacteria over that of harmful ones.

Prebiotics are defined as non-digestible or low-digestible food ingredients that benefit the host organism by selectively stimulating the growth or activity of one or a limited number of probiotic bacteria in the colon.

Classification of Prebiotics

Based on the number of monomers linked together, prebiotics can be classified:

Disaccharides

Oligosaccharides (3-10 monomers)

Polysaccharides

Commonly Used Prebiotics

Lactulose, galacto-oligosaccharides, fructo-oligosaccharides, inulin and its hydrolysates, malto-oligosaccharides, and transgalacto-oligosaccharides. The main end products of carbohydrate metabolism are short-chained fatty acids, namely acetate, butyrate and propionate, which are further used by the host organism as an energy source

Prebiotic Products

Prebiotic oligosaccharides can be produced in three different ways: by extraction from plant materials, microbiological synthesis or enzymatic synthesis, and enzymatic hydrolysis of polysaccharides. Prebiotics are naturally found plenty in certain fruits like bananas, asparagus, garlic, tomato and onion wheat.

Criteria for Prebiotics

Neither hydrolyzed nor absorbed in the upper part of the gastrointestinal tract

A selective substrate for one or a limited number of beneficial bacteria commensal to the colon, which is stimulated to grow and/or are metabolically activated

Consequently, be able to alter the colonic flora in favour of a healthier composition

Induce luminal or systemic effects that are beneficial to the host health.

Therapeutic Actions of Prebiotics

The positive effects of prebiotics include antimicrobial, anticarcinogenic, hypolipidemic, glucose modulatory and anti-osteoporotic activities. They may be used for the treatment of constipation, hepatic encephalopathy and inflammatory bowel disease. They can protect against some intestinal pathogens and may exert favourable lipid effects as well as have some benefit in diabetes mellitus. Besides, prebiotics also have a very important role in improving mineral absorption and balance, for instance, they may enhance the colonic absorption of some minerals.

Benefits of Prebiotic Supplemented Formulas

Clearly, breast milk is the “gold standard” for neonatal and infant nutrition and is recommended by the American Academy of Pediatrics as the nutrition.Use of prebiotic-supplemented infant formulas may have benefits for the infant who does not receive mother’s milk. The benefits are,

Higher counts of Bifidobacteria by 4 weeks of age. An increased number of Bifidobacteria is associated with lower numbers of intestinal pathogens.

The pattern of bifidobacterial sub-species is similar to the pattern of the breast-fed infant.

Prebiotic formulas result in stool pH and short-chain fatty acid patterns similar to the breast-fed infant.

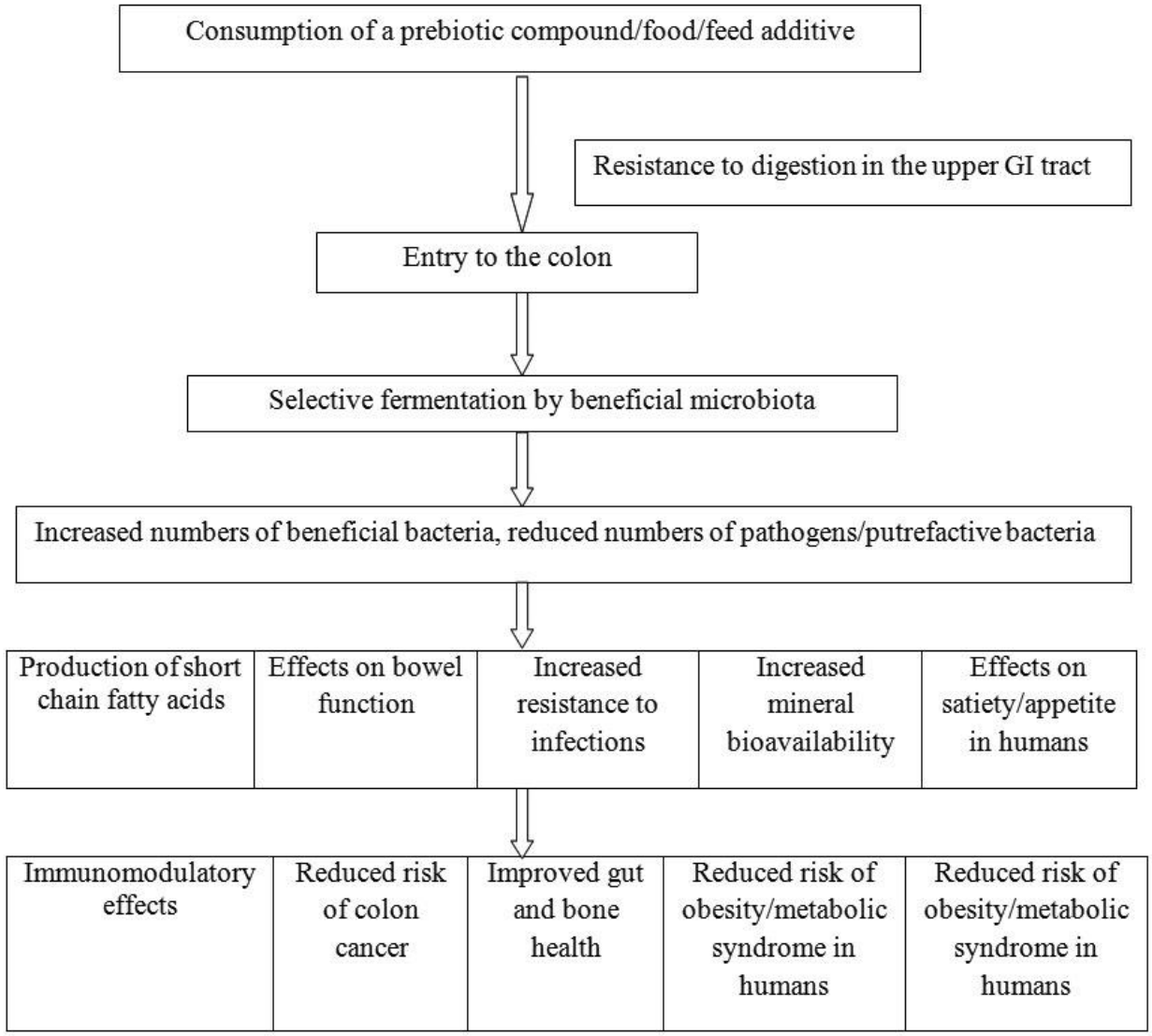
Stool frequency and consistency is more like the breast-fed infant.
Reduced allergic reaction (atopic dermatitis) and reduced URI in the first year of life.
Fewer episodes of acute diarrhoea.
Prebiotic-supplemented formula is easily tolerated, with no difference in growth patterns.

Studies Using Prebiotic-Supplemented Formulas

Study	Prebiotic & quantity	Outcomes
Bruzzese et al 2006	GOS/FOS or control	Infants on prebiotic formula had fewer episodes of acute diarrhea, fewer upper respiratory infections
Moro et al 2006	0.8 g/dL of GOS, FOS and control hydrolysed protein formula	Incidence of atopic dermatitis significantly reduced in the infant fed prebiotic formula
Costalos et al 2007	0.4 g/dL of GOS and FOS and control	Prebiotic formula well tolerated, normal growth trend toward higher percentage of Bifidobacterium and lower percentage of E. coli in stool, suppresses Clostridium in stool
Ziegler et al 2007	0.4 g/dL PDX,GOS or 0.8 g/dL PDX,GOS and LOS or control	Looser stools on either prebiotic formula.more adverse events: diarrhoea, eczema, in supplemented groups
Scholtens et al 2008	0.6 g /dL FOS and GOS	At 27 weeks the concentration of secretory IgA was higher in prebiotic group than control, also Bifidobacterium percentage higher than control and Clostridium lower
Arslonaglu et al 2008	0.8 g /dL GOS/FOS	Formula fed for first six months; follow up for 2 years. Prebiotic group had significantly lower allergic symptoms – atopic dermatitis, wheezing, urticaria, fewer upper respiratory infections than controls during the first 2 years

FAGA—full-term appropriate for gestational age; GOS—galacto-oligosaccharides; FOS—fructo-oligosaccharides; PDX—Polydextrose; LOS—Lactulose.

MODE OF ACTION OF PREBIOTICS AND HEALTH BENEFITS IN HUMANS AND ANIMALS[34]

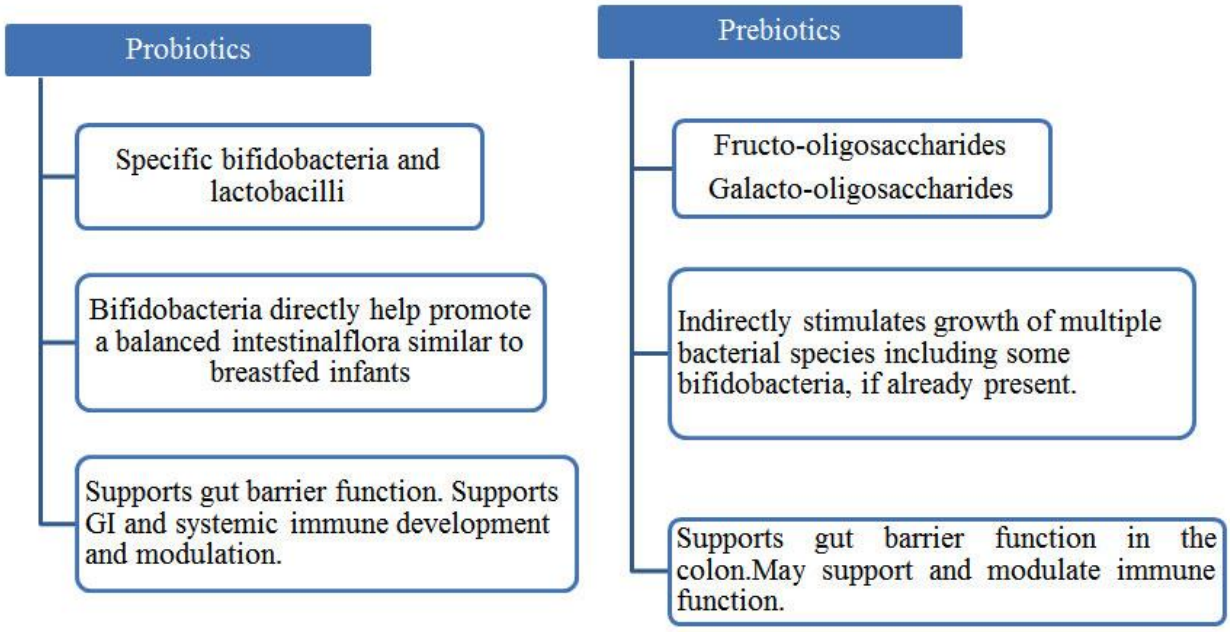


Relationship Between Prebiotics and Probiotics

Prebiotics when combined with probiotics have many advantages. Basically, prebiotics selectively stimulate the growth of probiotics, which is dose and strain dependent. Prebiotics serve as a selective growth substrate for the probiotics strain during fermentation, during the period of storage, or during its passage through the gut. These two combinations implant live microbial dietary supplements and create a congenial environment for their survival in gut flora. Thereby, this environment in gut flora improves healthy microbial balance. So, the combination of prebiotics and probiotics may have additive and synergistic effect in providing better oral health conditions. An essential requirement for a microorganism to be an oral probiotic is its ability to adhere to and colonize surfaces in the oral cavity. Microorganisms generally considered as probiotics may not have oral cavity as their inherent habitat and, subsequently, their

possibility to confer benefit on oral health is then questionable. Probiotics and prebiotics could affect the host in combination by synergistic action.

COMPARISON OF PROBIOTICS Vs PREBIOTICS



Synbiotics

A synbiotic has been defined as 'a mixture of probiotics and prebiotics that beneficially affects the host by improving the survival and implantation of live microbial dietary supplements in the GI tract, by selectively stimulating the growth and/or activating the metabolism of one or a limited number of health-promoting bacteria, and thus improving host welfare'.

The main reason for using a synbiotic is that a true probiotic, without its prebiotic food, does not survive well in the digestive system. Without the necessary food source for the probiotic, it will have a greater intolerance for oxygen, low pH, and temperature. As prebiotics provides a great place for probiotics to thrive, the population of these good bacteria is known to preserve. Studies have shown that by harnessing both the benefits of these prebiotics and probiotics into synergy, the number of good bacteria in the digestive systems increased many folds for the betterment of our health.

Synbiotics work in two ways i) by improving the viability of probiotics and ii) by delivering specific health benefits. The intake of a synbiotic food leads to a modulation of the gut metabolic activities with a maintenance of the gut biostructure. In particular, the significant increase of short chain fatty acids, ketones, carbon disulfide and methyl acetate following the feeding period suggested potential health promoting effects of the synbiotic food.

Therapeutic Actions Of Synbiotics

For therapeutic efficacy, the desirable characteristics of synbiotics include antimicrobial and anticarcinogenic qualities, antidiarrheal aspects, antiallergenic qualities, osteoporosis prevention,

reduction in serum fats and blood sugars, regulation of the immune system, and treating liver-related brain dysfunction.

Q.15 Note on Grastro retentive drug delivery system

Oral administration is the most convenient mode of drug delivery and is associated with superior patient compliance as compared to other modes of drug intake. Approximately 50% of the drug delivery systems available in the market are oral drug delivery systems which have more advantages due to patient acceptance and ease of administration. The oral absorption of drugs is often limited due to short gastric retention time (GRT), that is, the time required for the content of the stomach to enter small intestin. Drugs that are easily absorbed from the GIT and have a short half-life are eliminated quickly from the blood circulation, so they require frequent dosing. To avoid this drawback, the oral sustained-controlled release formulations have been developed in an attempt to release the drug slowly into the GIT and maintain an effective drug concentration in the serum for longer period of time. However, such oral drug delivery devices have a physiological limitation of gastric retention time (GRT), variable and short gastric emptying time can result in incomplete drug release from the drug delivery system (DDS) in the absorption zone (stomach or upper part of small intestine), leading to diminished efficacy of the administered dose.

When the drug is formulated with a gel forming polymer such as semisynthetic derivatives of cellulose, it swells in the gastric fluid with a bulk density less than one. It then remains buoyant and floats in the gastric fluid, and prolongs GRT. Single-unit formulations are associated with problem being obstructed in the gastrointestinal tract, which may have a potential danger of producing irritation. On the other hand, a floating system made of multiple unit forms has relative merits compared to a single-unit preparation. On each subsequent gastric emptying, sunk particles will spread out over a large area of absorption sites, increasing the opportunity for drug release profile and absorption in a more or less predictable way. Moreover, since each dose consists of many sub-units, the risk of dose dumping is reduced.

Gastric emptying of dosage form is an extremely variable process and its ability to prolong and control the emptying time is valuable asset for dosage forms, which reside in the stomach for a long period of time than conventional dosage forms. Several difficulties are faced in designing controlled released systems for better absorption and enhance the bio-availability. Conventional oral dosage forms such as tablets, and capsules provide specific drug concentration in systemic circulation without offering any control over drug delivery and also cause great fluctuations in plasma drug levels. Although single unit floating dosage forms have been extensively studied, these single-unit dosage forms have the disadvantage of a release all or nothing during emptying process while the multiple unit particulate system pass through the GIT to avoid the vagaries of gastric emptying and thus release the drug more uniformly. The uniform distribution of these multiple unit dosage forms along the GIT could result in more reproducible drug absorption and reduced risk of local irritation; this gave birth to oral controlled drug delivery and led to development of gastro retentive floating microspheres. This floating dosage form enhance bio-

availability, having a dissolution and/or stability problem in the small intestine fluids, being locally effective in the stomach, being absorbed only in the stomach and/or upper part of the intestine.

Functions of stomach

The stomach carries three major functions. It stores food, digest food and delivers food to the small intestine at a rate that the small intestine can handle.

1. Acts as a reservoir for holding food before it release into the small intestine.
2. Secrete gastrin into the blood.
3. Secretes gastric juice, which contains hydrochloric acid, pepsin, intrinsic factor and gastric lipase.
4. Mixes food and gastric juice to form chyme.

Regulation of gastric secretion and motility

Both neural and hormonal mechanisms control the secretion of gastric juice and the contraction of smooth muscles in the stomach wall. Events in gastric secretion occur in three overlapping phases; cephalic phase, gastric phase and intestinal phase.

Cephalic phase

The cephalic phase refers to the influence of the brain on secretion. Even before food enters the stomach, the sight, taste or thought of food initiate this phase, the secretion is brought about through stimulation of the nerve. This leads to presence of acid and pepsin in the stomach even before food enters the stomach.

Gastric phase

The gastric phase of secretion is brought about by the presence of food in the stomach. It is controlled by the hormone gastrin which is produced in the mucosa of the pyloric region of the stomach. Gastrin is released in response to stretching of the antrum caused by the presence of food in this region or in response to specific substances in the food; particularly proteins, alcohol and coffee are also potent stimulants of gastrin release. Once released, the gastrin is transported through the blood to stomach where it stimulates the secretion of hydrochloric acid and pepsinogen.

Intestinal phase

The intestinal phase of acid secretion refers to the influence of the small intestine on gastric secretion. If the material present in the duodenum of the small intestine is too acidic, a hormone is released by the intestinal mucosa. This hormone is carried out by the blood to the body of the stomach where it inhibits further acid secretion. This serves as a protective device for the small intestine which is not as well protected against acid as the stomach. The total volume of gastric secretion in response to all the stimuli mentioned above is approximately 2 to 3 L per day.

Gastric emptying

The process of gastric emptying occurs both during fasting and fed states. However, the pattern of motility differs markedly in the two states. In the fasted state, it is characterized by an inter-digestive cycle both through the stomach and small intestine, every 2 to 3 h. This activity is

called the inter-digestive myoelectric cycle or migrating myoelectric complex (MMC). It is composed of four phases. The activities during gastric emptying is shown.

1. Phase I (basal phase) lasts from 40 to 60 min with rare contractions.
2. Phase II (preburst phase) lasts for 40 to 60 min with intermittent action potential and contractions. As the phase progresses the intensity and frequency also increases gradually.
3. Phase III (burst phase) lasts for 4 to 6 min. It includes intense and regular contractions for short period. It is due to this wave that all the undigested material is swept out of the stomach down to the small intestine. It is also known as the housekeeper wave.
4. Phase IV lasts for 0 to 5 min and occurs between phases III and I of 2 consecutive cycles.

Factors affecting gastric retention

1. Gastric residence time of an oral dosage is affected by several factors. will be the gastric emptying time.
2. Composition of meal: fats promote the secretion of bile, which has an inhibitory effect on gastric emptying time.
3. Physical state of food and dosage form: viscous material empty slowly than less viscous materials.
4. Exercise: Retards gastric emptying time.
5. Emotion: Stress and anxiety promotes gastric motility where as depression retards it.
6. Circadian rhythms: Cardiac rhythms are increased in day time and less during night also affect the gastric retention time.
7. Size of the dosage form: Greater the energy content of meal (carbohydrate and high fat content), longer the duration of emptying.
8. Density of oral dosage form: The density of gastric fluid is reported to be 1.2g/cm3.The density of the dosage form should be less than this for buoyancy so that it is retained in the stomach for longer period of time.
9. Diseased state: state of the stomach also affects the environment for the dosage form as in case of ulcers, flatulence and spasms.
10. Drug therapy: It also plays an important role in gastric emptying e.g. prokinetic drugs like cisapride and mosapride increase gastric emptying time whereas imipramine and atropine retards it.
11. Age: Increase in age decreases gastric motility there by increasing the gastric emptying time.
12. Posture:Gastric emptying is favored while standing and by lying on right side since normal curvature of the stomach provides a downhill path whereas lying on the left side or in supine position retards it.

GASTRO RETENTIVE DRUG DELIVERY SYSTEMS (GRDDS)

It is evident from the recent scientific and patent literature that an increased interest in novel dosage forms that are retained in stomach for a prolonged and predictable period of the time exists today in academic and industrial research groups.

Criteria for selection of drug candidate for GRDDS

The gastro retentive drug delivery systems are suitable for following types of drug therapy:

1. Drugs those are locally active in the stomach e.g. misroprostol, antacids etc.
2. Drugs that have narrow absorption window in gastrointestinal tract (GIT) for example, LDOPA, paraaminobenzoic acid, furosemide, riboflavin etc.
3. Drugs that are unstable in the intestinal or colonic environment e.g. captopril, ranitidine HCl, metronidazole.
4. Drugs that disturb normal colonic microbes e.g. antibiotics against Helicobacter pylori.
5. Drugs that exhibit low solubility at high pH values e.g. diazepam, chlordiazepoxide, verapamil HCl.

Advantages of GRDDS

1. Enhanced bio-availability.
2. Reduced frequency of dosing.
3. Targeted therapy for local ailments in the upper GIT.
4. Patient compliance.
5. Improved therapeutic efficacy.

Gastro-retentive drug delivery system (GRDDS) greatly improves pharmacotherapy of the stomach through local drug release leading to high drug concentrations at gastric mucosa (eradicating helicobacter pylori from the sub mucosal tissue of the stomach), making it possible to treat stomach and duodenal ulcers, gastritis, and esophagitis, reduce the risk of gastric carcinoma, controlled release antacid formulations. GRDDS can be used as carriers for drugs which are absorbed from absorption windows in stomach. For example various antibiotics, antiviral and antifungal agents etc. (sulphonamides, quinolones, penicillins, cephalosporins, aminoglycosides and tetracyclines, etc.) are taken up only from very specific sites of the GI mucosa.

Disadvantages of GRDDS

There are certain situations where gastric retention is not desirable. Aspirin and non-steroidal anti-inflammatory drugs are known to cause gastric lesions and slow release of such drugs in the stomach is unwanted. Thus drugs that may irritate the stomach lining or are unstable in its acidic environment should not be formulated in gastro retentive systems. Furthermore, other drugs such as isosorbide dinitrate that are absorbed equally well throughout the GIT will not be suitable for incorporation into a gastric retention system.

Also GRDD's have some limitations such as:

1. Requirement of high levels of fluids in stomach for the delivery system to float and work efficiently.
2. Requires the presence of food to delay gastric emptying.
3. Drugs, which undergo significant first pass metabolism, may not be desirable candidates for floating drug delivery system since the slow gastric emptying.
4. May lead to alter systemic bioavailability.
5. Drugs having solubility or stability problems in the highly acidic gastric environment or which are irritants to gastric mucosa cannot be formulated as GRDDS.

On the other hand, violent gas generation, disintegration of dosage forms, burst release, dose dumping and alkaline micro-environment are the limitations of floating alginate beads. In case of bio-adhesive systems, the acidic environment, thick mucus as well as high turnover rate of mucous prevents bond formation at the mucous polymer interface. For swell-able systems, the dosage form must maintain a size larger than the aperture of the resting pylorus for required time period.

Applications of GRDDS

Floating drug delivery offers several applications for drugs having poor bioavailability because of the narrow absorption window in the upper part of the gastrointestinal tract. It retains the dosage form at the site of absorption and thus enhances the bioavailability

APPROACHES TO GASTRIC RETENTION

A number of approaches have been used to increase GRT of a dosage form in stomach by employing a variety of concepts. These Includes.

Sustained drug delivery

Hydro-dynamically balanced systems (HBS) can remain in the stomach for long periods and hence can release the drug over a prolonged period of time. The problem of short gastric residence time encountered with an oral controlled release formulation hence can be overcome with these systems. These systems have a bulk density less than 1 as a result of which they can float on the gastric contents. These systems are relatively large in size and passing from the pyloric opening is prohibited.

Site specific drug delivery

These systems are particularly advantageous for drugs that are specifically absorbed from stomach or the proximal part of the small intestine, for example riboflavin and furosemide.

Absorption enhancement

Drugs that have poor bio-availability because of site specific absorption from the upper part of the gastrointestinal tract are potential candidates to be formulated as floating drug delivery systems, thereby maximizing their absorption. This is illustrated in Figure.

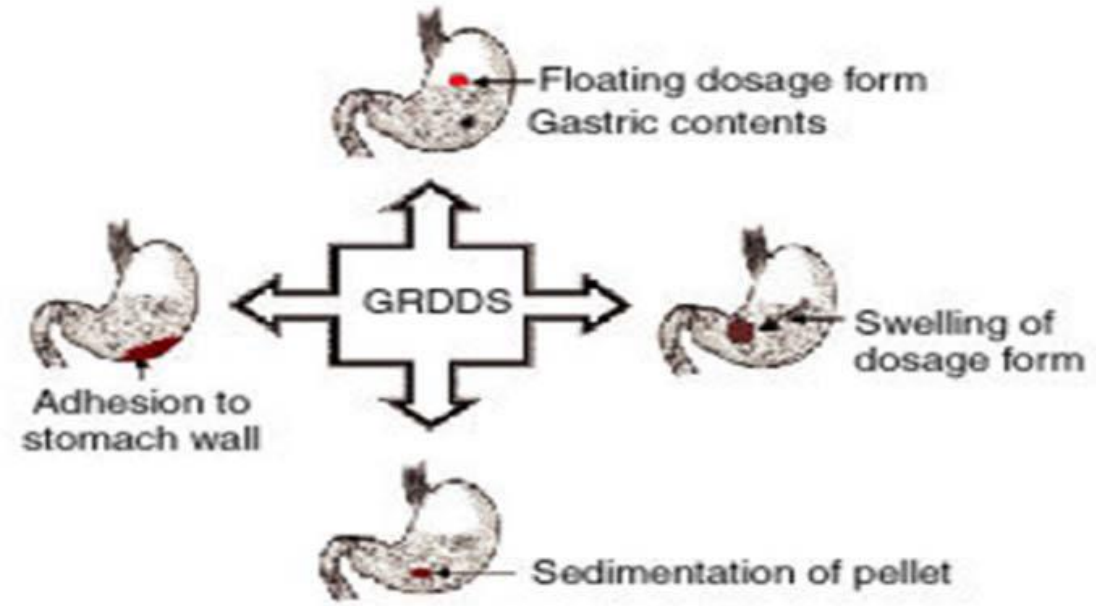


FIGURE: Illustration of types of gastro retentive drug delivery systems.

Floating systems

Floating drug delivery systems (FDDS) have a bulk density lower than gastric fluids and thus remain buoyant in stomach for a prolonged period of time, without affecting the gastric emptying rate. While the system floats on gastric contents, the drug is released slowly at a desired rate from the system. After the release of drug, the residual system is emptied from the stomach. This results in an increase in gastric retention time and a better control of fluctuations in plasma drug concentrations. Floating systems can be classified into two distinct categories, no effervescent and effervescent systems.

Bio/muco-adhesive systems

Bio/muco-adhesive systems are those which bind to the gastric epithelial cell surface or mucin and serve as a potential means of extending gastric residence time of drug delivery system in stomach, by increasing the intimacy and duration of contact of drug with the biological membrane. Binding of polymers to mucin/epithelial surface can be divided into three broad categories, name; Hydration-mediated adhesion bonding mediated adhesion and receptor-mediated adhesion.

Swelling and expanding systems

These are dosage forms, which after swallowing well to an extent that prevents their exit from the pylorus. As a result, the dosage form is retained in stomach for a long period of time. These systems may be named as “plug type system”, since they exhibit tendency to remain logged at the pyloric sphincter.

High density systems

These systems with a density of about 3 g/cm3 are retained in the rugae of stomach and are capable of withstanding its peristaltic movements. A density of 2.6 to 2.8 g/cm3 acts as a threshold value after which such systems can be retained in the lower parts of the stomach. High

density formulations include coated pellets. Coating is done by heavy inert material such as barium sulphate, zinc oxide, titanium dioxide, iron powder etc.

Incorporation of passage delaying food agents

Food excipients like fatty acids, for example salts of myristic acid change and modify the pattern of stomach to a fed state, thereby decreasing gastric emptying rate and permitting considerable prolongation of release. The delay in gastric emptying after meals rich in fats is largely caused by saturated fatty acids with chain length of C10 to C14.

Ion exchange resins

Ion exchange resins are loaded with bicarbonate and a negatively charged drug is bound to the resin. The resultant beads are then encapsulated in a semi permeable membrane to overcome the rapid loss of carbon dioxide. Upon arrival in the acidic environment of the stomach, an exchange of chloride and bicarbonate ions take place. As a result of this reaction carbon dioxide is released and trapped in the membrane thereby carrying beads towards the top of gastric content and producing a floating layer of resin beads in contrast to the uncoated beads, which will sink quickly.

Osmotic regulated systems

It is comprised of an osmotic pressure controlled drug delivery device and an inflatable floating support in a bioerodible capsule. In the stomach the capsule quickly disintegrates to release the intra-gastric osmotically controlled drug delivery device. The inflatable support inside forms a deformable hollow polymeric bag that contains a liquid that gasifies at body temperature to inflate the bagOsmotic system is shown in Figure.

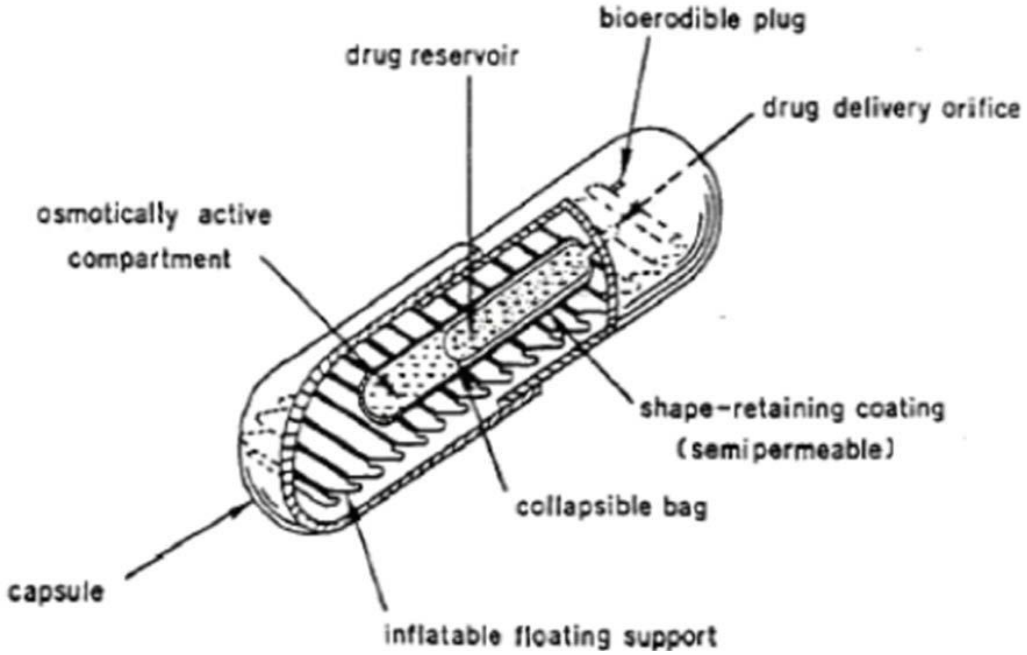


Figure . Osmotic controlled drug delivery system

The osmotic controlled drug delivery device consists of two components-drug reservoir compartment and osmotically active compartment.

FLOATING DRUG DELIVERY SYSTEMS (FDDS)

Based on the mechanism of buoyancy, two distinctly different technologies have been utilized in development of FDDS which are; effervescent system and non effervescent system Intragastric floating drug delivery devices are shown in Figure.

Effervescent systems

These buoyant delivery systems are prepared with swellable polymers such as methocel or polysaccharides for example, chitosan and effervescent components, e.g. sodium bicarbonate and citric or tartaric acid or matrices containing chambers of liquid that gasify at body temperature. The matrices are fabricated so that upon contact with gastric fluid, carbon dioxide is liberated by the acidity of gastric contents and is entrapped in the gelled hydrocolloid. This produces an upward motion of the dosage form and maintains its buoyancy. The effervescent systems are classified into:

Multiple-unit oral floating drug delivery system

Recently a multiple-unit type of floating pill, which generates carbon dioxide gas, has been developed (Figure).

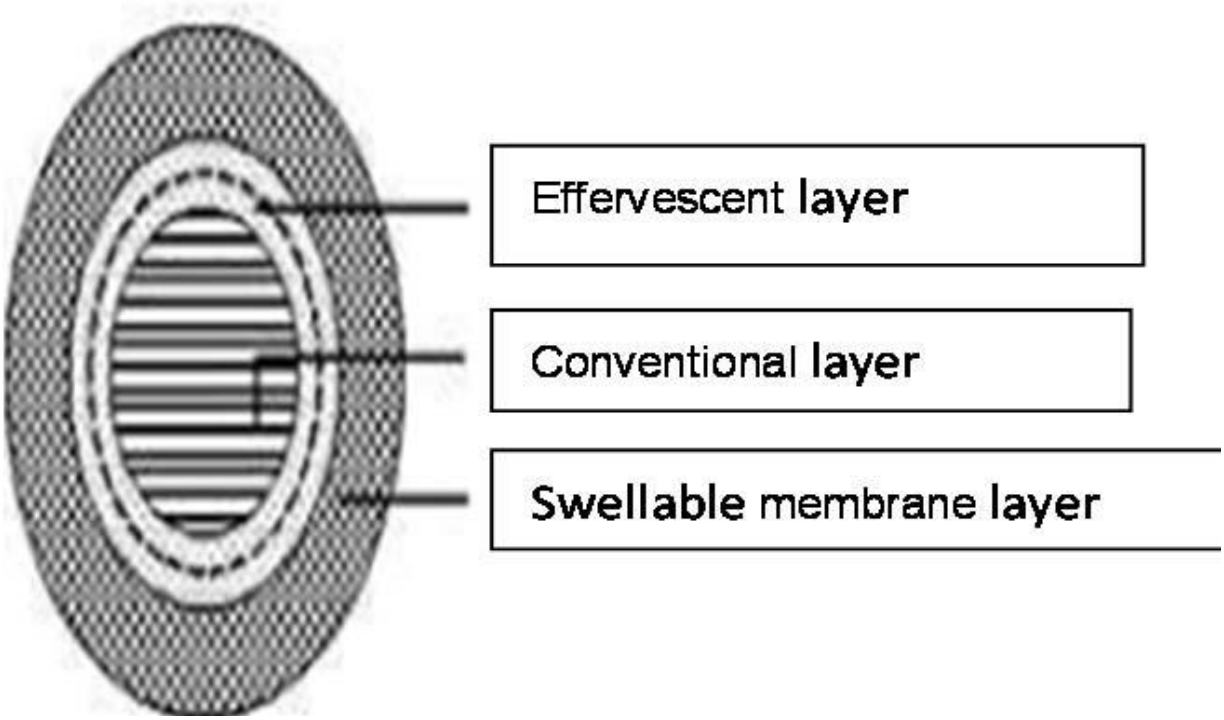


Figure . Multiple- unit oral floating drug delivery system.

The system consisted of sustained release pills as seeds surrounded by double layers. The inner layer is an effervescent layer containing both sodium bicarbonate and tartaric acid. The outer layer was a swell-able membrane layer containing mainly polyvinyl acetate and purified shellac. Moreover, the effervescent layer was divided into two sub layers to avoid direct contact between sodium bicarbonate and tartaric acid. Sodium bicarbonate was contained in the inner sub layer and tartaric acid was in the outer layer. When the formed swollen pills, like balloons, with a

density much lower than 1.004 g/cm3. The reaction was due to carbon dioxide generated by neutralization in the inner effervescent layer with the diffusion of water through the outer swellable membrane layer.

The system was found to float completing within 10 min and approximately 80%remained floating over a period of 5 h irrespective of pH and viscosity of the test medium. A floating system utilizing ion-exchange resins have been developed. The system consisted of resin beads, which were loaded with bicarbonate and a negatively charged drug that was bound to the resin. The resultant beads were then encapsulated in a semi permeable membrane to overcome rapid loss of carbon dioxide. Upon arrival in the acidic environment of stomach, an exchange of chloride and bicarbonate ion took place, as was expected. As result of this reaction, carbon dioxide was released and trapped in the membrane, thereby carrying beads toward the top of gastric contents and producing a floating layer of resin beads. In contrast, the uncoated beads sank quickly. Radioactivity measurement by scintigraphy showed that gastric residence was substantially prolonged, compared with a control, when the system was given after a light, mainly liquid meal.

Furthermore, the system was capable of slow release of drug. A property which widens the scope of such floating system for SR preparation of drugs possessing negative charge since they can be easily bound to the resin in combination with bicarbonate ions. Two patents on FDDS issued to the Alza Corporation disclosed drug delivery devices for the controlled and continuous administration of medicinal agents.

Inflatable gastrointestinal drug delivery system

The residence time of the drug delivery device in the stomach can also be sustained by incorporation of an inflatable chamber, which contains a liquid, e.g. ether that gasifies atbody temperature to cause the chamber to float in the stomach.

Intragastricosmotically controlled drug delivery system

It is comprised of an osmotic pressure controlled drug delivery and an inflatable floating support in a bioerodible capsule. When the drug delivery device reaches the site of drug administration e.g. the stomach, the capsule quickly disintegrates to release the. The inflatable floating support is made from a deformable hollow polymeric bag that contains a liquid that gasifies at body temperature to inflate the bag This system is shown in Figure.

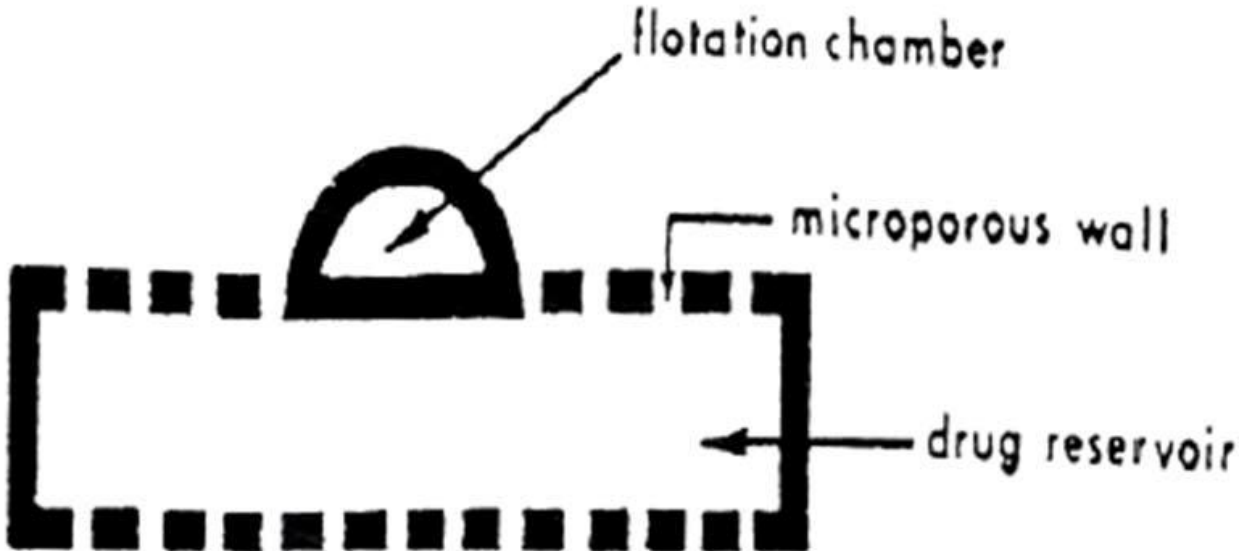


Figure. Intra gastric floating drug delivery devices.

Osmotic controlled drug delivery system

Although single unit floating dosage forms have been extensively studied, these single unit dosage forms have the disadvantage of a release all or nothing emptying process while the multiple unit particulate system pass through the GIT to avoid the vagaries of gastric emptying and thus release the drug more uniformly. The uniform distribution of these multiple unit dosage forms along the GIT could result in more reproducible drug absorption and reduced risk of local irritation; this gave birth to oral controlled drug delivery and led to development of gastroretentive floating microsphere.

Non-effervescent systems

Commonly used excipients, here are gel-forming or highly swell-able cellulose type hydrocolloids, polysaccharides and matrix forming polymers such as polycarbonate, polyacrylate, polymethacrylate and polystyrene. One of the approaches to the formulation of such floating dosage forms involves intimate mixing of drug with the gel-forming hydrocolloid, which swells in contact with gastric fluid after oral administration and maintains a relative integrity of shape and a bulk density of less than unity within the outer gelatinous barrier.The air entrapped by the swollen polymer confers buoyancy to these dosage forms. The gel structure acts as a reservoir for sustained drug release as the drug is slowly released by controlled diffusion through the gelatinous barrier. Non-effervescent systems include the following:

1. Hydrodynamically balanced intragastric delivery system.
2. Bilayer tablets.
3. Intragastric floating gastrointestinal drug delivery system.
4. Hollow/floating microspheres.

Hydrodynamicallybalanced intragastric delivery system (HBS)

The hydrodynamicallybalanced gastrointestinal drug delivery systems, in either capsule or tablet form, is designed to prolong GI residence time in an area of the GI tract to maximize drug reaching its absorption site in solution state and hence, ready for absorption. It is prepared by

incorporating a high level (20 to 75% w/w) of one or more gel-forming hydrocolloids, for examplehydroxyethylcellulose, hydroxypropylcellulose, hydroxypropylmethylcelluse and sodium carboxymethylcellulose into the formulation and then compressing these granules into a tablet (or encapsulating into capsules). On contact with gastric fluid the hydrocolloid in this intragastric floating device start to become hydrated and forms a colloid gel barrier around its surface with thickness growing with time. This get barrier controls the rate of solvent penetration into the device and the rate of drug release from the device (Indian Pharmacopoeia Commission,2007). It maintains a bulk density of less than 1 and thus remains buoyant in the gastric fluid inside the stomach for up to 6 hSystem is illustrated in Figure.

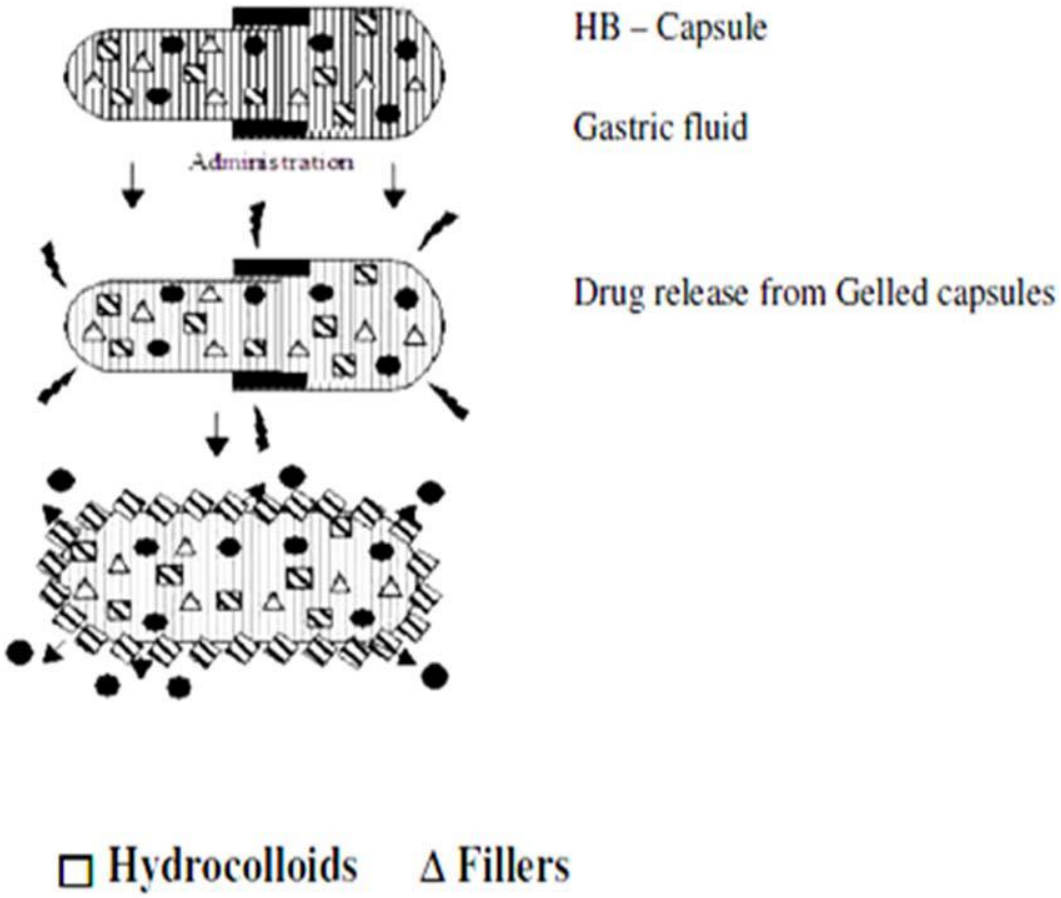


Figure . Hydrodynamically balanced intragastric delivery system (HBS).

Principle of hydrodynamically balance system

Bilayer tablet

A bilayer tablet can be prepared to contain one immediate-release layer and one sustained-release layer. After the initial dose is delivered by the immediate release layer, the sustained release layer absorbs the gastric fluid and forms a colloidal gel barrier on its surface. This produces a bulk density less than that of the gastric fluid and remains buoyant in the stomach for extended period of time Bilayer tablet is shown in Figure.

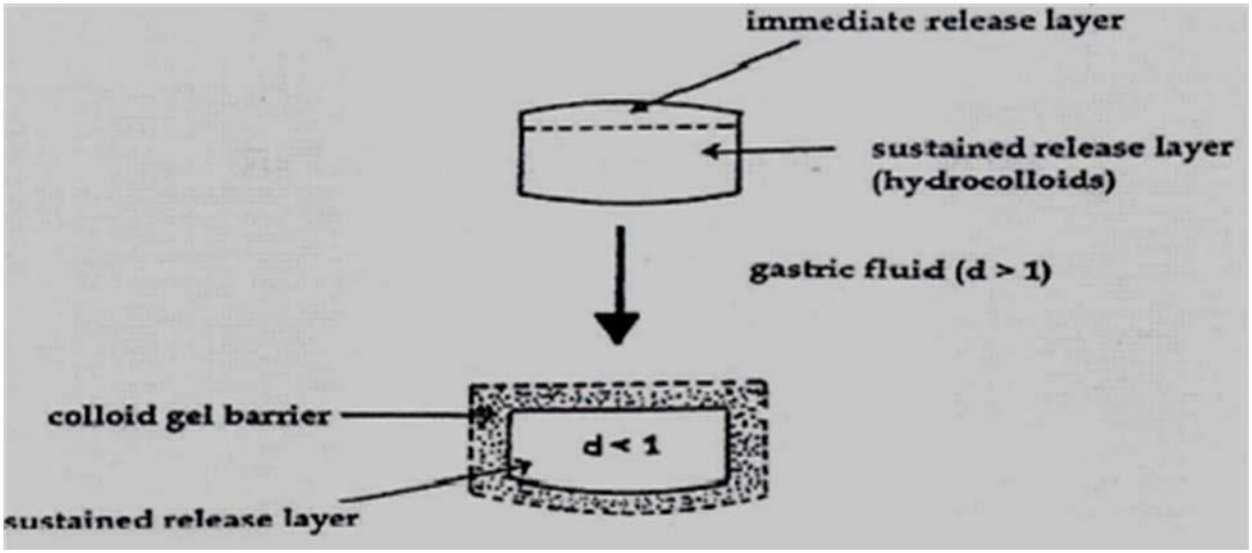


Figure. Bilayer tablet.

Intragastric floating gastro intestinal drug delivery system

A gastrointestinal drug delivery system (GIDS) can be made to float in the stomach by incorporating a floatation chamber, which may be a vacuum or filled with a harmless gas. A drug reservoir is encapsulated inside a microporous compartment with apertures along its top and bottom walls. The peripheral walls of the drug reservoir compartment are completely sealed to prevent any direct contact of the stomach mucosal surface with the undissolved drug. In the stomach the floatation chamber causes the GIDS to float in the gastric fluids. Fluids enter through the apertures, dissolve the drug, and carry and drug solute out of the drug delivery system for controlled transport to the intestine for absorption.

Hollow/floating microspheres

Floating microspheres are gastro retentive drug delivery systems based on non-effervescent approach. Hollow microspheres are in strict sense, spherical empty particles without core. These microspheres are characteristically free flowing powders consisting of proteins or synthetic polymers, ideally having a size less than 200 micrometer. Solid bio-degradable microspheres incorporating a drug dispersed or dissolved throughout particle matrix have the potential for controlled release of drugs. Gastro retentive floating microspheres are low density systems that have sufficient buoyancy to float over gastric contents and remain in stomach for prolonged period. As the system floats over gastric contents, the drug is released slowly at desired rate resulting in increased gastric retention with reduced fluctuations in plasma drug concentration Preparation of floating microspheres by solvent evaporation method is shown in Figure.

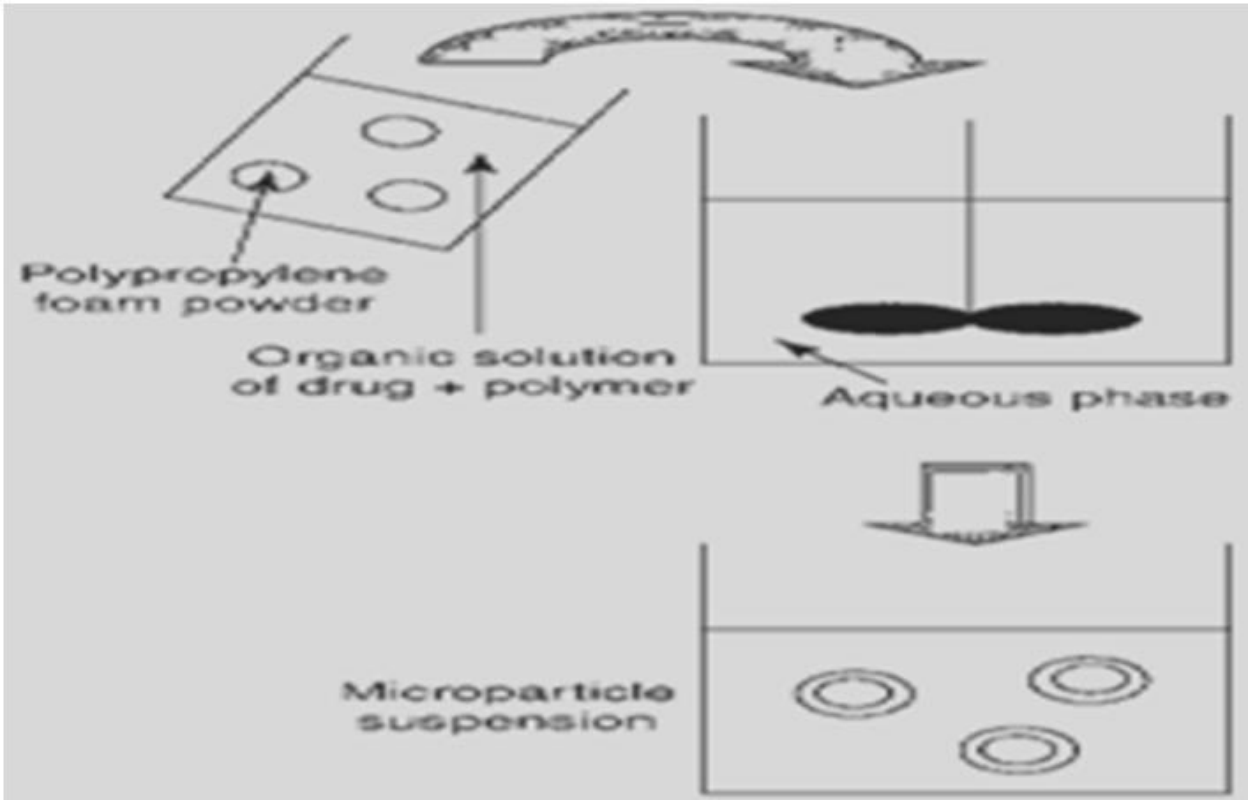


Figure. Preparation of floating microspheres using the solvent evaporation method.

List of polymers used in hollow microspheres

Cellulose acetate, chitosan, eudragit, acrycoat, methocil, polyacrylates, polyvinyl acetate, carbopol, agar, polyethylene oxide, polycarbonates, acrylic resins and polyethylene oxide.

Advantages of hollow microspheres

1. Improves patient compliance by decreasing dosing frequency.
2. Bioavailability enhances despite first pass effect because fluctuations in plasma drug concentration is avoided, a desirable plasma drug concentration is maintained by continuous drug release.
3. Gastric retention time is increased because of buoyancy.
4. Enhanced absorption of drugs which solubilize only in stomach
5. Drug releases in controlled manner for prolonged period.
6. Site-specific drug delivery to stomach can be achieved
7. Superior to single unit floating dosage forms as such microspheres releases drug uniformly and there is no risk of dose dumping.
8. Avoidance of gastric irritation, because of sustained release effect.
9. Better therapeutic effect of short half-life drugs can be achieved.

LIMITATIONS

Floating drug delivery system requires sufficiently high level of fluids in stomach for the drug delivery to float and to work efficiently. It is not suitable for those drugs that have solubility or stability problems in gastric fluids.

Drugs such as Nifedipine, which is well absorbed along the entire GI tract and which undergoes significant firstpass metabolism may not be desirable candidates for FDDS, since the slow gastric emptying may lead to reduce systemic bioavailability of FDDS for drugs that are irritant to gastric mucosa.

Methods of preparation of hollow microspheres

Hollow microspheres are prepared by solvent diffusion and evaporation methods to create the hollow inner core. Polymer is dissolved in an organic solvent and the drug is either dissolved or dispersed in the polymer solution. The solution containing the drug is then emulsified into an aqueous phase containing polyvinyl alcohol to form oil in water emulsion. After the formation of a stable emulsion, the organic solvent is evaporated either by increasing the temperature under pressure or by continuous stirring. The solvent removal leads to polymer precipitation at the o/w interface of droplets, forming cavity and thus making them hollow to impart the floating properties.

Mechanism of floating microspheres

When microspheres come in contact with gastric fluid the gel formers, polysaccharides, and polymers hydrate to form a colloidal gel barrier that controls the rate of fluid penetration into the device and consequent drug release.

As the exterior surface of the dosage form dissolves, the gel layer is maintained by the hydration of the adjacent hydrocolloid layer. The air trapped by the swollen polymer lowers the density and confers buoyancy to the microspheres. However a minimal gastric content needed to allow proper achievement of buoyancy. Hollow microspheres of acrylic resins, eudragit, polyethylene oxide, and cellulose acetate; polystyrene floatable shells; polycarbonate floating balloons and gelucire floating granules are the recent developments.

Q.16 Note on monoclonal antibodies

Monoclonal antibodies When a humoral immune response is provoked by an immunogen, such as tetanus toxoid, a plethora of antibodies are produced in an individual against diVerent parts or regions of this foreign substance. These are termed antigenic determinants, or epitopes, which usually comprise six to eight amino acids. It should be appreciated that most antibodies recognise and interact with a three dimensional shape composed of “discontinuous” residues brought into juxtaposition by the folding of a molecule. Alternatively, antibodies can also recognise linear stretches of amino acids or “continuous” epitopes.1 Of course, an important concept to bear in mind is that each antibody molecule is specific for a single epitope, and that each antibody is the product of a single B cell clone. Thus, an antibody of unique specificity, derived from a single B cell clone, is termed a monoclonal antibody. In our example cited above, tetanus toxoid would induce antibodies from numerous B cell clones; that is, this immunogen would produce a polyclonal antibody response. In contrast, the propagation of an isolated B cell clone would produce antibody of single specificity. However, a problem arises in that in tissue culture medium, B cells die within a few days of their isolation (for example, from a mouse spleen). Consequently, methods of conferring immortality on to B cells have been investigated.

Indeed, immortality has been accomplished by means of viral transformation (for example, using Epstein-Barr virus) and/or fusion to cancerous cells to generate hybrids or “hybridomas”. In general, the former technique is used for the immortalisation of peripheral blood B cells (and production of human monoclonal antibodies), whereas myeloma cells have mainly been used in the production of murine monoclonal antibodies.

So how do you make a monoclonal antibody? Let us start with a working definition: a monoclonal antibody is regarded as an antibody of single specificity, generated from the immortalisation of a plasma B cell in vitro. Although several recombinant approaches are possible, the process of demystifying monoclonal antibodies is best illustrated by the generation of murine monoclonal reagents. In essence, five main stages (fig 2) are highlighted: (1) immunisation, (2) fusion and selection, (3) screening, (4) characterisation, and (5) further developments.

STAGE 1: IMMUNISATION Substances that induce an immune response are usually foreign to the individual and are termed immunogens. In general, protein (50– 100 µg), cells (1 × 107), multiple antigenic synthetic peptides, or a short peptide (6–18 amino acids) linked to a carrier protein (for example, keyhole limpet haemocyanin) can be used for the primary immunisation of Balb/c mice. More often than not, an immunogen will be delivered in conjunction with an adjuvant, which is regarded as a non-specific immune enhancer. Typical examples include Freund’s complete/incomplete adjuvants and TiterMax® . Invariably, proteins are delivered subcutaneously whereas cells are given intraperitoneally. Regular boosting is needed to augment a polyclonal response, which can be monitored indirectly using tail bleeds. These oVer suYcient serum to ascertain the antibody titre to a desired antigen usually in an assay system—for example, enzyme linked immunosorbent assay (ELISA)—that is ultimately required for the monoclonal reagent. The eVect of boosting also encourages immunoglobulin class switching and the generation of higher aYnity antibodies through somatic hypermutation. In general, IgG monoclonal antibodies are preferred because they are less prone to degradation, and may potentially be more useful as therapeutic reagents.6 Of course the end point, particularly for in vivo strategies, is to select an appropriate mouse (generally the best responder from tail bleeds) and remove (aseptically) antigenically responding B cells from its spleen (or lymph node) to obtain viable cells for hybridisation. It is noteworthy that although in vivo immunisation (including intrasplenic administration) is the favourite choice in many laboratories, there is also the opportunity for in vitro immunisation. In this case, cultured splenic cells are stimulated with only a minimal amount of antigen.

STAGE 2: FUSION AND SELECTION The hybridisation process centres on the fusion of murine splenic B cells with histocompatible myeloma cells, such as Sp2/0. The latter (and various alternative myeloma cell lines, such as NS1, NSO, and X63Ag8) are preselected for a deficiency in the enzyme hypoxanthine guanine phosphoribosyltransferase (HGPRT)—for example, by culturing in medium containing 8-azaguanine. In essence, this enzyme is fundamental to the post-fusion hybridoma selection process. To understand this process it should be noted that cells possess two pathways of nucleotide biosynthesis: the de novo pathway and the

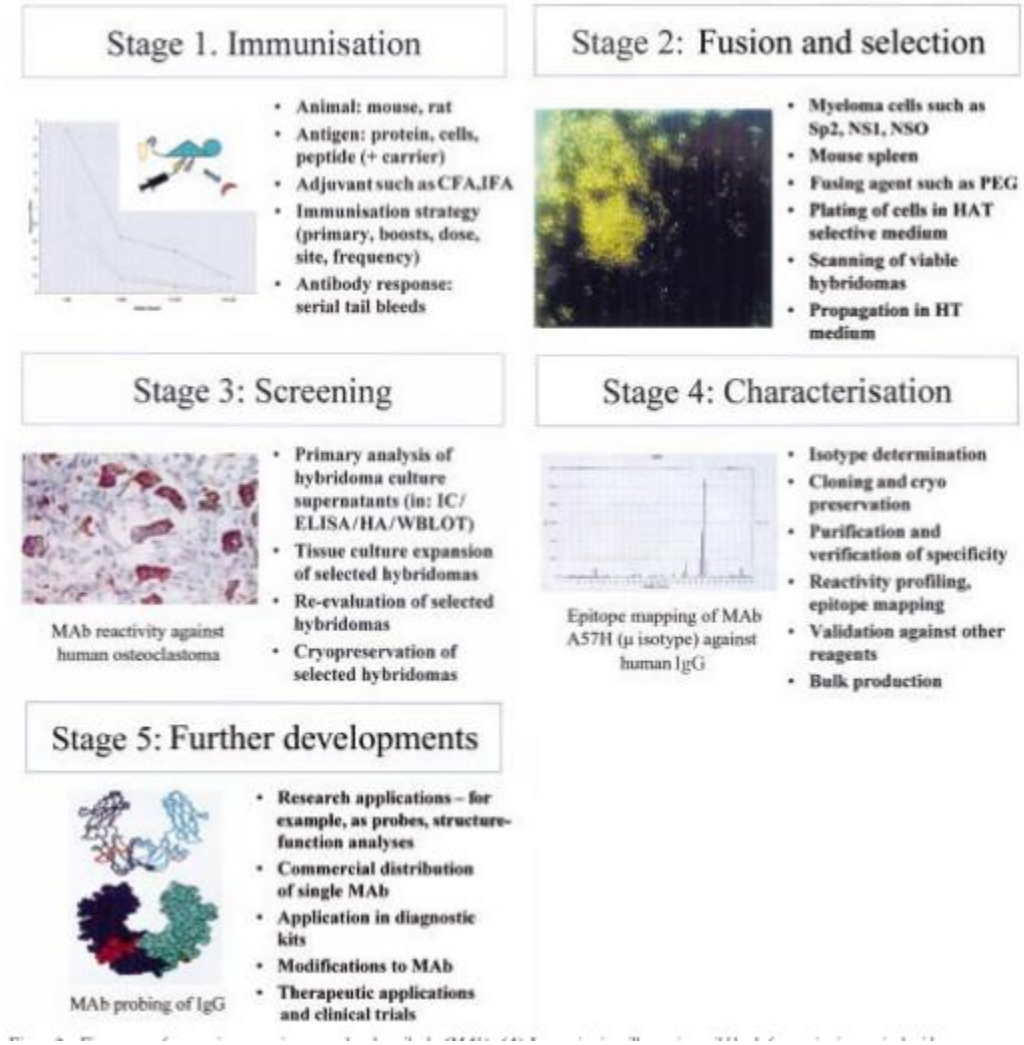
salvage pathway, which uses HGPRT. Consequently, myeloma cells that are HGPRT negative are unable to use the salvage or "alternative" pathway for purine biosynthesis and are thus entirely reliant on the de novo pathway for survival. In the fusion process, splenic B cells are mixed with HGPRT negative myeloma cells and a fusing agent, such as polyethylene glycol. Hopefully, the mixing and centrifugation steps generate myeloma– splenic B cell hybridomas. Once these hybrid cells are formed and plated into tissue culture wells, the priority shifts towards removing unfused myeloma cells. This is necessary because the latter have the potential to outgrow other cells, particularly weakly established hybridomas. This situation is resolved by using a selective medium containing hypoxanthine, aminopterin, and thymidine, otherwise known as "HAT". Of importance, is the fact that aminopterin blocks the de novo pathway—the only one available to HGPRT negative cells, and as a consequence all unfused myeloma cells will die. Of course, newly formed hybridomas survive this selection process because the salvage pathway enzyme is provided by its splenic B cell counterpart. Unfortunately, some hybridomas are unstable and regress. Hence, meticulous attention should be given to the visual examination of hybridomas using an inverted microscope. A record of poorly growing, newly emerging, or established hybridomas provides credibility to immunoassay screening data. Once established, a given hybridoma colony will continually grow in culture medium (such as RPMI1640 with antibiotics and fetal bovine serum) and produce antibody. Twenty to 30 days postfusion, hybridomas can be propagated in "HT" medium (hypoxanthine and thymidine only) because aminopterin is no longer required.

STAGE 3 : SCREENING This stage focuses on identifying and selecting those hybridomas that produce antibody of appropriate specificity. The selection process must be ruthless otherwise numerous unwanted (at least to you!) hybridomas will compete for your time and incur unnecessary expense in terms of culture plates and medium. Invariably, a rapid "primary" screening system is used that tests the hybridoma culture supernatant for antibody reactivity and specificity. As an example, an Epstein-Barr viral associated protein or peptide can be coated on to plastic ELISA plates. After incubation of hybridoma culture supernatant, secondary enzyme labelled conjugate, and chromogenic substrate, a coloured product indicates a positive hybridoma. Alternatively, immunocytochemical screening might be more appropriate. Ultimately, primary screening is necessary to "weed out" and eliminate non-specific hybridomas at the earliest opportunity. Obviously, it is important to screen supernatants with some degree of equity and, therefore, it might be wise to test hybridomas when at least three quarters confluent. Unfortunately, this approach means that screening becomes an almost daily task because not all hybridomas grow at similar rates. Of particular note, is the fact that slow growing (and often very stable) hybridomas can appear 25–30 days post-fusion, whereas most become established well before this time. Hybridomas can initially be grown in multiwell plates and then, once selected, expanded to larger tissue culture flasks. This progression is necessary not only to maintain the well being of the hybridomas but also to provide su Ycient cells for cryopreservation and supernatant for further investigations. As a rough guide, culture supernatant can yield anywhere between 1 and 60 µg/ml of monoclonal antibody: the latter being maintained at −20 °C or lower

until required. The numbers of hybridomas that can manageably be “taken through” in a given laboratory require continual validation. Furthermore, if a fusion has been particularly successful, some rationalisation of hybridomas will be needed; that is, selecting only those providing an intense immunocytochemical staining pattern. Of course, less favoured hybridomas can be cryopreserved and examined at a later date. What is important to bear in mind, is that the workload in generating hybridomas is generally exponential.

STAGE 4 : CHARACTERISATION Further analysis of a potential monoclonal antibody producing hybridoma in terms of reactivity, specificity, and crossreactivity can be achieved using culture supernatant or a purified immunoglobulin preparation. However, before any further work it is often necessary to re-clone hybridomas (for example, by limiting dilution) because an original colony might contain at least two populations of fused B cells. Unless resolved, a consequence of this situation could be ambiguous data resulting from antibodies of di Vering class, specificity, and a Ynity. For this reason, isotype determination serves not only to define the murine immunoglobulin class or subclass but also helps identify the presence of a single isotype— for example, IgG1 or a mixture, such as IgM and IgG2b. In addition, knowledge of a monoclonal antibody’s isotype will help dictate the most appropriate column purification technique for a culture supernatant—for example, protein G for IgG1. A crucial aspect of characterisation relates to monoclonal antibody profiling in di Verent assay systems. This is especially pertinent for the antibody’s potential as a diagnostic reagent because some monoclonal antibodies perform well in some systems but not others. This phenomenon, termed assay restriction,2 7 relates to how an antibody recognises its target epitope in the context of the assay system used. In this case, an important epitope could be masked, denatured, or rendered inaccessible by the immobilisation procedure adopted within a given technique. Characterisation also a Vords the opportunity to test against a wide panel of related antigens or tissue preparations, particularly if monoclonal antibodies are being targeted for histopathological purposes. Of course, these endeavours and the hand of serendipity might well lead to useful applications elsewhere, and thus help capitalise on the original investment of time, e Vort, and cost. Once certain of a hybridoma, bulk production of a monoclonal antibody can be achieved using surface expanded tissue culture flasks or hollow fibre systems, such as Technomouse. It is noteworthy that although a hybridoma may be the fused product of a single B cell and produce a monoclonal antibody of exquisite specificity, this same antibody can in fact crossreact with other antigens or exhibit dual specificity. 3 This corollary arises when an antibody combining site recognises more than one antigenic determinant, either because of some similarity in shape or chemical composition. Furthermore, the nuances of an assay system can also bias the exposure of a particular antigenic determinant or epitope. Consequently, stringent evaluation of a given monoclonal antibody and its target epitope is necessary, 8 which may therefore include epitope mapping.1 9 This particular technique allows precise determination of key amino acid residues that are important for antibody recognition and binding. Further characterisation might also include a Ynity measurements of antigen–monoclonal antibody interactions using surface plasmon resonance (for example, BIACore or IBIS).

STAGE 5: FURTHER DEVELOPMENTS Once derived, monoclonal antibodies can serve as investigative research tools, or find applications in diagnostic assays or as therapeutic agents. In addition to potential collaborative opportunities, commercial exploitation of monoclonal antibodies might provide some revenue for future research projects. Furthermore, epitope mapping of monoclonal antibodies in conjunction with molecular modelling can enable the visualisation and localisation of key antigenic regions on a molecule. This information might help to elucidate structure–function relations of proteins, carbohydrates, and other molecules of clinical relevance. Of course, an ultimate goal of monoclonal specialists is to widen the application of antibodies for the clinical treatment of patients. Certain murine monoclonal antibodies have proved eVective (depending on subclass) but might ultimately induce human antimouse responses. This problem has been circumvented either by cleavage of the immunogenic Fc portion of the immunoglobulin molecule or by recombinant methodologies. These have largely focused on producing chimeric antibodies containing a murine antibody recognition unit and human Fc region, or using a human IgG molecule and inserting murine complementary determining residues to retain antibody specificity.10 11 Clearly, further advances for so called magic bullets either alone (and reliant on the eVector characteristics of the immunoglobulin isotype) or armed with radionucleotides or toxins will undoubtedly obtain further prominence.



Q. 17 Write note on nasal formulaion

Aerosol

The aerosol container is referred to as a pressurized package in which the therapeutically active drug is dissolved or suspended in compressed or liquefied gas. The delivery of therapeutically active drug in the form of spray or foam or solid stream is dependent on the ability of the liquefied or compressed gas. The advantages of aerosols are as follows

- The drug sensitivity to the effect of oxygen or moisture is protected and stability is enhanced.
- The drug can be directly applied to the affected areas.
- Administration of drug by aerosol is a rapid process.
- It protects the drug from gastrointestinal tract degradation.
- Hepatic first pass metabolism is avoided.
- Aerosols are used for both systemic and local application.
- Easy to apply.

- A sterile dose of drug is dispensed and also the contamination of drug is prevented.

The delivery of contents of aerosol depends on its valve assembly, containers, and actuators as well as on the propellant. The two components of aerosol are product concentrate and propellant. The product concentrate contains the therapeutically active ingredients. The propellant having vapour pressure greater than atmospheric pressure at 40^{o}C (105^{o}F) is responsible for the development of proper pressure in the container to expel the product concentrate in the desired form like spray, mist, solid, foam, stream etc. Propellant can also act as the solvent or vehicle for the product concentrate. Thus aerosol components are classified as shown in Figure 1 and Figure 2.

PROPELLANT

The development of pressure within the container by the propellant causes the opening of valve which expels the product by atomisation or foam formation.

Types of propellant

Depending on the route of administration and use, the propellant can be classified as given in Table1 **Chlorofluorocarbon (CFC) propellants**

The basic characteristics of propellants are chemical inertness, lack of toxicity, lack of flammability and explosiveness. Due to the presence of these characteristics, the chlorofluorocarbon (CFC) propellants P-11, P-12, and P- 114 were used in aerosol products for several years. Now a day their uses have been declined as they cause the depletion of ozone layer. But due to their relatively low toxicity and inflammability, they are still use in low amount in the treatment of asthma and chronic obstructive pulmonary disease (COPD). P-134a and P-227 are now been developed and are being incorporated in aerosol formulations in place of P-12.

Principle of releasing out of product concentrates from container

Liquefied propellant or propellant mixture exists in equilibrium with the product concentrate in a sealed aerosol container. The liquefied propellant vapourises and occupies the upper portion of the aerosol container. As the liquefied propellant exists in equilibrium with the propellant in the vapour phase in an aerosol container, so a constant pressure is maintained within the aerosol container. Hence, it is called as a pressurised aerosol container. The pressure exerted by the propellant is called as vapour pressure, measured in psig; is the characteristic of specific propellant. Upon the actuation of the valve, the pressure exerted by the propellant is distributed equally in all direction in the aerosol container, forcing the product concentrate up the dip tube and out of the aerosol container. As the vapour pressure of the propellant in air is lower than inside the aerosol container, so the propellant evaporates on reaching the air and product concentrates dries up as dry particles.

Hydrocarbons Propellants

The environmental acceptance, low toxicity and nonreactivity are the characteristics of hydrocarbons propellants allowing them to be used as the propellant. Hydrocarbons are used in the preparation of water based aerosols as they are not susceptible to hydrolysis due to the absence of chlorine. Since they are immiscible with water, so they remain on the top of water.

They provide the force to push the contents out of the container. The disadvantage of Hydrocarbon propellant is flammability, explosiveness. It is being reduced by using a blend of propellant. Also the use of vapour tap valve reduces flammability.

Compressed gas propellants

The use of compressed gas like Nitrogen, Nitrogen dioxide and Carbon dioxide as propellant dispenses products in the form of fine mists, foams or semisolid. It produces fairly wet sprays and the foams are not as stable as produced by the liquefied gas propellant. Unlike the aerosol prepared with liquefied gas propellant, there is no propellant reservoir. The compressed gas propellant is contained in the headspace of the aerosol container which forces the product concentrate out of the container. So, higher gas pressure is required in this aerosol. This aerosol finds its application to dispense food products, dental creams, hair preparation and ointments.

CONTAINERS

Aerosol containers are generally made of glass, metals (e.g., tin plated steel, aluminium, and stainless steel), and plastics. The materials of aerosol container to be selected should be able to withstand high pressure. Thus the aerosol containers must withstand pressure as high as 140 to 180 psig (pounds per sq. inch gauge) at 130 ^{0}F. Also, the cost, compatibility of the material with the formulation is to be considered. The pressure limitation of aerosol container is as given in Table 2.

Glass

One of the materials is glass whose brittleness limits its use in aerosol containers. Thus glass containers are used in lower pressure and when low amount of propellant are in use such as if the pressure is less than 25psig and propellant content is less than 15%. In order to protect the glass containers against breakage due to high pressure, it is to be coated with plastic coating in two layers. Epoxy and vinyl resins can be used as linings. Vinyl resins are not resistant to high temperature of the steam about 200 ^{0}F. But epoxy resins are resistant to steam. These coatings are suitable for low pH water based products.

Metals

Tinplated steel: It provides light and inexpensive aerosol container. The both sides of the tin container are electroplated with sheets of steel plates so as to protect the inside of the container from corrosion and also to prevent the interaction between the tin and the formulation. Oleoresin, phenolic, vinyl, or epoxy coatings are used as the coating materials. The tin plated steel containers are used in topical aerosols.

Aluminium: The aluminium containers are light weight and are less prone to corrosion than other metals. Aluminium is used in most metered dose inhalers (MDIs) and many topical aerosols. Epoxy, vinyl, or phenolic resins coatings are done on aluminium containers to reduce the interaction between the aluminium and the formulation. The seamless aerosol containers manufactured by an impact extrusion process have greater safety against leakage, incompatibility, and corrosion. The container themselves available in sizes ranging from 10 ml to over 1,000 ml.

Stainless steel: As it is strong and resistant to corrosion; no coating is required. Also it can

withstand high pressure. The drawback is expensiveness which restricts its sizes to small sized containers.

Plastic

As plastics are highly permeable to vapours and air like oxygen, so interaction with the formulation may occur and also may lead to oxidative degradation of the formulation. Polyethylene tetra phthalate (PET) container as used for some non pharmaceutical products.

VALVES

A valve delivers the drug in desired form and regulates the flow of product concentrate from the container. The valve should be able to withstand the pressure encountered by product concentrate and the container, should be corrosion resistant. The two types of valves available are continuous spray valve and metering valve. The classifications of aerosol valve components are given in Figure 3.

Actuator: It is the button which the users press to activate the valve assembly and controls the easy opening and closing of valve; also directs the spray to the desired area. The actuator contains orifices of varying size and shapes as well as the expansion chamber which determines the type and quantity of propellant used, actuator design and the physical characteristics of the emitted product concentrate in the form of spray or foam, especially in the case of inhalation aerosols where it is necessary to control the proper particle size of the product concentrate. The types of actuator are given in Figure 4.

Stem: The actuator is supported by the stem and the formulation is delivered in the proper form to the chamber of the actuator by the stem. It is made up of Nylon, Delrin, Brass and Stainless steel.

Gasket: The stem and valve are placed tightly in their place by the gasket and the leakage of the formulation is prevented by gasket. It is made up of Buna N and Neoprene rubber.

Spring: The gasket is held in its place by the spring and also helps to keep the valve in closed position when the pressure is released upon actuation of the formulation.

Mounting Cup or Ferrule: The Mounting cup or Ferrule is generally made up of aluminium which serves to place the valve in its position, and attached to the aerosol container. As the underside of the mounting cup/ Ferrule is exposed to the contents of the container, so it is to be compatible with the contents so as to prevent any interaction. It may be coated with an inert material such as vinyl coating as it prevents any interaction with the contents also corrosion of aluminium is prevented.

Housing or Valve body: The Housing or Valve body located directly below the Mounting cup or Ferrule is made up of Nylon or Delrin work to connect the dip tube and the stem and actuator. The rate of delivery of product and the desired form in which the product is to be emitted is determined by its orifice.

Dip Tube: The dip tube is made up of polyethylene or polypropylene extends from the housing body or valve body down into the product concentrate works to bring the formulation from the container to the valve. The inner diameter of the dip tube depends on the viscocity and the desired rate of delivery of the product. The inner diameter of the dip tube increases with an

increase in the viscocity of the formulation. For less viscous solutions, the inner diameter ranges from 0.12 inch to 0.125 inch. While for viscous solution, inner diameter is as large as 0.195 inch.

TYPES OF INHALERS

Depending on the physical state of the dispersed phase and continuous medium, inhaled drug delivery system is classified into three principle categories

1. Pressurised metered dose inhalers (pMDIs)
2. Dry powder inhalers (DPIs)
3. Nebulisers.

Metered dose inhaler (pMDIs)

The pressurised metered dose inhalers (pMDIs) as shown in Figure 5; are composed of a canister, and actuator, and sometimes a spacer. The canister is composed of a metering dose valve with an actuating stem. The formulation (containing the active ingredient i.e. drug, a liquefied gas propellant, and a stabilizer) is present in the carnister. The drug may be suspended or dissolved in the liquefied gas propellant. Upon actuation, the metering dose valve is opened which releases a single metered dose of medication alongwith the liquified gas propellant to spray out of a carnister. This process is called cavitation. The liquefied gas propellant is volatile in nature; breaks down into liquid droplets which evaporates rapidly, and the dried micronized drug are inhaled to the lung. But the pressurised metered dose delivery suffers from various drawbacks as follows-

a. Till 1990s, various chlorofluorocarbons (CFC) were used as the propellant; it caused depletion of ozone layer; so later it was replaced with hydrofluorocarbons. Hydrofluorocarbons suffer from the drawback of greenhouse effect.
b. As pMDIs is pressurised, it emits the dose at high velocity and gets deposited in the oropharynx.
c. The propellant and the cosolvent may extract some of the organic compounds from the device components and leads to chemical degradation.
d. A careful coordination of actuation and inhalation are required.
e. High chances of pharyngeal depositions.

Later on, the formulation related short comings are reduced by Dry powder inhalers (DPIs).

i) Dry powder inhalers (DPIs)

The DPIs are advantageous than pMDIs due to the following reasons:

a) DPIs require little or no coordination of actuation and inhalation as they are activated by patient's inspiratory airflow.
b) DPIs don't extract organic compounds from the device components in contrast to the pMDIs; and the chances of chemical degradation are lesser than pMDIs.
c) The rate of drug delivery is better than pMDIs.
d) DPIs are efficient, more stable than pMDIs and easier to use than pMDIs.

DPIs are composed of micronized powdered drug particles. The micronized powdered drug particles (of sizes < 5µm) are mixed with much larger sugar particles (of size < 30 µm) eg.

Lactose monohydrate. The smaller drug particles forms loose aggregate with lactose monohydrate. The micronized powdered drug particles have high cohesive force, so they have a tendency of adhering to each other. The addition of large particle sized lactose monohydrate reduces the cohesive force of the micronized drug particles and form loose agglomerate with the micronized drug particles. It helps in an easy deaggregation of the agglomerates, upon inhalation, the agglomerates get broken down into its constituent particles, with the help of mechanical devices such as screens, on which the particles agglomerates impact. It releases the smaller sized powdered drug particles into the air to be inhaled to the lung. The larger sized lactose monohydrates particles are left behind in the device and in the mouse throat. The DPIs are classified into two types

- ✓ Unit dose devices
- ✓ Multi dose devices

Unit-dose devices: Unit dose devices are being developed as re-useable or disposable single-dose dry powder inhalers. They are designed to be easy to use and inexpensive to manufacture and may be suitable for a wide range of conditions that require a rapid onset of effect or that are for occasional use. One such unit dose device is the filled capsule placed in the device. The capsule shell is opened in the device and the powder is inhaled by the user. The capsule shell remaining in the device is to be discarded after use, so that the device can be reused with a new filled capsule. It cannot provide large dose as in the case of Asthma attack (Disadvantage). A wide range of unit dose dry powder inhalers are in use such as-

The Innova ™ (Inhale Therapeutic Systems, San Carlos, California, and U.S.A.) is a long term used unit dose dry powder inhaler placed in a transparent holding chamber consisting of a stored bolus of compressed air which generate aerosol independent of patient's inspiratory effort. The transparent holding chamber enables patients to view the aerosol to assure proper dosing. Further, the device is capable to fluidize and extract up to 90% of the dose from the reservoir, thus minimizing waste and enhancing the accuracy and precision of the dosage.

The Solo ™ device is a short term used patient-driven unit dose dry powder inhaler. It has a built-in flow control to maximize the reproducibility of dose to patient.

Multi dose Devices: Turbuhaler was the first developed multi dose DPIs by A.B. Draco (now a division of Astra Zeneca) capable of delivering carrier-free particles at moderate flow rates. However, one of the drawbacks of the Turbuhaler is that it has a variable rate of delivery due to different flow rate. To work out with the drawback and for multiple dosing and consistent performances, Turbuhaler was replaced by Diskhaler developed by Glaxosmith.

Diskhaler was used to deliver a range of drugs, including salbutamol and beclomethasone. This device uses a circular disk containing of either four or eight powder doses that are maintained in separate aluminum blister reservoirs. On priming the device, the aluminum blister is pierced, and the contents of the pouch are dropped into the dosing chamber. This product had limited commercial success and was superseded in the late 90's by the Diskuse.

Diskuse is a true multi dose device, having 60 doses in a foil– foil aluminum strip that is opened only at the point just prior to patient inspiration. Consistent performance and broad

patient acceptance has allowed the Diskuse to become the gold standard of multi dose powder delivery devices. Others like the GyroHaler® and OmniHaler® are cost-effective, multi-unit dose dry powder inhaler designed to deliver locally acting drugs to the lungs.

Clickhaler® is a multi-dose, reservoir dry powder inhaler. It is approved for use to deliver a number of drugs used to treat patients with asthma and COPD (salbutamol, beclometasone, formoterol, budesonide and procaterol) in Europe and Japan. Clickhaler® is an automated inexpensive multi - unit dose DPI device.

Duohaler® is a fixed dual-therapy, passive, multi-dose dry powder inhaler where two individual drug formulations are placed in two separate drug reservoirs that feed to two separate metering chambers from which the drugs are delivered to the user in the same breath.

PowderHale® is Vectura's patented dry powder inhaler formulation technology, designed to allow aerosolised drug particles to achieve high lung penetration with low dose variability. This is achieved by the incorporation of an additional pharmacologically inactive excipient, known as a Force Control Agent (FCA) to the drug formulation.

Although DPIs are advantageous yet it suffers from major drawbacks as under:

a. The dispensing / generalisation of aerosol depend on patient's inspiratory airflow.
b. DPIs suffer from dose uniformity problems.
c. Complex/expensive development and manufacturing process.
d. It may lead to pharyngeal deposition of the drug.

ii) Nebulisers

Nebulizer is a device used to administer aerosolised medication in the form of a mist inhaled into the lungs. Nebulizers use oxygen, compressed air or ultrasonic power to break up medical solutions and suspensions into small aerosol droplets called mists that can be directly inhaled from the mouthpiece of the device. Nebuliser produce a mist of drug containing water droplets for inhalation. The drug is present either in solution form or suspension form in the nebulizer. It is usually of two types:

Electronic nebulizer and Jet or ultrasonic nebulizer. Jet or ultrasonic nebulizer uses a source of pressurised air to blast a stream of ait through a drug containing water reservoir, producing water droplets. In contrast, electronic nebulizers develop mechanical vibration to produce water droplets.

The nebulisers are generally used for the treatment of acute conditions (e.g. acute asthma, respiratory infection) or in those patients who have difficulties using other respiratory dosage forms.

Some of the marketed products of nebulizers are as follow: **Omron Microair Nebulizer:**

The features of Omron Microair Nebulizer are as under:

a) A dense therapeutic aerosol is produced by electronic vibrating mesh technology.
b) It allows complete delivery of medication.
c) It consists of universal adapters.
d) As its lightweight weighs only 6 ounces (170 g) with batteries, so easily portable.
e) Ideal for pediatric asthma treatment.

f) It saves energy due to low power consumption: 4 hours of continuous operation on 2 alkaline batteries (batteries sold separately) 8 hours when used about 30 minutes a day.
g) Smallest size of any electronic nebulizer.
h) Detachable nebulizer head for easy cleaning.
i) It is an alternative to Metered Dose Inhalers (MDI).

DeVilbiss DeVilbiss PulmoMate Compressor / Nebulizer provides an incomparable combination of quality and value. Its design has been made in such a way that it fits easily into luggage, backpacks for easy transport. The DeVilbiss PulmoMate features an updated compressor/motor for long- term durability and performance.

Pari Trek S is the best compressor nebulizer machine for travelling. This nebulizer include a DC car adapter and good looking portable case which help those who travel a lot by making nebulization treatments in the car possible.

The wide use of nebulizer refers to the advantages of nebulizers as follows:

A. Patient coordination not required.
B. Effective with tidal breathing.
C. High dose possible.
D. No chlorofluorocarbon (CFC) is released.
E. It can be used with supplemental oxygen.
F. It can deliver combination therapy if compatible.
G. The ultrasonic nebulizer is quiet, has faster delivery; are smaller and more portable.

The disadvantages of nebulizer are as follows:

- They are expensive.
- More electrical power sources are required.
- Jet nebulizer requires pressurised form of gas.
- The frequent cleaning of the device is needed.
- There is a chance of contamination.
- The suspension of dosage cannot be aerosolized properly.
- The jet nebulizer produces large and variable sized particles.
- The ultrasonic stimulation and the rise in temperature cause drug degradation.

TYPES OF AEROSOL SYSTEMS

The aerosol systems are classified as shown in Figure 6

Solution system or two phase system

It is also called two-phase system as it contains both the vapour and the liquid. Based on the desired spray, the propellant can be used single or a mixture of propellants can be used. Propellant 12 is added alone or in mixture. If propellants having vapour pressure lower than propellant 12 is added to propellant 12, a reduction of vapour pressure is achieved but bigger sized aerosol particles are obtained. Also bigger sized aerosol particles are obtained on addition of cosolvents like ethyl acetate, propylene glycol, ethyl alcohol, glycerine and acetone. No other solvent is required if the drug is soluble in the propellant. The solution system is administered in topical application. Some of the commonly used propellant combinations in solution systems are

propellant 12/11 (30:70), propellant 12/114 (45:55), propellant (12/114) (55:45).

Water based system or three phase system

In the water based or three phase system, large quantity of water is present to solubilise the contents. The water is immiscible with the propellant. Generally water based system is a three phase system consisting of a water phase, vapour phase and the propellant. So, the solubility of propellant in water can be increased by adding a cosolvent such as ethanol and also by adding surfactants at a range of composition 0.5% to 2.0 %. The propellant composition ranges from 25 to 60%. The nonpolar surfactants such as esters of Oleic acid, palmitic acid, stearic acids are more preferred than the polar surfactants. The surfactants act by reducing the interfacial tension existing between the water phase and the propellant, and thus produce a uniform dispersion by increasing the solubility of the propellant in the water. The drawback associated with water based system is that the addition of ethanol, not only increases the solubility of propellant in water, but also increases its flammability. The presence of large quantities of water delivers content in liquefied form. The recent advancement is the vapour tap valve and the aquasol valve. In aquasol system, water or the mixture of water and alcohol are used to dissolve the drug. The addition of alcohol increases the solubility of propellant in water. Aquasol system is advantageous than water based system as a vapourised propellant is delivered rather than the liquefied propellant. The vapourised propellant delivers small sized, fine particles and dried contents in the form of fine mist or spray to the site of action. Moreover, the vapourised propellant is non-flammable in nature.

Suspension or dispersion systems

Suspension or dispersion system is the dispersion of the active ingredients in the propellant or the mixture of propellant by adding surfactants or the suspending agents.

Foam system

The liquefied propellant is emulsified. Aqueous or nonaqueous vehicles, propellant and the surfactants are its ingredients. Foam system is further classified as aqueous stable, nonaqueous stable and the quick breaking foam.

Aqueous stable foams: The aqueous stable foam consists of propellant in the range of 3.0 to 4.0 %. A dry spray is produced by the propellant .As the concentration of propellant goes on increasing, more and more contents are delivered in dried form. As the propellant is present in the internal phase, so the concentration of propellant is less. It finds its application in steroid antibiotics.

Non aqueous stable foams: The nonaqueous stable foam contains glycol as the emulsion base and is used as the emulsifying agent.

Quick breaking foams: Here the external phase is propellant. The product will come out as foam which soon merges to form liquid. This type of system can be applied to small area or larger surface. These are used for topical application. Cationic or anionic or non-ionic surfactants are used in the formulation.

Thermal foams: The aerosol which is delivered in the form of foam upon the application of heat is called thermal foam. They are used in shaving creams.

MANUFACTURING OF PHARMACEUTICAL AEROSOLS

The manufacturing of aerosol consists of three types of apparatus

Cold filling apparatus: It consists of an insulated box fitted with copper tubings. The insulated tubings are filled with dry ice or acetone. The copper tubings increase the surface area and cause faster cooling. The hydrocarbon propellant is not to be stored in the copper tubings as it might cause explosion.

Pressure filling apparatus: Pressure filling apparatus consists of a metering burette capable of measuring the amount of propellant to be filled to the aerosol container. The propellant is added through the inlet valve present to the bottom of the valve under its own vapour pressure. A cylinder of nitrogen or compressed gas is attached to the top of the valve and the pressure of nitrogen causes the propellant to flow to the container through the metering burette. The propellant flows to the container stops when the pressure of the flowing propellant becomes equal to the pressure of the container.

Compressed gas filling apparatus: A compressed gas propellant is used. As the compressed gas is under high pressure, so the pressure is reduced by pressure reducing valve. A pressure of 150 pounds per square inch gauge is required to fill the compressed gas propellant in the aerosol container. The product concentrate is placed in the pressure gauge and the valve is crimped in its place. The air is evacuated. The filling head is inserted into the valve opening. Upon the depression of the valve, the compressed gas propellant is allowed to flow into the container. The compressed gas stops flowing when the pressure of the compressed gas flowing to the container from the burette becomes equal to the pressure within the container. In case of increasing the solubility of the gas in the product concentrate and also when an increased amount of compressed gas is required, carbon dioxide and Nitrous dioxide is used. The container is needed to be shaken during and after the filling operation to enhance the solubility of the gas in the product concentrate.

The filling of aerosol product into the container is by two methods:

Cold filling method : Two methods are involved:

- In the first method, the product concentrates are chilled to a temperature of – 30 to – 40^0 F. The chilled product concentrates are added to the chilled aerosol container. The chilled propellant is added through an inlet valve present under side of the valve of the aerosol container.
- In the second method, both the product concentrate and the propellant are chilled to – 30 to – 40^0 F. Then the mixture is added to the chilled container.

In both the above methods, after the aerosol containers are filled, the valves are set in its place and the filled aerosol containers are passed through a water bath in which the contents of the containers are heated to 130 ^{0} F to test for leaks and strength. Then the containers are air dried, capped and labelled. Cold filling method is advantageous for the filling of metering valve containing aerosol container. The pressure filling method is more prominant than cold filling method as most of the formulations cannot be cooled to very low temperatures

Pressure filling method: The product concentrate is filled to the aerosol container through the metering pressure filling burette at room temperature. The propellant is added through the inlet valve located at the base of the valve or under the valve after the crimping of valve. The flow of propellant to the aerosol container continues till the pressure of the filling propellant becomes equal to the pressure within the container. The aerosol container are capped and labelled. The pressure filling methods have the following advantages over the cold filling method:

- The emulsion, suspensions are unstable at very low temperature. So the pressure filling method is the preferred method then that of cold filling method.
- The absence of moisture reduces the chance of contamination.
- The rate of production is high.
- The chance of loss of propellant is low.

Concentrate filler, Valve placer, Purger and vacuum crimper, Pressure filler, Leak test tank equipments are used for large scale of production.

QUALITY CONTROL OF PHARMACEUTICAL AEROSOLS

Quality control of pharmaceutical aerosol includes the testing of propellant, valves, actuator and dip tubes, containers, weight checking, leak testing and spray testing.

PROPELLANT

All quality control testings of propellents are accompanied by specification sheets:

A sample is taken out and vapour pressure is determined which then is compared to specifications. The density is also checked when necessary. Other tests include –

- Identification of two or more blends of propellant by Gas chromatography.
- Purity of the propellant is checked by moisture, halogen, and non-volatile residue determinations.

VALVES, ACTUATORS, AND DIP TUBES

Both physical and chemical examinations are done. They are sampled according to the standard procedures as found in "Military Standard Mil – STD-105D".A test method was developed for metered dose pharmaceutical aerosol by Aerosol specifications committee, Industrial Pharmaceutical Technology section, Academy of Pharmaceutical Sciences with an objective of determining the magnitude of valve delivery and degree of uniformity between individual valves. The composition of the test solution is given in Table 3:

Testing procedure

- Take 25 valves and placed on suitable containers.
- The containers are filled with specific test solutions.
- A button actuator with 0.02 inch orifice is attached to the valves.
- The filled containers are placed in a suitable atmosphere at a temperature of 25 ± 1^0 C
- When the products have attained the temperature of 25 ± 1^0 C, the filled containers are actuated to fullest extent for 2 seconds.
- This procedure is repeated for a total of 2 deliveried from each 25 test units.

The valve delivery per actuation in µl = $\frac{\text{Individual delivery weight in mg}}{}$

Specific gravity of test solution

The limits for acceptance as given in Table 4 Out of 50 deliveries:
If 4 or more deliveries are outside limits, then valves are rejected.

- If 3 or more deliveries are outside limits, another 25 valves are tested.
  - Lot is rejected if more than 1 delivery is outside specification.
- If 2 deliveries from 1 valve are beyond limits: another 25 valves are tested.
  - Lot is rejected if more than 1 delivery is outside specification.

CONTAINERS

Containers are examined for defects in linings. Quality control aspects include degree of conductivity of electric current as measure of exposed metals. Glass containers examined for flaws.

WEIGHT CHECKING

It is done by periodically adding empty tared containers to filling lines which after filling with product concentrate are removed and reweighed. Same procedure is used for checking weight of the propellant.

LEAK TEST

It is done by measuring the crimp's valve dimension and comparing. Final testing of valve enclosure is done by passing filled containers through the water bath.

SPRAY TESTING

It is done to clear up dip tube of pure propellant and concentrate and to check any defects in the valve and the spray pattern.

EVALUATION TESTS OF PHARMACEUTICAL AEROSOLS

FLAMMABILITY AND COMBUSTIBILITY

It includes Flame projection and Flame extension.

Flame projection: The aerosol product is sprayed to an open flame for about 4 second and the extension of the flame is measured with the help of a ruler.

Flash point: Tag Open Cup apparatus is the standard test apparatus. The aerosol product is chilled to a temperature of about – 25 ^{0} F and transferred to the test apparatus. The temperature of the test liquid is increased slowly and the temperature at which the vapours ignite is taken as the flash point.

Physicochemical characteristics are given in Table 5.

PERFORMANCE TEST

It includes the following tests

Aerosol Valve Discharge Rate: An aerosol product of known weight is taken and its contents are discharged using standard apparatus for a given period of time. The container is reweighed. Then the change in weight per time dispensed is the discharge rate. The discharge rate can also be expressed as grams per second.

Spray patterns: The method involves the impingement of sprays on a piece of paper that has been treated with dye – talc mixture. It gives a record of the spray pattern.

Dosage with metered valves: The doses are dispensed into the solvents or onto a material that absorbs the active ingredients. The assay of the solution gives the amount of active ingredients present. Another method involves accurate weighing of the filled container followed by dispensing of several doses. The container is then reweighed, and the difference in weight divided by the number of doses dispensed gives the average dose. This process is repeated and the results are compared.

Net contents: The tared cans are placed onto the filling line are weighed, the difference in weight is equal to the net contents. The other method is a Destructive method and consists of weighing a full container and then dispensing the contents. The contents are then weighed. The difference in weight gives the amount of contents present in the container.

Foam stability: The life of a foam ranges from a few seconds (for quick breaking foam) to one hour or more depending on the formulation. The methods which are used to determine the foam stability includes visual evaluation, time for a given mass to penetrate the foam, time for a given rod that is inserted into the foam to fall and rotational viscometer.

Particle size determination: Cascade impactor and light scattering decay methods are used for particle size determination. It is based on the principle that for a stream of particles projected through a series of nozzle and glass slides, the larger particles are impacted first on the lower velocity stage and the smaller particles are impacted on the higher velocity stage.

BIOLOGIC TESTING

Therapeutic activity and Toxicity are considered in Biologic testing.

Therapeutic Activity:

For Inhalation Aerosols: The determination of therapeutic activity is dependent on the particle size.

For Topical Aerosols: Therapeutic activity of aerosol products are determined by applying the therapeutically active ingredients topically to the test areas and the amount of therapeutically active substances absorbed is determined.

Toxicity study:

For Topical Aerosols: The topically administered aerosols are checked for chilling effect or irritation in the skin. When aerosol are topically applied, thermistor probe attached to the recording thermometer are used to determine the change in skin temperature for a given period of time.

For Inhalation Aerosols: Inhalation toxicity study is done by exposing test animals to vapours sprayed from the aerosol container.

EXTRACTABLE SUBSTANCES

The composition and the quality of materials used in the manufacturing of elastomeric and plastic components of valve (eg. Stem, gaskets, housing etc) are to selected and checked properly because as organic solvents are the major constituents of the propellant and also used as a vehicle, so it may increase the chance of leaching of constituents from the elastomeric and plastic components of valve into the formulation. This may lead to distortion of the components of valve, changes in the delivery rate of medication, increase in the leak rate and also lead to

contamination. So the selected elastomeric and plastic components of valve should be compatible with the formulation. Thus the established profile of each of the elastomeric and plastic components of valve should be correlated to the extractable profile of the aged drug products or placebo, to ensure reproducible quality and purity of the drug product. Specifications and limits for individual and total extractable from different valve components may require the use of different analytical methods.

LABELLING

Medicinal aerosols should contain at least the following warning information on the label as in accordance with appropriate regulations according to USP:

Warning— Avoid inhaling. Avoid spraying into eyes or onto other mucous membranes.

NOTE—The statement "Avoid inhaling" is not necessary for preparations specifically designed for use by inhalation. The phrase "or other mucous membranes" is not necessary for preparations specifically designed for use on mucous membranes.

Warning— Contents under pressure. Do not puncture or incinerate container. Do not expose to heat or store at temperatures above 120 ^{0}F (49 ^{0}C). Keep out of reach of children.

In addition to the aforementioned warnings, the label of a drug packaged in an aerosol container in which the propellant consists in whole or in part of a halocarbon or hydrocarbon shall, where required under regulations of the FDA, bear either of the following warnings:

Warning— Do not inhale directly; deliberate inhalation of contents can cause death.

Warning— Use only as directed; intentional misuse by deliberately concentrating and inhaling the contents can be harmful or fatal.

Table 1: Types of propellant

Application	**Name of propellant**
For oral and inhalation	**Fluorinated hydrocarbons** Di-chloro di-fluro methane (propellant 12) Trichloromonoflouromethane (propellant 11) Di-chloro tetra-fluro ethane (propellant 114)
Topical preparation	Propane, Butane, Isobutane
Compound gases	Nitrogen,Carbon dioxide, Nitrous oxide

Table 2: Pressure limitations of aerosol container

Contain Material	**Maximum Pressure (psig)**	**Temperature (^{0}F)**
Tin -plated steel	180	130
Uncoated glass	< 18	70
Coated glass	< 25	70
Aluminum	180	130
Stainless Steel	180	130
Plastic	< 25	70

Table 3: Preparation of test solutions.

Ingredients % w/w	Test solution A	Test solution B	Test solution C
Isopropyl myristate	0.1 %	0.1%	0.1%
Dichlorodifluoromethane	49.95%	25%	50.25%
Dichlorotetrafluoroethane	49.95%	25%	24.75%
Trichloromonofluoromethane	-	-	24.95%
Alcohol USP	-	49.9%	-
Specific Gravity at 25 ^{0} C	1.384	1.092	1.388

Table 4: Limits for acceptance of aerosol valves

Deliveries	Limits
54 µl or less	± 15 %
55 to 200 µl	± 10 %

Table 5: Physicochemical characteristics of propellants and product concentrates

Characteristics	Measuring device
Vapour pressure	Can puncturing device, Pressure gauge.
Density	Hydrometer, Pycnometer.
Moisture content	Karl Fischer method, Gas chromatography.
Identification of propellant	Gas chromatography, Infrared spectrophotometry.

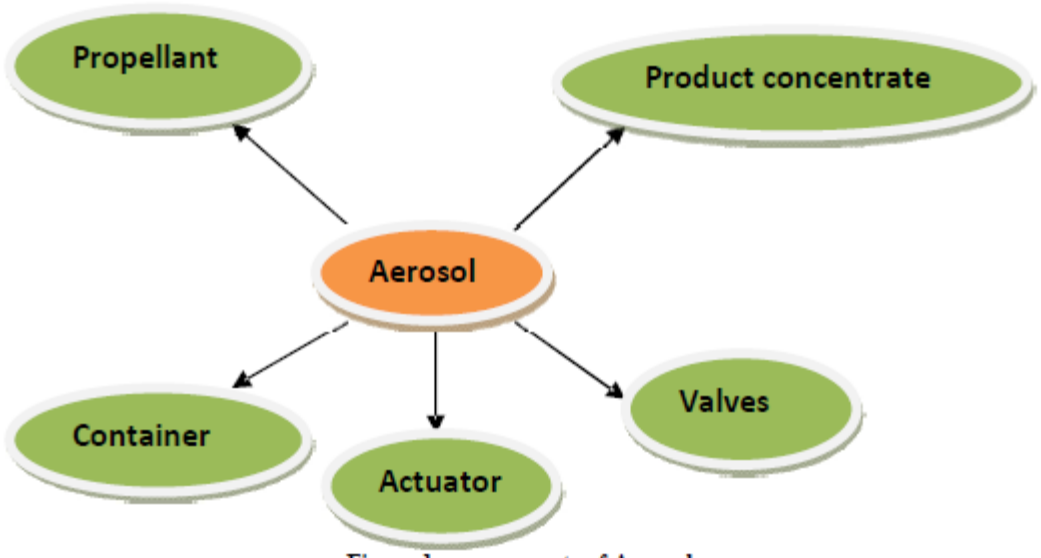


Figure 1: components of Aerosol

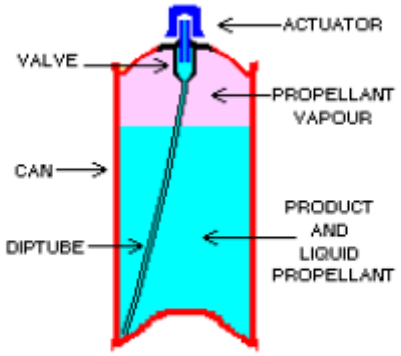


Figure 2: components of Aerosols[9]

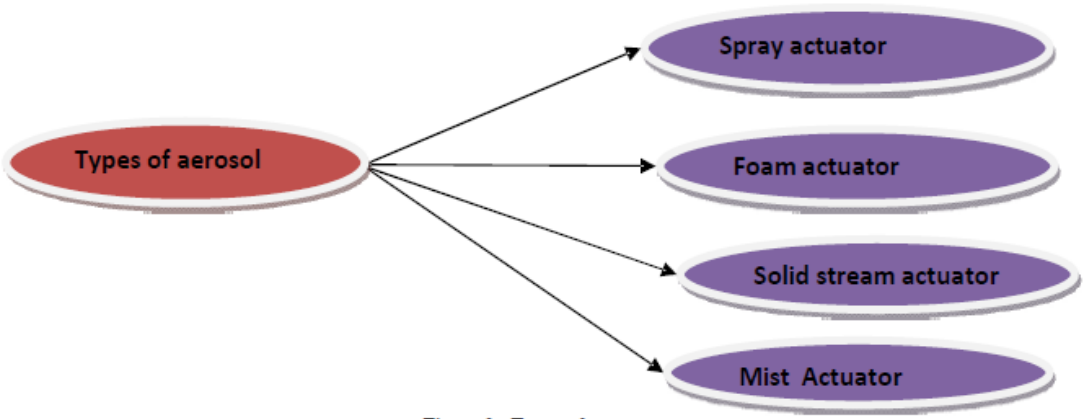


Figure 3: Types of actuator

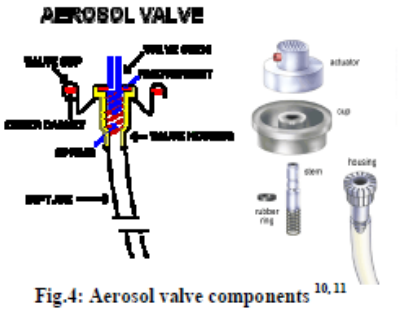


Fig.4: Aerosol valve components [10, 11]

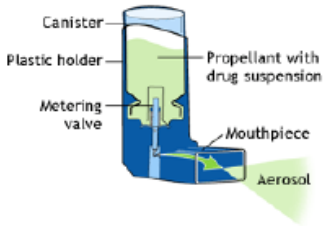


Figure 5: Pressurised metered dose inhalers (pMDIs) [12]

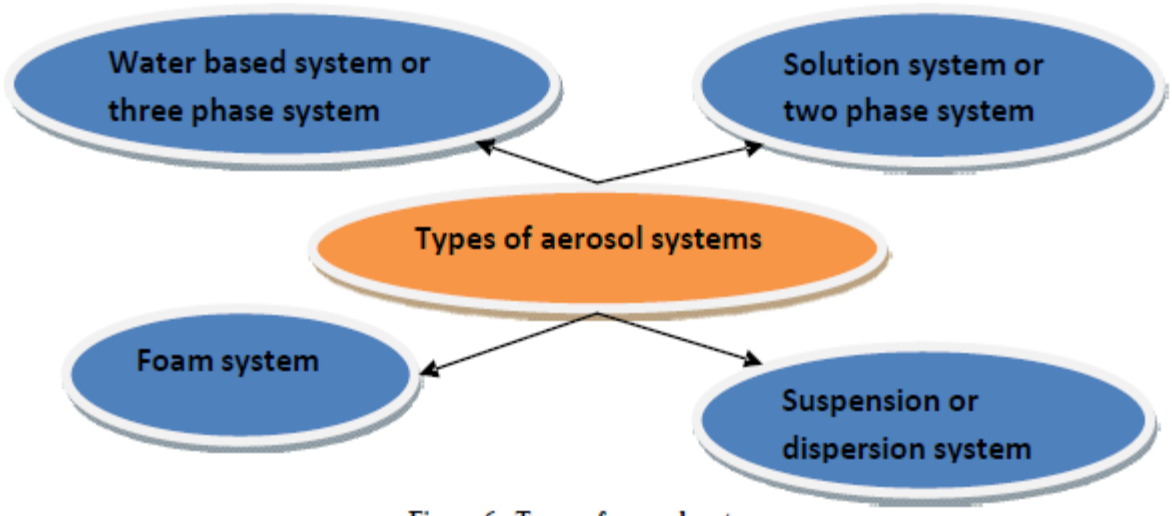


Figure 6: Types of aerosol system

Q. 18 Write a note on merits, demerits and application of microencapsulation

Microencapsulation is a process by which very tiny particles or droplets of solid or liquid material are coated or surrounded with a continuous film of polymeric material. These micro-capsules have a number of benefits such as converting liquids to solids, providing environmental protection, separating reactive compounds and improved material handling properties. Active materials are then encapsulated in micron-sized capsules of barrier polymers (gelatin, plastic, wax ...). In the process of microencapsulation, tiny particles or droplets are surrounded by a coating to give small capsules with many useful properties. The material inside the microcapsule is referred to as Core, whereas the wall is called a shell, coating, or membrane . An appropriate motto for studying micro encapsulation would be "Small is better". Entrapment of a biologically active substance (from DNA to entire cell or group of cells) is known as Bioencapsulation, which is a part of microencapsulation. Micro encapsulation involves the coatings of particles ranging dimensions from several tenths of a micron to 5000 micron in size and provides the means of converting liquids to solids, of altering surface and colloidal properties of providing environmental protection and of controlling the release characteristics or availability of coated materials. The process targeted at creating a barrier between the core material in fine powder form or droplet form and its environment known as High performance micro encapsulation. Micro encapsulation is a process by which solids or liquids or even gases may be encapsulated into microscopic size particles through the formation of thin coating of wall material around the substance being encapsulated.

REASONS FOR MICROENCAPSULATION

(1) In some cases, the core must be isolated from its surroundings, because

· As in isolating vitamins from the deteriorating effects,

· Retarding evaporation of a volatile core,

· Improving the handling properties of a sticky material or

· Isolating a reactive core from chemical attack.
(2) In other cases, the objective is not to isolate the core completely but to control the rate at which it leaves the microcapsule, as in the controlled release of drugs or pesticides.
(3) As masking the taste or odor of the core,
(4) As complex as increasing the selectivity of an adsorption or extraction process.

ADVANTAGES

1. Converts liquid into free flowing solid and pseudo solid which improves handling and storage like Eprazinone, Clofibrate, Castor oil, Cod-liver oil etc.
2. Reduces volatility of substances like methyl salicylate, peppermint oil, flavors, perfumes etc.
3. Avoid incompatibilities in drug combinations like aspirin and chlorpheniramine maleate, eutectic combinations etc.
4. Masks unpleasant taste of drug like penicillin derivatives like ampicillin, aminophylline, prednisolone, cod liver oil etc.
5. Mask unpleasant or unacceptable odor of cores like castor oil, cod liver oil, methionine, cysteine etc.
6. Reduces gastro intestinal irritation due to irritant drugs like ferrous sulphate, potassium chloride, paracetamol, phenylbutazone, indomethacin, nitrofurantoin etc.
7. Reduce hygroscopicity of core like sodium chloride etc.
8. Provides sustain / prolong / delay / control drug release.
9. Reduces hazards to operators in case of toxic chemicals like insecticides, pesticides and sensitizers like penicillins etc.
10. Improve flow properties, compaction and compressibility of the core like Vitamins etc.
11. For immobilization of enzymes for improving their stability and retention of activity.
12. By this chemical incompatible ingredients can produce in single form like Aspirin, Citric acid etc.

DISADVANTAGE

1. Quite expensive,
2. The technique is not adaptable to all core materials,
3. Sometimes coating may be uncompleted and discontinuous,
4. No single method can be applied to all core materials,
5. Because of the inadequate stability and shelf life, Sensitive pharmaceuticals cannot used,
6. For different cores and different applications, Individual design approach is required,
7. Coated products may have non reproducible and unstable release characters, may be too bulky,
8. Limited choice of safe, approved, biocompatible and biodegradable materials,
9. May damage the coat or the product due to mechanical stress like compression, compaction, packaging, transport, handling etc.
10. Micro particles may not be suitable for parenteral applications due to size restrictions,
11. Need of sterilization, necessity of non-allergic, biocompatible and biodegradable nature of the carrier etc.

12. Most information on microencapsulation is still patented and hence there may be difficulty in choosing suitable technique and methodology for individual applications,
13. There may be difficulties in scale up and large scale manufacturing the process
APPLICATION OF MICROENCAPSULATION Microencapsulation technologies are applied in any area of the industry. It can be found in:
(1) Cell immobilization In plant cell cultures microencapsulation, provides cell natural environment, improves efficiency in production of different metabolites used for medical, pharmacological and cosmetic purposes. Human tissue by microencapsulation are turned into bio-artificial organs in natural polymers and transplanted to control hormone-deficient diseases such as diabetes and severe cases of hepatic failure. In continuous fermentation processes immobilization is used to increase cell density, productivity and to avoid washout of the biological catalysts from the reactor and applied in ethanol and solvent production, sugar conversion or wastewater treatment.
(2) Beverage production Using immobilization technologies beverage products are beer, wine, vinegar and other food drinks production are to boost yield, improve quality, change aromas, etc...
(3) Protection of molecules from other compounds Some chemicals are very dangerous for our body. Micro encapsulation solve simple problem like the difficulty to handle chemicals (detergents dangerous if directly exposed to human skin) as well as many other molecule inactive or incompatible if mixed in any formulation.
(4) Drug delivery Microencapsulation has permitted controlled release delivery systems (allow controlling the rate, duration and distribution of the active drug.) after designing the right biodegradable polymers. One of the main advantages of such systems is to protect sensitive drug from drastic environment (pH,) and to reduce the number of drug administration's for patient and with these systems, micro particles sensitive to the biological environment are designed to deliver an active drug in a sitespecific way (stomach, colon, heart and specific organs).
(5) Quality and safety in food, agricultural & environmental sectors Encapsulated bio-systems enhanced development of the "biosensors" has been by used to control environmental pollution, food cold chain etc.
(6) Soil inoculation Rhizobium bacteria which improves nitrate adsorption and conversion. But cells are washed out by rain so inoculation is often unsuccessful. By cell encapsulation processes, it is possible to maintain continuous inoculation and higher cell concentration. Nutraceuticals (e.g. probiotics, vitamins...) improvement of their efficiency and stability by protecting and offering targeting release of the active materials.
(7) Pharmaceuticals In Pharmaceutical field's micro encapsulation is used to increase duration of action of drug, increase the stability of drug, increase the bioavailability, taste masking, increase the dissolving properties etc

Q. 19 Discuss factors variable and design of experiment

The term **experiment** is defined as the systematic procedure carried out under controlled conditions in order to discover an unknown effect, to test or establish a hypothesis, or to illustrate

a known effect. When analyzing a process, experiments are often used to evaluate **which process inputs have a significant impact** on the process output, and **what the target level of those inputs should be** to achieve a desired result (output). Experiments can be **designed** in many different ways to collect this information. **Design of Experiments (DOE)** is also referred to as **Designed Experiments** or **Experimental Design** - all of the terms have the same meaning.

Components of Experimental Design

Consider the following diagram of a cake-baking process (Figure 1). There are three aspects of the process that are analyzed by a designed experiment:

- **Factors**, or inputs to the process. Factors can be classified as either controllable or uncontrollable variables. In this case, the controllable factors are the ingredients for the cake and the oven that the cake is baked in. The controllable variables will be referred to throughout the material as factors. Note that the ingredients list was shortened for this example - there could be many other ingredients that have a significant bearing on the end result (oil, water, flavoring, etc). Likewise, there could be other types of factors, such as the mixing method or tools, the sequence of mixing, or even the people involved. People are generally considered a Noise Factor (see the glossary) - an uncontrollable factor that causes variability under normal operating conditions, but we can control it during the experiment using blocking and randomization. Potential factors can be categorized using the Fishbone Chart (Cause & Effect Diagram) available from the Toolbox.
- **Levels**, or settings of each factor in the study. Examples include the oven temperature setting and the particular amounts of sugar, flour, and eggs chosen for evaluation.
- **Response**, or output of the experiment. In the case of cake baking, the taste, consistency, and appearance of the cake are measurable outcomes potentially influenced by the factors and their respective levels. Experimenters often desire to avoid optimizing the process for one response at the expense of another. For this reason, important outcomes are measured and analyzed to determine the factors and their settings that will provide the best overall outcome for the critical-to-quality characteristics - both measurable variables and assessable attributes.

The design and analysis of experiments revolves around the understanding of the effects of different variables on other variable(s). In mathematical jargon, the objective is to establish a *cause-and-effect* relationship between a number of *independent variables* and a *dependent variable* of interest. The dependent variable, in the context of DOE, is called the *response*, and the independent variables are called *factors*. Experiments are run at different factor values, called *levels*. Each run of an experiment involves a combination of the levels of the investigated factors. Each of the combinations is referred to as a *treatment*. In a single factor experiment, each level of the factor is referred to as a treatment. In experiments with many factors, each combination of the levels of the factors is referred to as a treatment. When the same number of response observations are taken for each of the treatments of an experiment, the design of the experiment is said to be *balanced*. Repeated observations at a given treatment are called *replicates*. The number of treatments of an experiment is determined on the basis of the

number of factor levels being investigated in the experiment. For example, if an experiment involving two factors is to be performed, with the first factor having *x* levels and the second factor having *z* levels, then *x z* treatment combinations can possibly be run, and the experiment is an *x z* factorial design. If all *x z* combinations are run, then the experiment is a full factorial. If only some of the *x z* treatment combinations are run, then the experiment is a fractional factorial. In full factorial experiments, all of the factors and their interactions are investigated, whereas in fractional factorial experiments, all interactions are not considered because not all treatment combinations are run.

It can be seen that the size of an experiment escalates rapidly as the number of factors, or the number of the levels of the factors, increases. For example, if two factors at three levels each are to be used, nine different treatments are required for a full factorial experiment (3 3 = 9). If a third factor with three levels is added, 27 treatments are required (333 = 27) and 81 treatments are required if a fourth factor with three levels is added (3333 = 81). If only two levels are used for each factor, then in the four factor case, 16 treatments are required (2 2 2 2 = 16). For this reason, many experiments are restricted to two levels. Fractional factorial experiments further reduce the number of treatments to be executed in an experiment.

DOE Types

The following is a summary of some of the most common DOE types.

1 One Factor Designs

These are the designs where only one factor is under investigation, and the objective is to determine whether the response is significantly different at different factor levels. The factor can be *qualitative* or *quantitative*. In the case of qualitative factors (*e.g.* different suppliers, different materials, etc.), no extrapolations (*i.e.* predictions) can be performed outside the tested levels, and only the effect of the factor on the response can be determined. On the other hand, data from tests where the factor is quantitative (*e.g.* temperature, voltage, load, etc.) can be used for both effect investigation and prediction, provided that sufficient data are available.

2 Factorial Designs

In factorial designs, multiple factors are investigated simultaneously during the test. As in one factor designs, qualitative and/or quantitative factors can be considered. The objective of these designs is to identify the factors that have a significant effect on the response, as well as investigate the effect of interactions (depending on the experiment design used). Predictions can also be performed when quantitative factors are present, but care must be taken since certain designs are very limited in the choice of the predictive model. For example, in two level designs only a linear relationship between the response and the factors can be used, which may not be realistic.

General Full Factorial Designs

In general full factorial designs, each factor can have a different number of levels, and the factors can be quantitative, qualitative or both.

Two Level Full Factorial Designs

These are factorial designs where the number of levels for each factor is restricted to two. Restricting the levels to two and running a full factorial experiment reduces the number of treatments (compared to a general full factorial experiment) and allows for the investigation of all the factors and all their interactions. If all factors are quantitative, then the data from such experiments can be used for predictive purposes, provided a linear model is appropriate for modeling the response (since only two levels are used, curvature cannot be modeled).

Two Level Fractional Factorial Designs

This is a special category of two level designs where not all factor level combinations are considered and the experimenter can choose which combinations are to be excluded. Based on the excluded combinations, certain interactions cannot be determined.

Plackett-Burman Designs

This is a special category of two level fractional factorial designs, proposed by R. L. Plackett and J. P. Burman, where only a few specifically chosen runs are performed to investigate just the main effects (*i.e.* no interactions).

Taguchis Orthogonal Arrays

Taguchis orthogonal arrays are highly fractional designs, used to estimate main effects using only a few experimental runs. These designs are not only applicable to two level factorial experiments, but also can investigate main effects when factors have more than two levels. Designs are also available to investigate main effects for certain mixed level experiments where the factors included do not have the same number of levels.

3 Response Surface Method Designs

These are special designs that are used to determine the settings of the factors to achieve an optimum value of the response.

4 Reliability DOE

This is a special category of DOE where traditional designs, such as the two level designs, are combined with reliability methods to investigate effects of different factors on the life of a unit. In Reliability DOE, the response is a life metric (*e.g.* age, miles, cycles, etc.), and the data may contain censored observations (suspensions, interval data). One factor designs and two level factorial designs (full, fractional, and Plackett-Burman) are available in **DOE++** to conduct a Reliability DOE analysis.

Q. 20 Describe introduction to two level factorial design

Two level factorial experiments are factorial experiments in which each factor is investigated at only two levels. The early stages of experimentation usually involve the investigation of a large number of potential factors to discover the "vital few" factors. Two level factorial experiments are used during these stages to quickly filter out unwanted effects so that attention can then be focused on the important ones.

2^k Designs

The factorial experiments, where all combination of the levels of the factors are run, are usually referred to as *full factorial experiments*. Full factorial two level experiments are also referred to as 2^k designs where k denotes the number of factors being investigated in the experiment.

A full factorial two level design with k factors requires 2^k runs for a single replicate. For example, a two level experiment with three factors will require $2 \times 2 \times 2 = 2^3 = 8$ runs. The choice of the two levels of factors used in two level experiments depends on the factor; some factors naturally have two levels. For example, if gender is a factor, then male and female are the two levels. For other factors, the limits of the range of interest are usually used. For example, if temperature is a factor that varies from 45^oC to 90^oC, then the two levels used in the 2^k design for this factor would be 45^oC and 90^oC.

The two levels of the factor in the 2^k design are usually represented as -1 (for the first level) and 1 (for the second level). Note that this representation is reversed from the coding used in General Full Factorial Designs for the indicator variables that represent two level factors in ANOVA models. For ANOVA models, the first level of the factor was represented using a value of 1 for the indicator variable, while the second level was represented using a value of -1. For details on the notation used for two level experiments refer to Notation.

The 2^2 Design

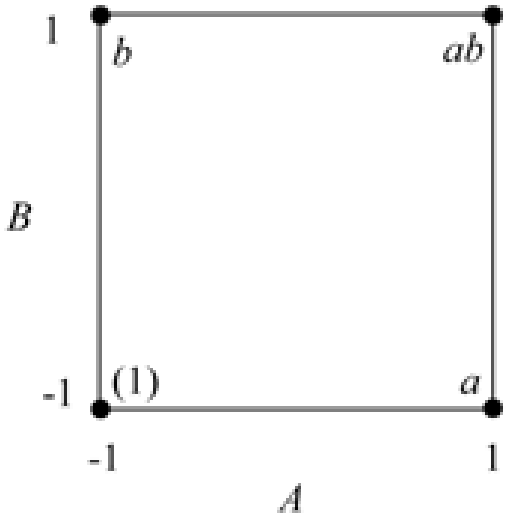
The simplest of the two level factorial experiments is the 2^2 design where two factors (say factor A and factor B) are investigated at two levels. A single replicate of this design will require four runs ($2^2 = 2 \times 2 = 4$) The effects investigated by this design are the two main effects, A and B, and the interaction effect AB. The treatments for this design are shown in figure (a) below. In figure (a), letters are used to represent the treatments. The presence of a letter indicates the high level of the corresponding factor and the absence indicates the low level. For example, (1) represents the treatment combination where all factors involved are at the low level or the level represented by -1; a represents the treatment combination where factor A is at the high level or the level of 1, while the remaining factors (in this case, factor B) are at the low level or the level of -1. Similarly, b represents the treatment combination where factor B is at the high level or the level of 1, while factor A is at the low level and ab represents the treatment combination where factors A and B are at the high level or the level of the 1. Figure (b) below shows the design matrix for the 2^2 design. It can be noted that the sum of the terms resulting from the product of any two columns of the design matrix is zero. As a result the 2^2 design is an *orthogonal design*. In fact, all 2^k designs are orthogonal designs. This property of the 2^k designs offers a great advantage in the analysis because of the simplifications that result from orthogonality. These simplifications are explained later on in this chapter. The 2^2 design can also be represented geometrically using a square with the four treatment combinations lying at the four corners, as shown in figure (c) below.

Treatment Name	Factors	
	A	*B*
(1)	-1	-1
a	1	-1
b	-1	1
ab	1	1

(a)

I	*A*	*B*	*AB*
1	-1	-1	1
1	1	-1	-1
1	-1	1	-1
1	1	1	1

(b)



(c)

The 2^3 Design

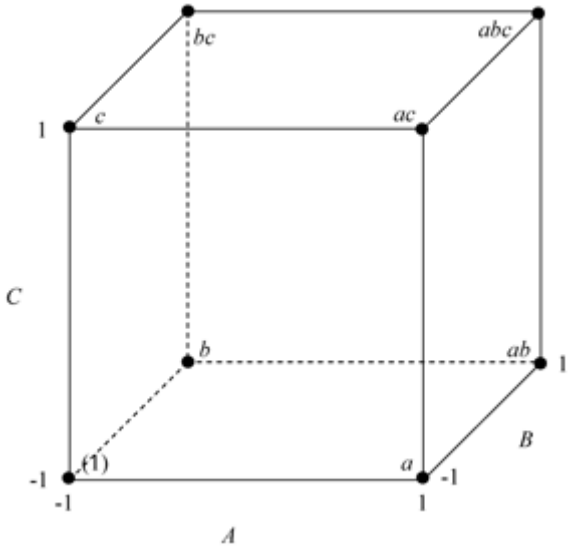
The 2^3 design is a two level factorial experiment design with three factors (say factors A, B and C). This design tests three ($k = 3$) main effects, A, B and C; three ($\binom{k}{2} = \binom{3}{2} = 3$) two factor interaction effects, AB, BC, AC; and one ($\binom{k}{3} = \binom{3}{3} = 1$) three factor interaction effect, ABC. The design requires eight runs per replicate. The eight treatment combinations corresponding to these runs are (1), a, b, ab, c, ac, bc and abc. Note that the treatment combinations are written in such an order that factors are introduced one by one with each new factor being combined with the preceding terms. This order of writing the treatments is called the *standard order* or *Yates' order*. The 2^3 design is shown in figure (a) below. The design matrix for the 2^3 design is shown in figure (b). The design matrix can be constructed by following the standard order for the treatment combinations to obtain the columns for the main effects and then multiplying the main effects columns to obtain the interaction columns.

Treatment Name	Factors		
	A	*B*	*C*
(1)	-1	-1	-1
a	1	-1	-1
b	-1	1	-1
ab	1	1	-1
c	-1	-1	1
ac	1	-1	1
bc	-1	1	1
abc	1	1	1

(a)

I	*A*	*B*	*AB*	*C*	*AC*	*BC*	*ABC*
1	-1	-1	1	-1	1	1	-1
1	1	-1	-1	-1	-1	1	1
1	-1	1	-1	-1	1	-1	1
1	1	1	1	-1	-1	-1	-1
1	-1	-1	1	1	-1	-1	1
1	1	-1	-1	1	1	-1	-1
1	-1	1	-1	1	-1	1	-1
1	1	1	1	1	1	1	1

(b)



The 2^3 design can also be represented geometrically using a cube with the eight treatment combinations lying at the eight corners as shown in the figure above.

Analysis of 2^k Designs

The 2^k designs are a special category of the factorial experiments where all the factors are at two levels. The fact that these designs contain factors at only two levels and are orthogonal greatly simplifies their analysis even when the number of factors is large. The use of 2^k designs in investigating a large number of factors calls for a revision of the notation used previously for the ANOVA models. The case for revised notation is made stronger by the fact that the ANOVA and multiple linear regression models are identical for 2^k designs because all factors are only at two levels. Therefore, the notation of the regression models is applied to the ANOVA models for these designs, as explained next.

Notation

Based on the notation used in General Full Factorial Designs, the ANOVA model for a two level factorial experiment with three factors would be as follows:

$$Y = \mu + \tau_1 \cdot x_1 + \delta_1 \cdot x_2 + (\tau\delta)_{11} \cdot x_1x_2 + \gamma_1 \cdot x_3 + (\tau\gamma)_{11} \cdot x_1x_3 + (\delta\gamma)_{11} \cdot x_2x_3 + (\tau\delta\gamma)_{111} \cdot x_1x_2x_3 + \epsilon$$

where:

- μ represents the overall mean
- τ_1 represents the independent effect of the first factor (factor A) out of the two effects τ_1 and τ_2
- δ_1 represents the independent effect of the second factor (factor B) out of the two effects δ_1 and δ_2
- $(\tau\delta)_{11}$ represents the independent effect of the interaction AB out of the other interaction effects
- γ_1 represents the effect of the third factor (factor C) out of the two effects γ_1 and γ_2

- $(\tau\gamma)_{11}$ represents the effect of the interaction AC out of the other interaction effects
- $(\delta\gamma)_{11}$ represents the effect of the interaction BC out of the other interaction effects
- $(\tau\delta\gamma)_{111}$ represents the effect of the interaction ABC out of the other interaction effects

and ϵ is the random error term.

The notation for a linear regression model having three predictor variables with interactions is:

$$Y = \beta_0 + \beta_1 \cdot x_1 + \beta_2 \cdot x_2 + \beta_{12} \cdot x_1 x_2 + \beta_3 \cdot x_3 + \beta_{13} \cdot x_1 x_3 + \beta_{23} \cdot x_2 x_3 + \beta_{123} \cdot x_1 x_2 x_3 + \epsilon$$

The notation for the regression model is much more convenient, especially for the case when a large number of higher order interactions are present. In two level experiments, the ANOVA model requires only one indicator variable to represent each factor for both qualitative and quantitative factors. Therefore, the notation for the multiple linear regression model can be applied to the ANOVA model of the experiment that has all the factors at two levels. For example, for the experiment of the ANOVA model given above, β_0 can represent the overall mean instead of μ, and β_1 can represent the independent effect, τ_1, of factor A. Other main effects can be represented in a similar manner. The notation for the interaction effects is much more simplified (e.g., β_{123} can be used to represent the three factor interaction effect, $(\tau\beta\gamma)_{111}$).

As mentioned earlier, it is important to note that the coding for the indicator variables for the ANOVA models of two level factorial experiments is reversed from the coding followed in General Full Factorial Designs. Here -1 represents the first level of the factor while 1 represents the second level. This is because for a two level factor a single variable is needed to represent the factor for both qualitative and quantitative factors. For quantitative factors, using -1 for the first level (which is the low level) and 1 for the second level (which is the high level) keeps the coding consistent with the numerical value of the factors. The change in coding between the two coding schemes does not affect the analysis except that signs of the estimated effect coefficients will be reversed (i.e., numerical values of $\hat{\tau}_1$, obtained based on the coding of General Full Factorial Designs, and $\hat{\beta}_1$, obtained based on the new coding, will be the same but their signs would be opposite).

ASSIGNMENT 1				
Question	**Details**	**Unit no. as per syllabus**	**CO mapped**	**Bloom's Taxonomy Level**
1	Discuss in detail prerequisite for drug candidate	1	1	2
2	Write a note on factors affecting selection of polymers for modified release system	2	2	2
ASSIGNMENT 2				
1	Note on evaluation techniques of polymer	2	2	2
2	Write a note on method of preparation of microencapsulation	5	3	2

CLASS TEST-1					
Question	**Details**	**Marks**	**Unit no. as per syllabus**	**CO mapped**	**Bloom's Taxonomy Level**
1	Write a note on mucosal drug delivery system	5	3	3	2
2	Note on TDDS	5	3	3	2
CLASS TEST-2					
1	Write a note on gastroretentive DDS	5	3	3	2
2	Explain reasons for microencapsulation and its application	5	5	3	3

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