Shree H. N. Shukla Institute of Pharmaceutical Education and Research, Rajkot

B. Pharm
Semester-VII

Subject Name: Novel Drug Delivery System
Subject Code: BP704TT

CHAPTER-1- CONTROLLED DRUG DELIVERY SYSTEM

SYLLABUS:

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.

This subject is designed to impart basic knowledge on the area of novel drug delivery systems.

Learning objectives

Upon completion of the course the student shall be able to

1. To understand various approaches for development of novel drug delivery systems.
2. To understand the criteria for selection of drugs and polymers for the development of Novel drug delivery systems, their formulation and evaluation.

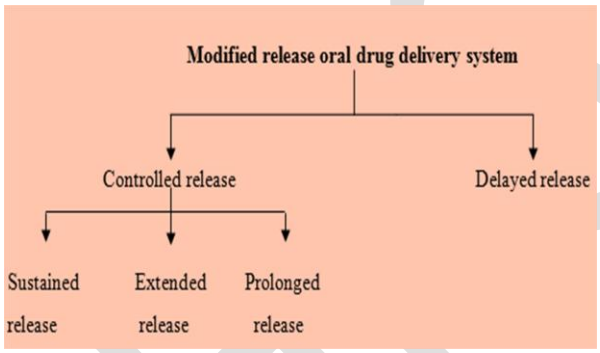
Controlled Drug Delivery System

What Is Drug Delivery Systems?

- Drug delivery systems refer to the technology utilized to present the drug to the desired body site for drug release and absorption.
- Newer discoveries and advancements in technology have lead to various new techniques of delivering the drugs for maximum patient compliance at minimal dose and side effects.

Ideal Drug Delivery System

- First, it should deliver drug at a rate dictated by the needs of the body over the period of the treatment.
- Second, it should channel the active entity solely to the site of action.
- This is achieved by development of new various modified drug release dosage forms, like.



Sustained Release Drug Delivery:

- Any of the dosage form that maintains the therapeutic blood or tissue levels of drug by continuous release of medication for a prolonged period of time, after administration of a single dose.
- In case of injectable dosage forms, it may vary from days to months.

Site Specific and Receptor Targeting:

- Targeting a drug directly to a certain biological location.
- For site specific release the target is the adjacent to or in the diseased organ or tissue, for receptor release the target is the particular drug receptor within an organ or tissue.

Controlled Release Drug Delivery:

- Delivery of the drug at a predetermined rate and /or to a location according to the needs of the body and disease states for a definite period of time.

Timed Release Or Delayed Release:

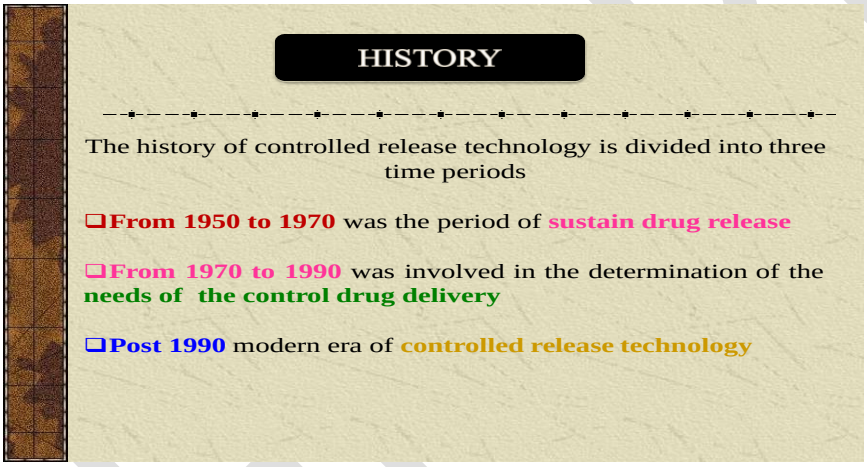
- These are the systems that use repetitive, intermittent dosing of a drug from one or more immediate release units incorporated into a single dosage form or an enteric delayed release systems.
- e.g. Repeat action tablets and capsules and enteric coated tablets where time release is achieved by barrier coating, or wherein the release of the drug is intentionally delayed until it reaches the intestinal environment.

Repeat Action Dosage Form:

- Contain 2 or 3 full doses which are so designed that the doses are released sequentially one after the other.

Other Novel (New) Dosage Forms:

- Includes-Microspheres, Nanoparticles,, Trans-dermal delivery systems, Ocular drug delivery, Nasal drug delivery, Implants etc.



Comparison of drug release profile

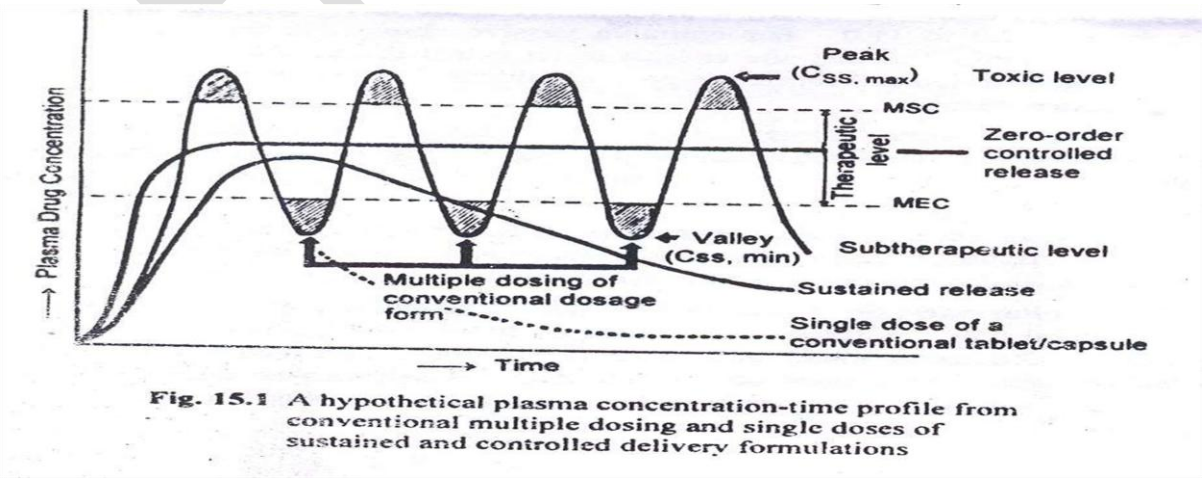


Fig. 15.1 A hypothetical plasma concentration-time profile from conventional multiple dosing and single doses of sustained and controlled delivery formulations

One Word Question Answer

SR NO.	QUESTION	ANSWER
1	The technology utilized to present the drug to the desired body site for drug release and absorption is called?	Drug Delivery System
2	In which drug therapy, the fluctuation in plasma drug concentration level occurs.	Conventional Drug delivery System
3	Delivery of the drug at a predetermined rate and /or to a location according to the needs of the body and disease states for a definite period of time.	Controlled Drug Delivery System
4	Targeting a drug directly to a certain biological location is called?	Receptor Targeting System
5	Which dosage form Contain 2 or 3 full doses which are so designed that the doses are released sequentially one after the other.	Time dependent release system
6	Microspheres, Nanoparticles are example of?	Novel Drug Delivery System
7	Period of sustained release is ?	From 1950 to 1970
8	Post modern area of controlled release is ?	From 1990

OBJECTIVES OF DRUG DELIVERY

Temporal drug delivery:

- Controlling the rate or specific time of drug delivery to the target tissue.

Spatial drug delivery:

- Targeting a drug to a specific organ or tissue.

Advantages

- Reduction in blood level fluctuations of drug, thus better management of the disease.
- Reduction in dosing frequency.
- Enhanced patient convenience and compliance.
- Reduction in adverse effects (both systemic and local), esp. of potent drugs, in sensitive patients.
- Reduction in health care costs.
- Improved efficiency of treatment.
- Reduces nursing and hospitalizing time.
- Maximum bioavailability with a minimum dose.
- Minimize drug accumulation with chronic dosing.
- Cure or control condition more promptly.
- Make use of special effects, e.g. Treatment of Arthritis.
- Constant blood levels achieve desired effect and this effect is maintained for an intended period.
- Drug susceptible to enzymatic inactivation or by bacterial decomposition can be protected by encapsulation in polymer system suitable for SR.

Disadvantages

- Administration of sustained release medication dose not permits prompt termination of therapy. Immediate changes in the drug if needed during therapy when significant adverse effects are noted cannot be accommodated.
- The physician has less flexibility in adjusting dosage regimen, as it is fixed by dosage form design.
- Sustained release dosage forms are designed for normal population i.e. on basis of average biologic half-life. Consequently, disease states that alter drug disposition, significant patient variation, and so forth are not accommodated.
- More costly process and equipment are involved in manufacturing.
- Dose dumping
- Unpredictable and poor *in-vitro* and *in-vivo* relationship.
- Effective drug release time period is influenced and limited by GI residence time.

- Need additional patient education.(such as not to chew or crush the dosage form before swallowing)
- Drugs having very short half life or very long half life are poor candidates for
- Delayed onset of action, hence sometimes not useful in acute conditions.

Rationality in designing Dosage form

- The basic objective in dosage form design is to ***optimize the delivery of medication*** to achieve the control of therapeutic effect in the *face of uncertain fluctuation* in the vivo environment in which drug release take place.
- This is usually concerned with maximum drug availability by attempting to attain a maximum rate and extent of drug absorption however; ***control of drug action*** through formulation also implies controlling bioavailability to reduce drug absorption rates.

Difficulties arise in maintaining the drug concentration in the therapeutic range.

- Patient incompliance due to ***increase frequency of dosing***, therefore ***chances of missing the dose*** of the drugs with short half-life.
- Difficulty to attain steady state drug concentration.
- Fluctuation may lead to under medication or over medication.

These difficulties may be overcome by:

- Developing the new ***better and safer drug*** with long half-life & large therapeutic indices.
- ***Effective and safer use*** of existing drugs through concept and techniques of controlled and targeted drug delivery.

Drug Properties Relevant to Dosage Form

- The design of sustained release delivery system is subjected to several variables and each of variables are inter-related.
- For the purpose of discussion, it is convenient to describe the properties of the drugs as being either physico-chemical or biological, these may be divided in two types.
    1. Physicochemical properties
    2. Biological properties

One Word Question Answer

SR NO.	QUESTION	ANSWER
1	Approach of Controlling the rate or specific time of drug delivery to the target tissue is called?	Temporal drug delivery
2	In which approach Constant blood levels achieve desired effect and this effect is maintained for an intended period of time.	Controlled Release Dosage Form
3	Which Dosage Form Reduces health care costs?	Controlled Release Dosage Form
4	Which dosage form is exhibited maximum bioavailability with a minimum dose.	Controlled Release Dosage Form
5	Which dosage form sometime produces unpredictable and poor *in-vitro* and *in-vivo* relationship	Controlled Release Dosage Form
6	Physichemical and Biological properties are of?	Drug Properties
7	***Effective and safer use*** of existing drugs through concept and techniques is developed by?	Controlled Release Dosage Form
8	Costly process and equipment are involved in manufacturing of?	Controlled Release Dosage Form

1. Biological Factors

- ✓ Absorption, Distribution, Metabolism, Biological half-life (excretion, Margin of safety

2. Physiological Factors

- ✓ Dosage size, Partition coefficient and molecular size, Aqueous Solubility, Drug stability, Protein binding, Pka

Physicochemical Properties:–

***1. Aqueous solubility* & pK_a:–**

Aqueous solubility:–

- A drug with good aqueous solubility, especially if pH independent, serves as a good candidates
- Drug to be absorbed it first must dissolve in the aqueous phase surrounding the site of administration and then partition into absorbing membrane.
- Since drugs must be in solution before they can be absorbed, compounds with very ***low aqueous solubility*** **usually suffer oral** ***bioavailability Problems***, because of limited ***GI transit time*** of undissolved drug particles and limited solubility at the absorption site.
- E.g.: Tetracycline dissolves to greater extent in the stomach than in the intestine; therefore, it is best absorbed in the intestine.
- Most of drugs are *weak acids or bases,* since the unchanged form of a drug preferentially ***permeates across lipid membranes*** **drugs**
- Aqueous solubility will generally be decreased by conversion to an unchanged form. For drugs with low water, solubility will be difficult to incorporate into sustained release mechanism.

Aqueous solubility and pKa

- These are the most important to influence its absorptive behavior and its aqueous solubility (if it is a weak acid or base) and its pKa.
- The aqueous solubility of the drug influences its dissolution rate which in turn establishes its concentration in solution and hence the driving force for diffusion across the membranes as shown by Noye's Whitney's equation which under sink condition that is

  $dc/dt = K_d.A.C_s$

  Where, dc/dt = dissolution rate

  K_d= dissolution rate constant

  A = total surface area of the drug particles C_s= aqueous solubility of the drug
- Dissolution rate (dc/dt) is constant only when Surface Area A is the initial rate is directly proportional to the Aqueous solubility (C_s) hence

Drug with low aqueous solubility have low dissolution rate and its suffer low bioavailability problem.

- The aqueous solubility of weak acid and bases are controlled by pKa of the compound and pH the medium.

For weak acids

- **$S_t = So(1+K_a/H^+) = So\ (1+10^{pH-pKa})$**
  Where, S_t = total solubility of weak acid. S_o = solubility of unionized form
  K_a= Acid dissociation constant, H^+= H ion concentration

Similarly for weak bases

$S_t = S_o\ (1+H^+/K_a) = S_o\ (1+10^{pKa-pH})$

- If a poorly soluble drug was, consider as a suitable candidate for formulation into controlled release system.
- Since weakly acidic drugs will exist in the stomach pH 1-2, primarily in the unionized form their absorption will be favored from this acidic environment on the other hands weakly basic drugs will be exist primarily in the ionized form (Conjugate Acids) at the same site, their absorption will be poor.
- In the upper portion of the small intestine the pH is more alkaline pH 5-7 and the reverse will be expected for weak acids.

2) Partition coefficient:

- When the drug is administered to the GIT, it must cross a variety of biological membranes to produce therapeutic effects in another area of the body.
- It is common to consider that these membranes are lipidic, therefore the Partition coefficient of oil soluble drugs becomes important in determining the effectiveness of membranes barrier penetration.
- Partition coefficient is the ***fraction of drug*** in an oil phase to that of an adjacent aqueous phase.
- High partition coefficient compound are predominantly ***lipid soluble and have very low aqueous solubility*** and thus these compound persist in the body for long periods.
- Partition coefficient and molecular size influence not only the ***penetration of drug*** across the membrane but also ***diffusion*** across the rate limiting membrane
- The ability of drug to diffuse through membranes it's so called ***diffusivity*** & diffusion coefficient is function of molecular size (or molecular weight).
- Generally, ***values of diffusion coefficient*** for intermediate molecular weight drugs, through flexible polymer range from *10^{-8} to 10^{-9} cm^2 / sec.*

- **One Word Question Answer**

SR NO.	QUESTION	ANSWER
1	Absorption, Distribution, Metabolism are included in?	Biological Factors
2	Dosage size, Partition coefficient and molecular size are included in?	Physiochemical Factors
3	Drugs with low aqueous solubility usually suffer Main Problems of?	Bioavailability
4	The fraction of drug in an oil phase to that of an adjacent aqueous phase is called?	Partition Coefficient
5	The ability of drug to diffuse through membranes is called?	Diffusivity
6	Diffusion coefficient is function of?	Molecular weight
7	Which type of drugs will exist in the stomach pH 1-2, primarily in the unionized form their absorption will be favored from this acidic environment?	Weak Acidic Drug
8	$S_t = So(1+K_a/H^+) = So\ (1+10^{pH-pKa})$ this equation is for?	Weak acid
9	$S_t = S_o\ (1+H^+/K_a) = S_o\ (1+10^{pKa-pH})$ this equation is for?	Weak base
10	What is Noye's Whitney's equation?	$dc/dt = K_d.A.C_s$

- Thus high molecular weight drugs or polymeric drugs should be expected to display very slow release kinetics using diffusion through polymer membrane.
- Phenothiazines are representative of this type of compound
- Between the time a drug is administered and is eliminated from the body, it must diffuse through a variety of biological membranes.
- Oil/Water partition coefficient plays a major role in evaluating the drug penetration.
- According to ***'Hanch correlation'*** a parabolic relationship between the log of its partition coefficient has with that of the log of its activity or ability to be absorbed.
- There is an optimum partition coefficient for a drug in which it permeates membrane effectively and shows greater activity.
- Partition coefficient with higher or lower than the optimum are poorer candidates for the formulation
- Values of partition coefficient below optimum result in the decreased lipid solubility and remain localized in the first aqueous phase it contacts.
- Values larger than the optimum, result in poor aqueous solubility but enhanced lipid solubility and the drug will not partition out of the lipid membrane once it gets in.

3) Drug stability:

- The stability of drug in environment, to which it is exposed, is another physico-chemical factor to be considered in design at sustained/ controlled release systems, ***drugs*** that are ***unstable*** in ***stomach*** can be ***placed*** in slowly soluble forms or have their release delayed until they reach the ***small intestine.***
- Orally administered drugs can be subject to both ***acid, base hydrolysis and enzymatic degradation***. Degradation will proceed at the reduced rate for drugs in the solid state, for drugs that are unstable in stomach; systems that prolong delivery ever the entire course of transit in GI tract are beneficial.
- Compounds that are ***unstable*** in the small intestine may demonstrate decreased bioavailability when administered form a sustaining dosage from. This is because more drug is delivered in small intestine and hence subject to degradation.
- However for some drugs, which are unstable in small intestine, are undergo extensive Gut–Wall metabolism have decreased the bioavailability.

- When these drugs are administered from a sustained dosage form to achieve better bioavailability, at different routes of the drugs administered should be chosen Eg. Nitroglycerine
- The presence of metabolizing enzymes at the site or pathway can be utilized.

4. Protein Binding:

- It is well known that many ***drugs bind to plasma protein*** with the influence on duration of action.
- Drug-protein binding serve as a depot for drug producing a ***prolonged release profile***, especially it is high degree of ***drug binding occurs***.
- ***Extensive binding*** to plasma proteins will be evidenced by a ***long half-life of elimination*** for drugs and such drugs generally most require a sustained release dosage form.
- However, drugs that exhibit high ***degree of binding to plasma proteins*** also might ***bind to bio-polymers in GI tract*** which could have influence on sustained drug delivery.
- The presence of ***hydrophobic moiety*** on drug molecule also ***increases the binding potential***.
- The binding of the drugs to plasma proteins (eg. Albumin) results in retention of the drug into the vascular space the drug protein complex can serves as reservoir in the vascular space for sustained drug release to extra vascular tissue but only for those drugs that exhibited a high degree of binding.
- The main force of attraction are Wander-vals forces, hydrogen binding, electrostatic binding.
- In general charged compound have a greater tendency to bind a protein then uncharged compound, due to electrostatic effect. Egamitryptline, cumarin, diazepam, digoxide, dicaumarol, novobiocin.

5. Molecular Size and Diffusivity

- The ability of a drug to diffuse through membranes is called ***diffusivity, which*** is a function of molecular weight.
- In most polymers it is possible to relate log D to some function of molecular size as,

$$\textbf{Log D} = -\ S_v \log v + K_v = -\ S_M \log M + K_m$$

where,V – Molecular volume. M – Molecular weight.

S_v, S_m, K_v & K_m are constants.

- The value of D is related to the size and shape of the cavities, as well as the drugs.
- The drugs with high molecular weight show very slow kinetics.

- **One Word Question Answer**

SR NO.	QUESTION	ANSWER
1	Which plays a major role in evaluating the drug penetration?	Oil/Water partition coefficient
2	Partition coefficient with higher or lower than the optimum indicate?	poorer candidates for the formulation
3	What are the ideal partition coefficients for a drug in which it permeates membrane effectively and shows greater activity?	Optimum Partition coefficient
4	Compounds that are ***unstable*** in the small intestine indicates?	Lower bioavailability
5	The drugs are undergo extensive Gut–Wall metabolism indicates?	Lower bioavailability
6	Duration of drug action can be affected by?	Plasma-protein binding
7	Prolonged drug release profile can be achieved by?	Greater degree of plasma protein binding
8	Which property of drug molecule helps to increase the binding potential?	Hydrophobic property of drug
9	What is main bond between drug and protein molecule?	Wander-vals forces
10	Diffusivity is functions of?	Molecular weight
11	Log D = - S_v log v + K_v = - S_M log M + K_m is equation of?	Diffusivity

6. Dose Size

- For those drugs requiring large conventional doses, the volume of sustained dose may be too large to be practical.
- The compounds that require large dose are given in multiple amounts or formulated into liquid systems.
- The greater the dose size, greater the fluctuation.
- Therefore, the dose should have proper size.
- In general, a single dose of *0.5 - 1.0 gm* is considered for a conventional dosage form this also holds for sustained release dosage forms.
- If an oral product has a dose size greater that 500 mg it is a poor candidate for sustained release system, Since addition of sustaining dose and possibly the sustaining mechanism will, in most cases generates a substantial volume product that unacceptably large.

7. pK_a (Dissociation constant)

- The ***relationship*** between pK_a of compound and ***absorptive environment***, presenting drug in an ***unchanged*** form is ***adventitious for drug permeation but solubility decrease*** as the drug is in unchanged form.
- An important assumption of the there is that unionized form of the drug is absorbed and permeation of ionized drug is negligible, since its rate of absorption is 3-4 times lesser than the unionized form of the drug.
- The pK_a range for acidic drug whose ionization is pH sensitive and around 3.0- 7.5 and pK_a range for basic drug whose ionization is pH sensitive around 7.0- 11.0 are ideal for the optimum positive absorption.

Biological Factors

1. Absorption

- Absorption of drug need dissolution in fluid before it reaches to systemic circulation.
- The rate, extent and uniformity in absorption of drug are important factor when considering its formulation in to controlled release system.
- Absorption= dissolution
- The characteristics of absorption of a drug can be greatly effects its suitability of sustained release product. The rate of release is much slower than rate of absorption.
- ***The maximum half-life for absorption should be approximately 3-4 hr*** otherwise; the device will pass out of potential absorptive region before drug release is complete.
- Compounds that demonstrate true ***lower absorption rate*** constants will probably be ***poor candidates*** for sustaining systems.

- The ***rate, extent and uniformity of absorption*** of a drug are important factors considered while formulation of sustained release formulation.
- As the rate, limiting step in drug delivery from a sustained-release system is its release from a dosage form, rather than absorption.
- It we assume that transit time of drug must in the absorptive areas of the GI tract is about 8-12 hrs.
- If the rate of absorption is below 0.17/hr and above the 0.23/hr then it is difficult to prepare sustained release formulation.
- An another important criteria is the through absorption of drug in GIT tract, drug like Kanamycine and gentamycine shows absorption are different sites, Riboflavin like drug absorbed effectively by carrier transport and at upper part of GIT that make it preparation in SRDF difficult.

2. 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 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 on time course of drug disposition.
- For design of sustained/ controlled release products, one must have information of disposition of drug.
- Two parameters that are used to describe distribution characteristics are its apparent volume of distribution and the ratio of drug concentration in tissue that in plasma at the steady state the so- called T/P ratio.
- The apparent volume of distribution V_d is nearly a proportional constant that release drug concentration in the blood or plasma to the amount of drug in the body. In case of one compartment model
- **V_d = Dose/C_0 ....(1)**
  V_{ss} = (1+K12/K21)/V1.....(2)
- Where:
- V_1= volume of central compartment
- K_{12}= rate constant for distribution of drug from central to peripheral
- K_{21}= rate constant for distribution of drug from peripheral to central
- V_{ss}= estimation of extent of distribution in the body

V_{ss} results concentration in the blood or plasma at steady state to the total amount of the drug present in the body during respective dosing or constant rate of infusion. Equation 2 is limited to that instance where steady state drug concentration in both the compartment has been reached.

- **One Word Question Answer**

SR NO.	QUESTION	ANSWER
1	How much single dose of is considered for a conventional dosage form this also holds for sustained release dosage forms	0.5 - 1.0 gm
2	An oral product has a dose size greater that 500 mg indicates.	Unsuitable for formulation
3	The rate, extent and uniformity in absorption of drug are important factor for?	Controlled release formulation
4	In which form of pK_a drug permeation but solubility decrease?	Unchange form of pKa
5	The permeation of ionized drug is?	Negligible
6	For which form of drug, the rate of absorption is 3-4 times lesser than the unionized form of the drug.	Ionized
7	The maximum half-life for absorption should be approximately is?	3-4 hour
8	Which drug is absorbed effectively by carrier transport?	Riboflavin
9	$Dose/C_0$ =	V_d
10	Estimation of extent of distribution in the body =	(1+K12/K21)/V1
11	Which pK_a range for basic are ideal for the optimum positive absorption?	7-11

3. Metabolism

Two areas of concern relative to metabolism significantly *restrict* sustained release formulation.

1. If drug upon ***chronic administration*** is capable of either ***inducing or inhibition enzyme synthesis*** it will be poor candidate for sustained release, formulation because of difficulty of maintaining uniform blood levels of drugs.
2. If there is a ***variable blood level of drug*** through a ***first-pass effect***, this also will make preparation of sustained release ***product difficult***.

- Drugs that are significantly ***metabolized before absorption***, either in lumen of intestine, can show ***decreased bioavailability*** from slower-releasing dosage forms.
- Most intestinal wall enzymes systems are saturable.
- As drug is released at a slower rate to these regions, less total drug is presented to the enzymatic.
- Process device a specific period, allowing more complete conversion of the drug to its metabolite.

4. Biological Half-Life

- The usual goal of sustained release product is to ***maintain therapeutic blood level over an extended period***, to this drug must enter the circulation at approximately the same rate at which it is eliminated. The ***elimination rate*** is quantitatively described by the ***half-life (t1/2).***
- Therapeutic compounds with ***short half-life*** are excellent candidates for sustained release preparation since these can ***reduce dosing*** *frequency.*
- The usual goal of sustained release product is to ***maintain therapeutic blood level over an extended period***, to this drug must enter the circulation at approximately the same rate at which it is eliminated. The ***elimination rate*** is quantitatively described by the ***half-life ($t_{1/2}$).***
- Therapeutic compounds with ***short half-life*** are excellent candidates for sustained release preparation since these can ***reduce dosing frequency.***
- Drugs with half-life shorter than 2 hours. Such as e.g.: ***Furosemide, levodopa*** are poor for sustained release formulation because it requires ***large rates and large dose compounds with long*** half-life.

5. Margin of Safety

- In general the larger the volume of therapeutic index indicates safer the drug.
- Drug with very small values of therapeutic index usually are poor candidates for SRDF due to pharmacological limitation of control over release rate .e.g.- Induced digtoxin, Phenobarbital, phenotoin.

- **M.S.=TD50/ED50**
- Larger the TI ratio the safer is drug.
- It is imperative that the drug release pattern is precise so that the plasma drug concentration achieved in under therapeutic range.

Characteristics of Drugs suitable for CRDDS

Table 2: Physicochemical and pharmacokinetic parameters for drug selection

Parameters	Criteria for drug selection
Physicochemical parameters for drug selection	
Molecular size	< 1000 Daltons
Aqueous Solubility	More than 0.1 mg/ml for pH 1 to pH 7.8
Apparent partition coefficient	High
Absorption mechanism	Diffusion
General absorbability from all GI segments	Release Should not be influenced by pH and enzymes
Pharmacokinetic parameters for drug selection	
Elimination half-life ($t_{1/2}$)	Between 2 to 8 hours
Absolute bioavaliability	Should be 75% or more
Absorption rate constant (Ka)	Must be higher than release rate
Apparent volume of distribution (Vd)	Larger Vd and MEC, Larger will be the required dose
Total clearance	Not depend on dose
Elimination rate constant	Required for design
Therapeutic concentration (Css)	The lower Css and smaller Vd, the loss among of drug required.
Toxic concentration	Apart the value of MTC And MEC safer the dosage form

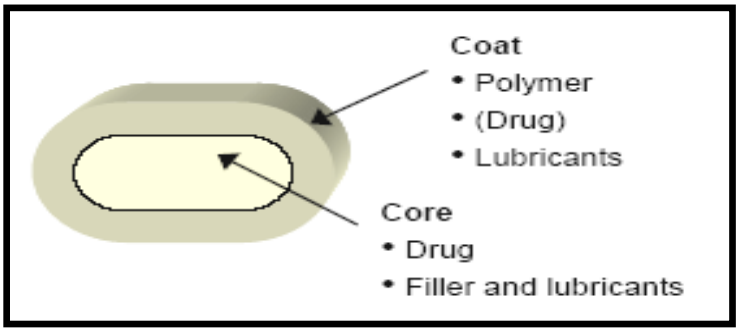
Characteristics of Drugs Unsuitable for Peroral Dosage form

1. Those which are absorbed and excreted rapidly; short biological half life (<1 hr). Ex- Penicillin G , Furosemide.
2. Those with long biologic half-life (>12 hrs). Ex- Diazepam, Phenytoin.
3. For those which require large doses (>1 gm) Ex- Sulfonamides.
4. Extensive binding of drugs to plasma proteins will have long elimination half life and such drugs generally do not require to be formulated to SRDF.
5. Those with cumulative action and undesirable side effects. Ex Phenobarbital
6. Those with low therapeutic indices. ex- Digitoxin.
7. That requiring precise dosage titration for every individual. Ex- Warfarin, Digitoxin.
8. In general, a very highly soluble drug or a highly insoluble drug are undesirable for formulation into SRDF product.

- **One Word Question Answer**

SR NO.	QUESTION	ANSWER
1	Drugs that are significantly metabolized before absorption is indicated?	Low Bioavailability
2	Most intestinal wall enzymes systems are?	Saturable
3	The elimination rate is quantitatively described by ?	half-life (t1/2)
4	How much value of half-life are excellent candidates for sustained release preparation?	Short half life and high dosing frequency
5	What is half life of Furosemide, levodopa?	Less than 2 hr
6	Larger the volume of therapeutic index indicates?	More Safer drug
7	The equation of Margin of Safety is?	TD50/ED50
8	How much Absolute bioavailability is suitable for CRDDS?	More than 75%
9	How much molecular weight is suitable for CRDDS?	<1000 Dalton
10	How much elimination half-life is suitable for CRDDS?	Between 2 to 8 hr
11	How much aqueous solubility of drug is suitable for CRDDS?	More than 0.1mg/ml

General structure of controlled release tablet



Mechanism aspects of Oral drug delivery formulation

1. Dissolution controlled release:

1. Matrix
2. Encapsulation

2. Diffusion controlled release:

1. Matrix
2. Reservoir

3. Erosion controlled release:

1. Surface erosion
2. Bulk erosion

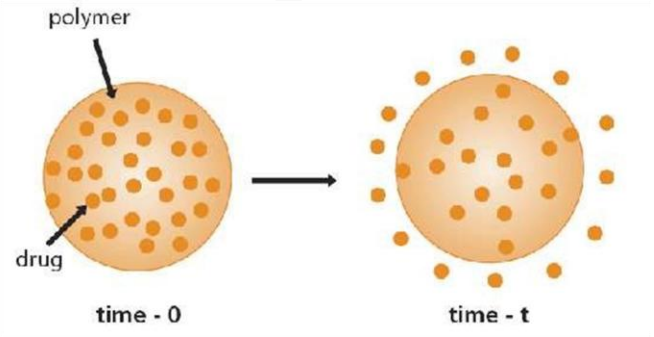
4. Combination of both dissolution & diffusion controlled release.

Diffusion Controlled Mechanism

- The diffusion controlled mechanism also involved in Matrix and Reservoir type diffusion.
- Major process for absorption.
- No energy required.
- Drug molecules diffuse from a region of higher concentration to lower concentration until equilibrium is attained.
- Directly proportional to the concentration gradient across the membrane

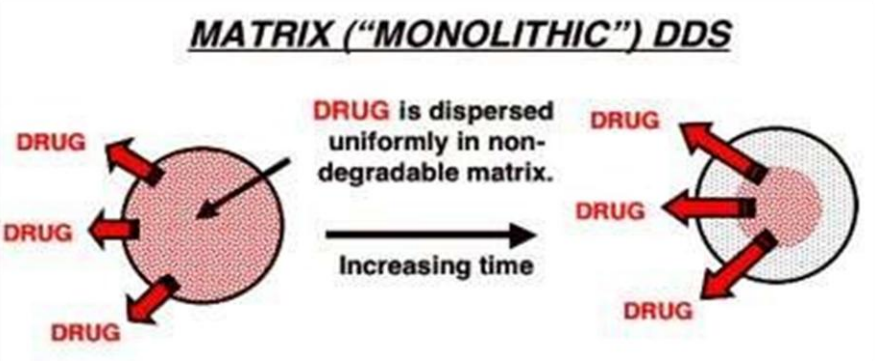
MONOLITHIC-MATRIX SYSTEMS

- The drug is uniformly dispersed in a polymer matrix and release is controlled by its diffusion from the matrix into the surrounding environment.



Rate controlling steps are Polymeric content in coating, thickness of coating, hardness of microcapsule.

- Also called as Laminated matrix device.
- Hollow system containing an inner core surrounded in water insoluble membrane.
- Polymer can be applied by coating or micro encapsulation.
- Rate controlling mechanism-partitioning into membrane with subsequent release into surrounding fluid by diffusion.
- Commonly used polymers - HPC, ethyl cellulose & polyvinyl acetate.
- Examples: Nico-400, Nitro-Bid



- Also called as Monolith dissolution controlled system.
- Controlled dissolution by: 1. Altering porosity of tablet. 2. Decreasing its wettebility. 3. Dissolving at slower rate. Drug release determined by dissolution polymer.

Types of matrix systems

Two types of matrix systems

1. Slowly eroding matrix
2. Inert plastic matrix

1. Slowly eroding matrix

- Consists of using materials or polymers which erode over a period of time such as waxes, glycerides, stearic acid, cellulosic materials etc.

Principle:

- Portion of drug intended to have sustained action is combined with lipid or cellulosic material and then granulated.
- Untreated drug granulated
- Both mixed

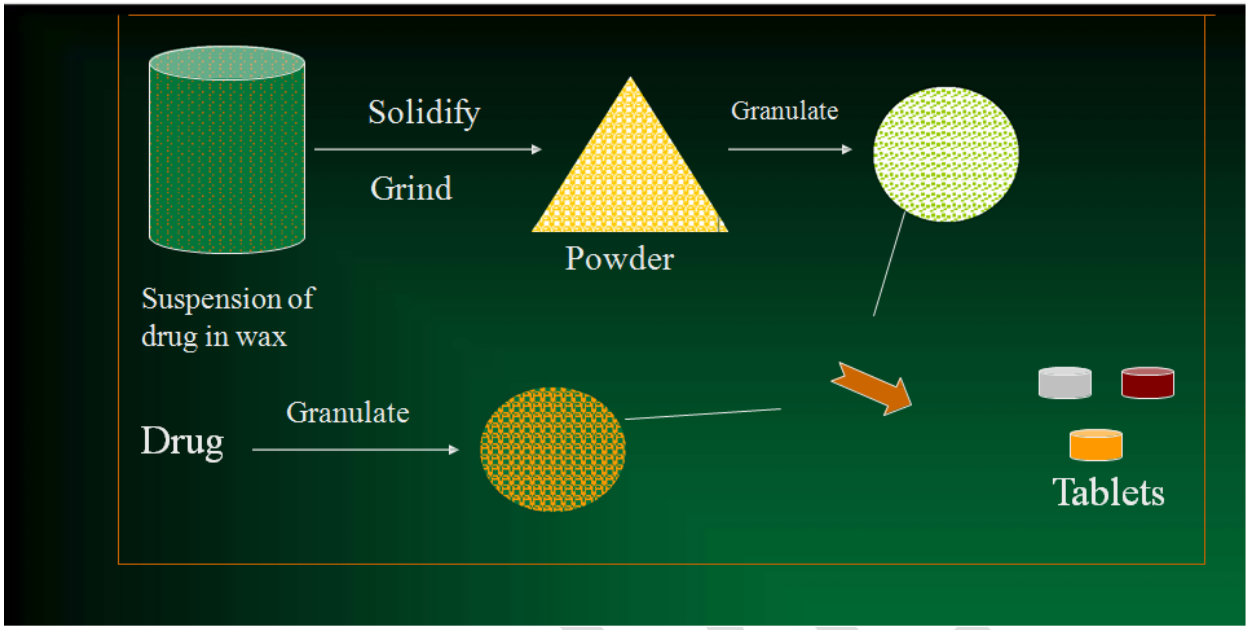
2. Embedding drug in inert plastic matrix polymethacrylate.

- Granulation is compressed results in **MATRIX**
- Drug is slowly released from the inert plastic matrix by leaching of body fluids
- Release of drug is by diffusion.

- **One Word Question Answer**

SR NO.	QUESTION	ANSWER
1	Which mechanism is involved in Matrix and Reservoir type diffusion	Diffusion controlled
2	Which mechanism is major process for absorption	Diffusion controlled
3	Drug molecules diffuse from a region of higher concentration to lower concentration until equilibrium is attained is called	Diffusion mechanism
4	Which system contains diffusion from the matrix into the surrounding environment?	Monolithic-matrix systems
5	Polymeric content in coating, thickness of coating, hardness of microcapsule are act as?	Rate controlling steps
6	Commonly used polymer in system are?	HPC, ethyl cellulose & polyvinyl acetate
7	How many types of matrix systems?	Two
8	Waxes, glycerides are used as?	Slow eroding matrix polymer

Preparation of Matrix tablet



Materials used as retardants in matrix tablet formulations :

Rigid Matrix Diffusion

- Materials used are insoluble plastics such as PVP & fatty acids.

Swellable Matrix Diffusion

1. Also called as Glassy hydrogels. Popular for sustaining the release of highly water soluble drugs.
2. Materials used are hydrophilic gums. Examples: Natural- Guar gum, Tragacanth.

Semisynthetic -HPMC, CMC, Xanthum gum.

Synthetic -Polyacrilamides.

Examples: Glucotrol XL, Procardia XL

Higuchi Equation

$Q = DE/T \quad (2A.E\ Cs)Cs.t)^{1/2}$

Where ,

Q=amt of drug release per unit surface area at time t.

D=diffusion coefficient of drug in the release medium.

E=porosity of matrix.

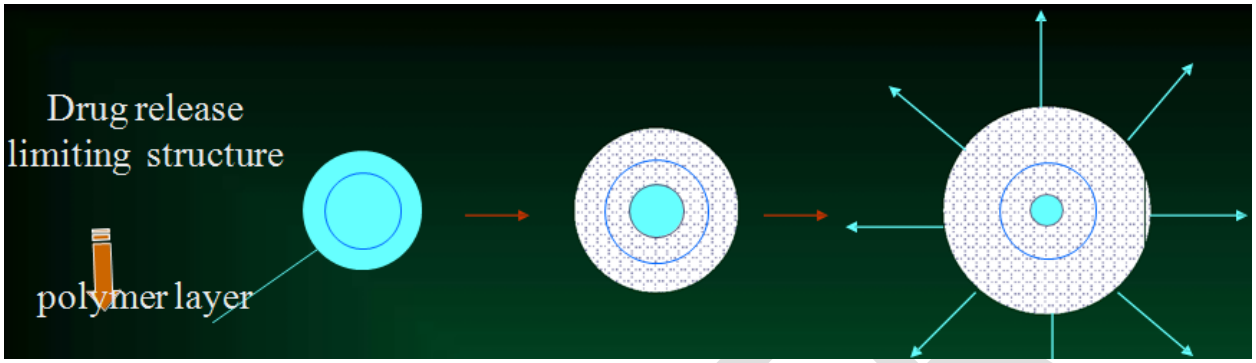
C_s=solubility of drug in release medium. T=tortuosity of matrix.

A=concentration of drug present in matrix per unit volume.

RESERVOIR SYSTEM

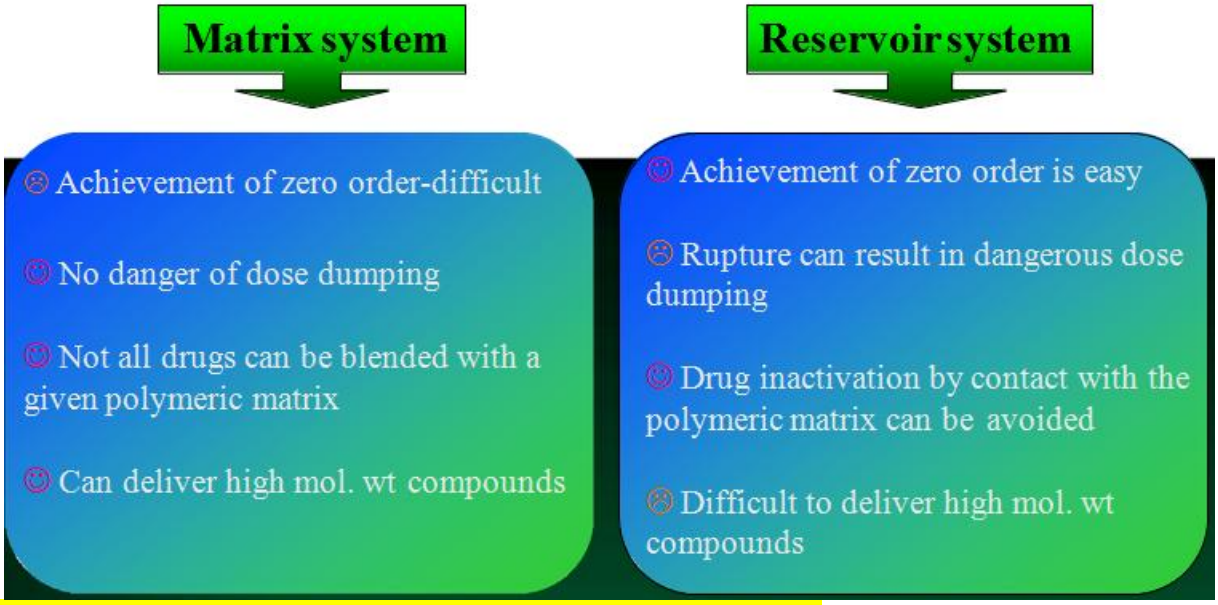
- The drug is contained in a core, which is surrounded by a polymer membrane & release by diffusion through the rate limiting membrane.
- Also called as Laminated matrix device.

- Hollow system containing an inner core surrounded in water insoluble membrane.
- Polymer can be applied by coating or micro encapsulation.



- Rate controlling mechanism - partitioning into membrane with subsequent release into surrounding fluid by diffusion.
- Commonly used polymers - HPC, ethyl cellulose & polyvinyl acetate.
- Examples: Nico-400, Nitro-Bid

Diffusion Controlled System



DISSOLUTION CONTROLLED RELEASE SYSTEMS

Two classes:

1. Matrix dissolution control

2. Encapsulation dissolution control

1. Matrix dissolution control

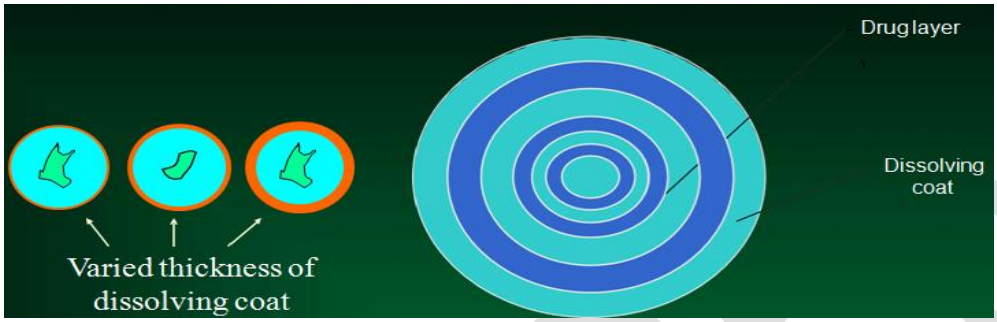
- The rate of penetration of dissolution fluid in to the matrix determines the drug dissolution and subsequent release.

- **One Word Question Answer**

SR NO.	QUESTION	ANSWER
1	Which type of Materials are used as insoluble plastics?	PVP & Fatty acid
2	Which type of Materials are used as hydrophilic gums?	Guar gum, Tragacanth
3	Which type of Materials are used as Semisynthetic?	HPMC, CMC
4	Give Higuchi equation for matrix type diffusion mechanism.	**$Q = DE/T (2A.E Cs) Cs.t)^{1/2}$**
5	Reservoir system is also called as?	Laminated matrix device
6	The drug is contained in a core, which is surrounded by a polymer membrane & release by diffusion through the rate limiting membrane is called?	Reservoir system
7	Polymer can be applied in system by?	micro encapsulation
8	How many classes of dissolution controlled release system?	Two
9	Which system is difficult for high m.w. compound?	Reservoir type system
10	In which system, the achievement of zero order release is easy?	Reservoir type system
11	Which type of system involves rate of penetration of dissolution fluid in to the matrix determines the drug dissolution and subsequent release?	Matrix dissolution controlled system

Encapsulation Dissolution Controlled SYSTEM

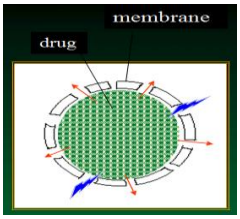
- By microencapsulation or altering layers of drug with rate controlling coats.
- Called coating dissolution controlled system.
- Dissolution rate of coat depends upon stability & thickness of coating.
- Masks colour, odour, taste, minimising GI irritation. Examples: Ornade spansules, Chlortrimeton Repetabs



Coating the drug or a dosage form containing the drug (microencapsulation).

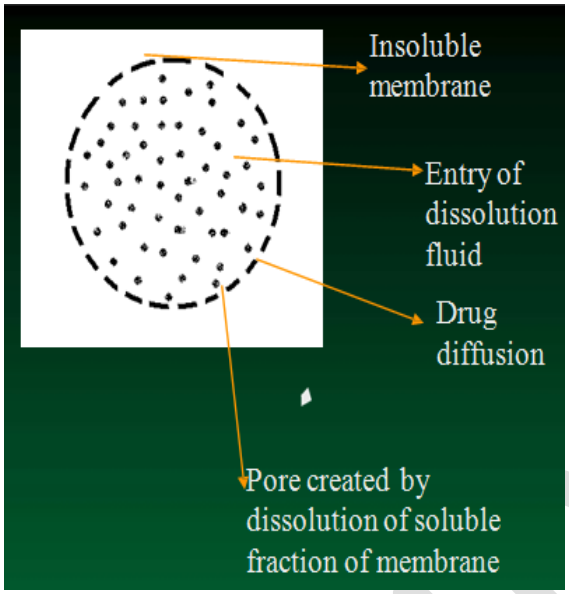
- The method for retarding drug release from the dosage form is to coat its surface with a material (polymers) that retards penetration by the dispersion fluid.
- Drug release depends upon the physiochemical nature of coating material.
- Microencapsulation is rapidly expanding technique as a process; it is a means of applying relatively thin coating to small particles of solid or droplets of liquids and dispersion.
- The application of microencapsulation might will include sustained release or prolonged action medication, taste masked, chewable tablet, powder and suspension, single layer tablets.
- Containing chemically incompatible ingredient & new formulation concepts for creams, ointments, aerosols, dressing, plasters, suppositories & injectables.
- **Polymers:** - polyvinyl alcohol, polyacrylic acid, ethyl cellulose, polyethylene, polymethacrlate, poly (ethylene-vinyl acetate), cellulose nitrite, silicones, poly (lactide-co-glcolide)

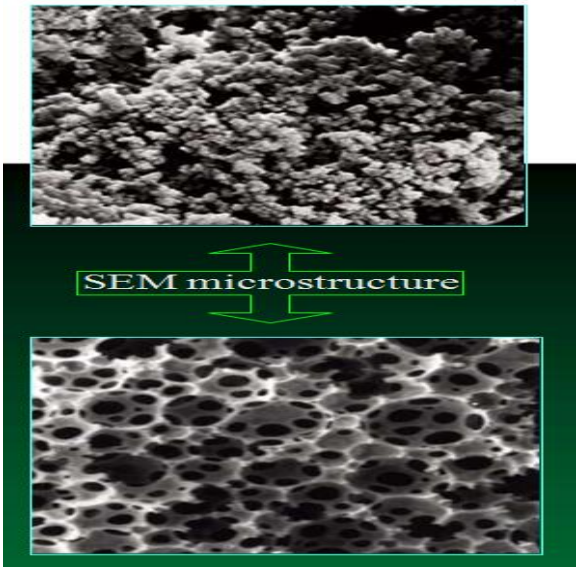
Diffusion and Dissolution Controlled System



- Release rate is dependent on
  Fraction of soluble ingredient in the coating
  diffusion coefficient of drug though pore in coating
  conc. of drug in dissolution media and in core
- Drug encased in a partially soluble membrane.
- Pores are created due to dissolution of parts of membrane.

- Diffusion of dissolved drug out of system.
- Ex- Ethyl cellulose & PVP mixture dissolves in water & create pores of insoluble ethyl cellulose membrane.





ION-EXCHANGE RESIN

- Water in soluble, cross-linked polymer containing salt forming groups in repeating positions on the polymer chain.
- + -
- R X
- The Drug is released by exchanging with appropriately charged ions in GIT. The drug is then diffuses out of the resin.
- The rate of diffusion control by: the area of diffusion, diffusion path length & rigidity of resin.
- Thus, drug release depends on the ionic environment (pH, electrolyte conc.) & the properties of resin
- **Advantage:** For drug that are highly susceptible to degradation by enzymatic process.
- **Limitation:** variable diet, water intake can affect the release rate of drug. Sustained delivery of ionizing acidic & basic drug can be obtained by complexing them with insoluble non-toxic anion exchanger and cation exchanger resin respectively.
  Here the drug is released slowly by diffusing through the resin particle structure.
- The **complex** can be prepared by **incubating** the **drug-resin solution** or passing the drug solution through a column containing ion exchange resin.

- **One Word Question Answer**

SR NO.	QUESTION	ANSWER
1	Dissolution rate of coat depends upon?	Stability and thickness of coating
2	It is a process; it is a means of applying relatively thin coating to small particles of solid or droplets of liquids and dispersion is called?	Microencapsulation
3	Which technique is used to masks colour, odour, taste, minimising GI irritation is called?	Coating technique
4	In which concept, Drug is encased in a partially soluble membrane?	Dissolution & diffusion controlled
5	Example of Dissolution & diffusion controlled release system.	Ethyl cellulose & PVP mixture
6	The Drug is released by exchanging with appropriately charged ions in GIT. The drug is then diffuses out of the resin.	Ion-exchange
7	In which system, the drug release depends on the ionic environment (pH, electrolyte conc.) & the properties of resin	Ion-exchange
8	In which system, the drug that are highly susceptible to degradation by enzymatic process.	Ion-exchange
9	In which system, the Drug is released by exchanging with appropriately charged ions in GIT.	Ion-exchange

Principle:

Is based on preparation of totally insoluble ionic material

- Resins are insoluble in acidic and alkaline media
- They contain ionizable groups which can be exchanged for drug molecules
- IER are capable of exchanging positively or negatively charged drug molecules to form insoluble poly salt resinates.

Types:

There are two types of IER

Resins functional groups

1. Cationic Exchange resins - $RSO_3^-H^+$
2. Anionic Exchange resins – $RNH_3^+ OH^-$

Structurally made up of a stable acrylic polymer of styrene-divinyl benzene copolymer.

Mechanism of action

IER combine with drug to form insoluble ion complexes

1. $R\text{-}SO_3^- H^+ + H_2N - A \rightleftharpoons R\text{-}SO_3^- NH_3^+ - A$

2. $R\text{-}NH_3^+ OH^- + HOOC - B \rightleftharpoons RNH_3^+ \cdot OOC\text{-}B + H_2O$

Where A- NH_2 is basic drug

B-COOH is acidic drug

These resinates are administered orally

2 hrs in stomach in contact with acidic fluid at pH 1.2

Intestinal fluid, remain in contact with slightly basic pH for 6hrs.

Drug can be slowly liberated by exchange with ions present in G.I.T.

In the stomach

$$®\text{-}SO_3^-NH_3^+\text{-}A + HCl \rightleftharpoons ®\text{-}SO_3^-H^+ + A\text{-}NH_3^+Cl^-$$

$$®\text{-}NH_3^+{}^-OOC\text{–}B + HCl \rightleftharpoons ®\text{-}NH_3^+Cl + HOOC\text{-}B$$

Un dissociated

Thus carboxylic acid will be poorly dissociated in stomach and thus absorbed.

In the Intestine

$$®\text{-}SO_3^-NH_3^+\text{-}A + NaCl \rightleftharpoons ®\text{-}\text{-}SO_3^-Na^+ + A\text{-}NH_3^+Cl^-$$

Basic pH un dissociated

$$®\text{-}NH_3^+{}^-OOC\text{–}B + NaCl \rightleftharpoons ®\text{-}NH_3^+Cl^- + Na^+{}^-OOCB \longrightarrow$$

Sodium salt of acid

(dissociation of acid salt unabsorbed)

Amine salt will be poorly dissociated in intestine and thus absorbed.

Polymers Classification based on Origin

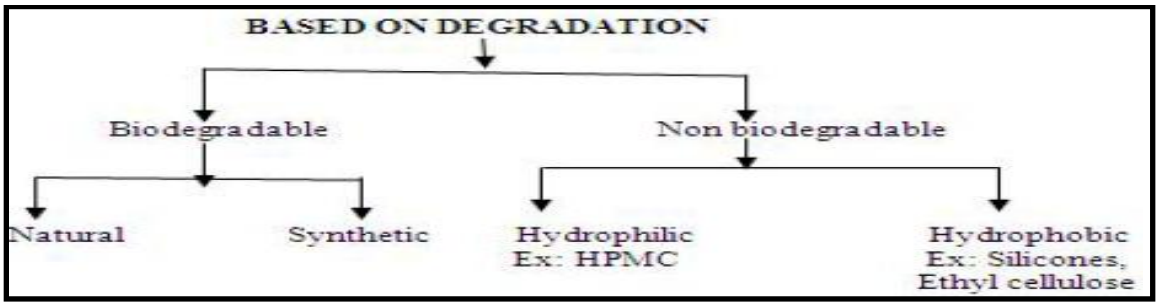
Classification of polymers

Natural polymers	Semi synthetic polymers	Synthetic polymers
eg. Xanthan gum, polyurethanes, Guar gum, polycarbonates, Karaya gum etc	eg. Celluloses such as HPMC, NaCMC, Ethyl cellulose etc.	eg. Polyesters, polyamides, polyolefins etc

- **One Word Question Answer**

SR NO.	QUESTION	ANSWER
1	What is solubility of Resins in acidic and alkaline media?	Insoluble
2	How many types of resin?	Two
3	Resins form insoluble salt is called?	Resinates
4	What is example of Cationic exchange resin?	$RSO_3^-H^+$
5	What is example of Anionic exchange resin?	RNH_3^+ OH
6	What is example of Natural polymers?	Xanthen, Guar gum
7	What is example of semisynthetic polymers?	HPMC
8	What is example of synthetic polymers?	Polyamines

Based on Degradation



Characteristics of Ideal Polymer

- Should be inert and compatible with environment
- Should be non toxic
- Should be easily administered
- Should have good mechanical strength
- Should be biodegradable and biocompatible

Advantages of Polymers

- Localised delivery of drug
- Sustained delivery of drug
- Decrease in dosing frequency
- Reduce side effect
- Improve patient compliance
- Biodegradable and biocompatible

Disadvantages of Polymers

- Exhibit dose dumping effect
- High initial drug release after administration
- Low mechanical properties

Applications

As a coating material ex: HPMC Methyl cellulose polyethylene glycol

As a binder in tablet granulation ex: acacia, gelatin, sodium alginate ,starch paste.

As disintegrate ex: starch, hpmc

As a thickening agent ex: methyl cellulose

Recent Developments in Use of Polymers for Drug Delivery Systems:

- The oral drug delivery has been known for decades as the most widely utilized route of administered among all the routes that have been employed for the systemic delivery of drug via various pharmaceutical products of different dosage forms. The reasons that the oral route achieved such popularity may be in part attributed to its ease of administration1.
- A large number of both natural and synthetic polymers have been studied for possible application in drug delivery.
- The great advantage of synthetic polymers is their advantageous properties and a wide choice availability.
- Two promising synthetic polymers, which have been developed for biomedical applications, are polyvinylpyrolidone and polyethylene glycol acrylate based hydrogels.
- Both of them are biodegradable and forms copolymers with natural macromolecules.
- On the other hand, natural polymers have the advantage of high biocompatibility and less immunogenicity.
- Among the natural polymers studied, a special mention has to be made to collagen and gelatin.
- Other natural polymers include chitosan, alginate, starch, pectin, casein and cellulose derivatives.
- Polylactides are known to be more hydrophobic as compared to PLGA and take a longer time to degrade.
- Among the polylactides, DL-PLA, which is a polymer of D and L-lactide, degrades faster than L-PLA, which is a homopolymer of L-lactide, presumably due to lesser crystallinity.
- Similarly, the more hydrophobic endcapped PLGA polymers degrade faster than the carboxyl-ended PLGA. In spite of the several apparent advantages of PLA and PLGA based polymers, commercialization of products based on these polymers has certain limitations.

- **One Word Question Answer**

SR NO.	QUESTION	ANSWER
1	Methylcellulose, polyvinyl pyrrolidone and polyvinyl alcohol are example of?	Coating substance
2	Property for polymers must be chemically inert and free of leachable impurities are suitable for?	Controlled drug delivery system
3	Polylactides are example of?	Hydrophobic polymer
4	collagen and gelatine are example of?	Natural Polymer