UNIT 1
CONTROLLED DRUG DELIVERY SYSTEMS-3

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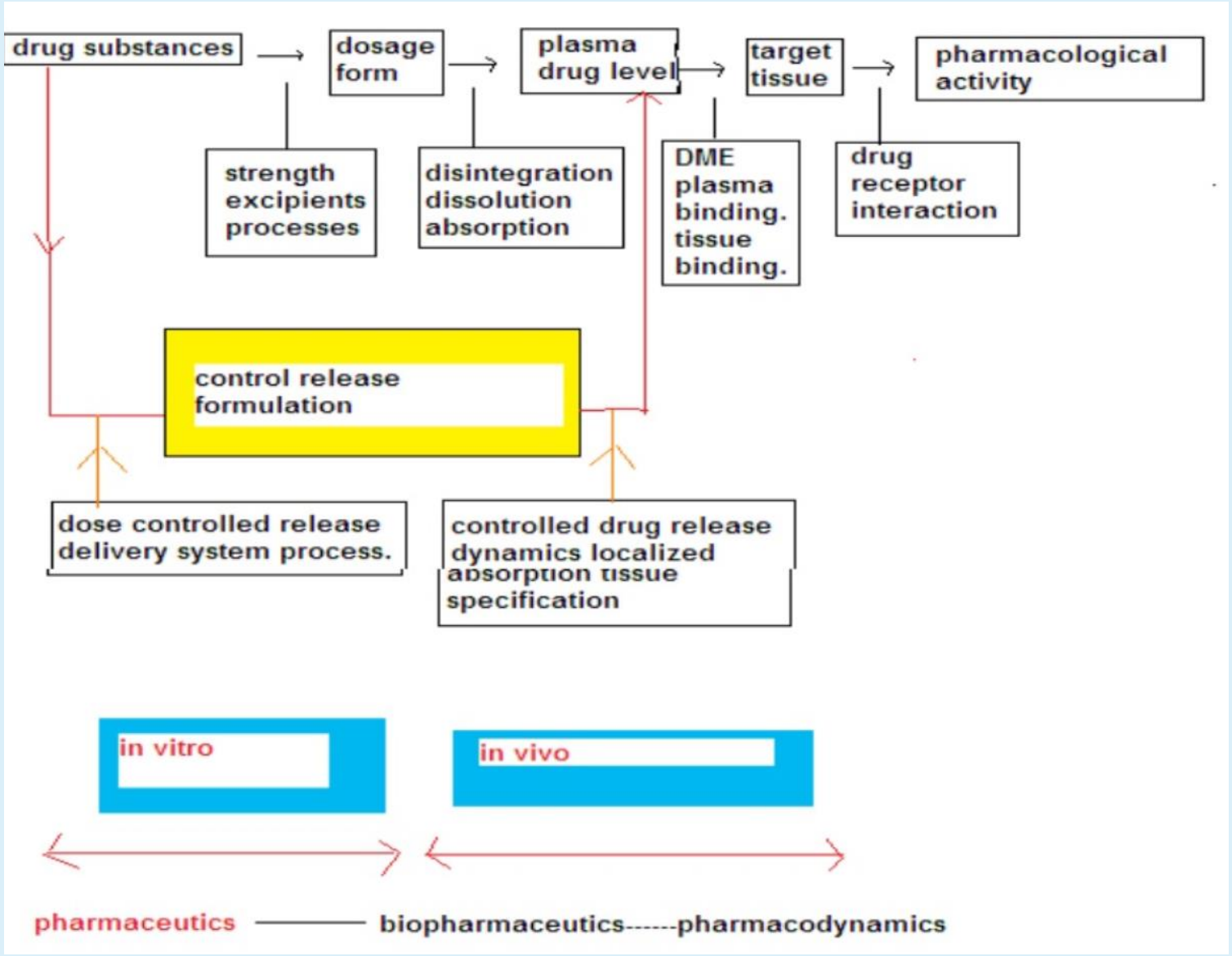
Contents

- Factors influencing designing of CDDS
- Physicochemical and biological properties of drugs relevant to controlled release formulations
- Selection of drug candidates.
- Approaches to design controlled release formulations based on
  - diffusion, dissolution and ion exchange principles.

Factors influencing designing of CDDS

1. Pharmaceutical Phase
2. Biopharmaceutical/Pharmacokinetic Phase
3. Pharmacodynamic Phase

- Behaviour of drug in DDS(In-Vitro Experiments)
- Behaviour of drug & DDS in the body(In-Vivo Experiments)



https://www.slideshare.net/ganapati123/concept-and-system-design-for-rate-controlled-dds

Factors influencing designing of CDDS

- Properties of Drug- Physico-chemical Properties & biological properties
- Route of administration-Physiological constrains(BBB, GIT motility, GIT transit time, first pass metabolism, blood supply)
- Target site
- Acute/Chronic Disease-expected length of therapy
- Patient-ambulatory/ bedridden,young/old,

Physico-chemical properties of drug influencing the designing of CDDS

Solubility

Definition-the concentration at which the solution phase is in equilibrium with a given solid phase at a stated temperature & pressure.

- Mostly drugs are **weakly acidic or basic** in nature that affect the water solubility of API.
- **Weak water soluble** drugs are **not good candidate** for controlled release formulations.
- **High aqueous solubility** drug show burst release followed by a rapid increment in plasma drug concentration and **are good candidate** for CDDS.
- The pH dependent solubility also creates a problem in formulating CDDS.
- as per the permeability & solubility profile, BCS classification is given
- BCS class-III & IV drugs are not a suitable candidate for this type of formulations

Partition coefficient (P-value)

- The partition coefficient is defined as“ the concentration ratio of unionized drug distributed between two phases at equilibrium.”
- P-value denotes the fraction of the drug into oil & aqueous phase that is a significant factor that affects the passive diffusion of the drug across the biological membrane.
- The drugs are having **high or low P value not suitable for CDDS** it should be appropriate to dissolve in both phases.

Drug pKa

- determine the ionization of drug at physiological pH in GIT.
- the high ionized drugs are poor candidates for CDDS.
- The absorption of the unionized drug occurs rapidly as compared to ionized drugs from the biological membranes.
- The pKa range for an acidic drug that ionization depends on the pH is 3.0 to 7.5 and for a basic drug it lay between 7 and 11.

Drug stability

- Drugs that are stable in acid/base, enzymatic degradation, and other gastric fluids are good candidates for CDDS.
- If drug degraded in the stomach and small intestine, it not suitable for controlled release formulations because it will decrease in bioavailability of concern drug.

Size of dose

- The CDDS formulated to eliminate the repetitive dosing, so **it must contain the large dose** than conventional dosage form.
- the dose used in conventional dosage form give an indication of the dose to be used in CDDS
- If the dose of a drug in conventional dosage form is high, then it is less suitable candidate for CDDS.
- This is because the size of a unit dose controlled release oral formulation would become too big to administer without difficulty.

Molecular weight or Molecular size and Diffusivity

- **The ability of drug to pass through membranes is called diffusivity, is a function of its molecular size (or molecular weight).**
- The molecular size & molecular weight are two important factors that affect the molecular diffusibility across a biological membrane.
- The molecular size less than 400D is easily diffuse but greater than 400D create a problem in drug diffusion.
- drugs in many CDDS must diffuse through a rate controlling membrane or matrix.
- Mass spectroscopy are generally used as the most common methods to determine the molecular size of the drug.
- Fourier Transform IR- spectroscopy (FTIR) is also used to determine the molecular structure.

Protein binding

- The drug-protein complex act as a reservoir in plasma for the drug.
- Drug showing **high plasma protein binding** are **not a good candidate** for CDDS because Protein binding increases the biological half-life.
- So there is no need to sustain the drug release

Biological factors

Biological half-life (t1/2)

- duration of action dependent on the biological half- life.
- drug having **short half-life** required frequent dosing and are **most suitable** candidate for controlled release system.
- Ideally, the drugs having $t_{1/2}$ 2-3 hrs are a suitable candidate for CDDS.
- Drugs have $t_{1/2}$ more than 7-8 hrs not used for controlled release system
- Very short (1 hrs) or very long half-life drugs are not suitable for CDDS

Therapeutic index

- **Margin of safety** can be described by therapeutics index, the ratio of median toxic dose and median effective dose**.**
- Therapeutic index = TD50/ED50.
- Drugs with low therapeutics index are unsuitable for drug incorporation in controlled release formulation**.**
- The side effects can be minimized by controlling the concentration within therapeutic range.

Absorption

- Uniformity in rate and extent of absorption is an important factor in formulating the CDDS.
- The absorption rate should rapid then release rate to prevent the dose dumping.
- If the transit time of dosage forms in the GI tract is about 8-12 hrs, the half-life for absorption should be approximately 3-4 hrs.
- Otherwise, the **dosage form will pass out of absorptive regions** before drug release is complete. Therefore, the compounds with lower absorption rate constants are poor candidates.
- The various factors like aqueous solubility, log P, acid hydrolysis, which affect the absorption of drugs.

Characteristics of Drug Unsuitable For Control release Dosage Form

- Short elimination half-life
- Long elimination half-life
- Narrow therapeutic index
- Poor absorption
- Active absorption
- Low or slow absorption
- Extensive first pass effect

Selection of Drug Candidate

1. **Biological Half Life**-For design of CDDS, it is required to determine the half-life of the drug candidate. It should be either **too high or too low**. Drugs showing higher $t_{1/2}$, are capability to reside in the body for longer periods, so if formulated in CDDS, then this will further enhance the same property & may lead to toxicity.
2. **First pass metabolism-** Conventional dosage form are incapability to by-pass the first pass metabolism and thereby most of the drug is converted to their respective metabolites and becomes inactive. But while formulating CDDS, it is important to ensure that CDDS of same drug is able to bypass the same.
3. **Poor absorption throughout the GI tract-** Most of the drug molecules show very poor absorption throughout the GIT tract. It is important to determine the solubility profile as thereby it'll easier to determine the targeted site of delivery.

Selection of Drug Candidate

- **Frequency of dosing is large-**If the dosing frequency of drug is higher due to low bioavailability or higher elimination rate, then the formulation of CRDDS, expels out all such problems and leads to patient compliance.
- **Narrow therapeutic window-** Drugs with low therapeutic window, are administered frequently as therapeutic effects decreases fast along with several side effects. So, in order to extend its therapeutic window, CRDDS is the ideal method.

Selection of drug candidates

- Drugs which show poor absorption from stomach or intestine are the best candidates for colon specific delivery.
- Peptides, proteins, oligonucleotides and vaccines are potential candidates for colon targeted DDS.

Approaches to design CDDS

Approaches to design CDDS

1. Diffusion Control Release :
    1. Matrix
    2. Encapsulation

2. Dissolution Control Release :
    1. Matrix
    2. Reservoir

3. Combination of both dissolution & diffusion

4. Osmotic pressure controlled system

Diffusion Control Release Device

- Basically diffusion process shows the movement of drug molecules **from a region of a higher concentration to one of lower concentration until equilibrium is attained**.
- The flux of the drug J (in amount / area -time), across a membrane in the direction of decreasing concentration is given by Fick's law

$$J = - D \, dc/dx$$

Where,

D = diffusion coefficient in area/ time

dc/dx = change of concentration 'c' with distance 'x'

- Directly proportional to the concentration gradient across the membrane.

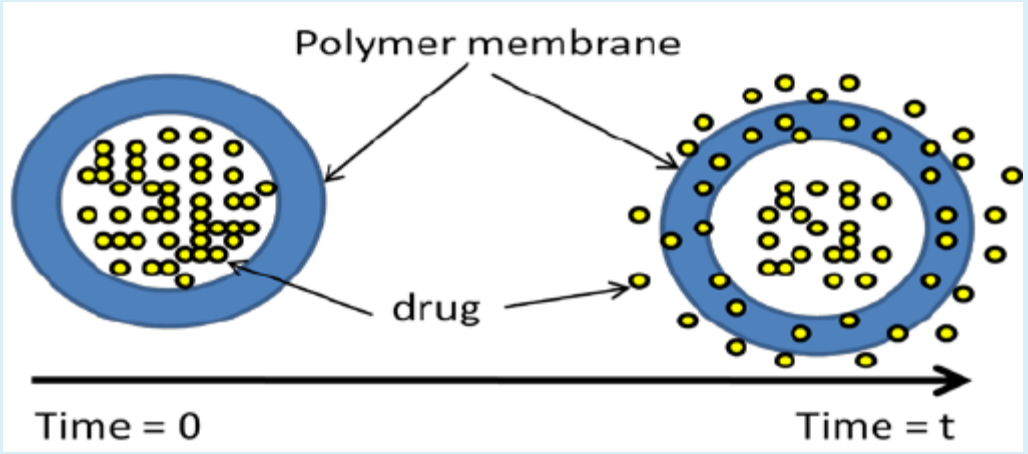
Diffusion Control Release Device

- Diffusion systems are characterized by **release rate of drug is dependent on its diffusion** through inert **water insoluble membrane barrier**.
- There are basically two types of diffusion devices

1. **Reservoir Type**
2. **Matrix Type**

Diffusion Control Release Systems: Reservoir Type

- In the system, a **water insoluble polymeric material** encloses a core of drug, which controls release rate.
- Polymer can be applied by coating or micro encapsulation.
- Drug will partition into the rate controlling membrane with subsequent release into surrounding fluid by diffusion.
- The polymers commonly used in such devices are Ethyl cellulose and Poly-vinyl acetate.



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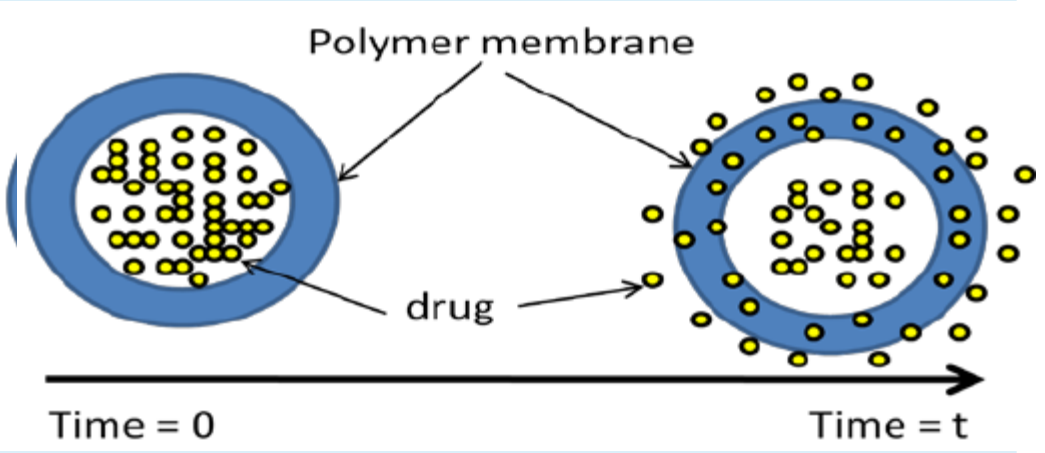
Diffusion Control Release Systems: Reservoir Type

- The rate of drug released (dm/dt) can be calculated using the following equation

$$\frac{dm}{dt} = ADK \frac{\Delta C}{\ell}$$

- Where, A = Area,
- D = Diffusion coefficient,
- K = Partition coefficient of the drug between the drug core and the membrane,
- ℓ = Diffusion pathlength and
- ΔC= Concentration difference across the membrane.



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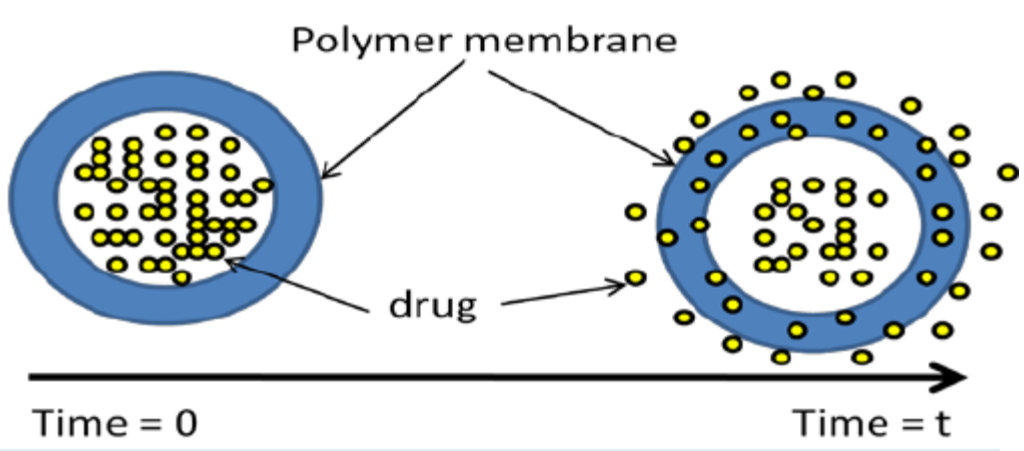
Diffusion Control Release Systems: Reservoir Type

Advantage:

- Zero order delivery is possible,
- release rates variable with polymer type.

Disadvantages:

- System must be physically removed from implant sites.
- Difficult to deliver high molecular weight compound,
- generally increased cost per dosage unit, potential toxicity if system fails.



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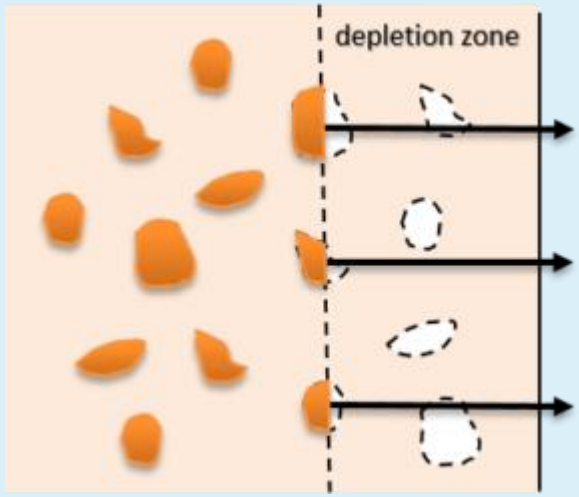
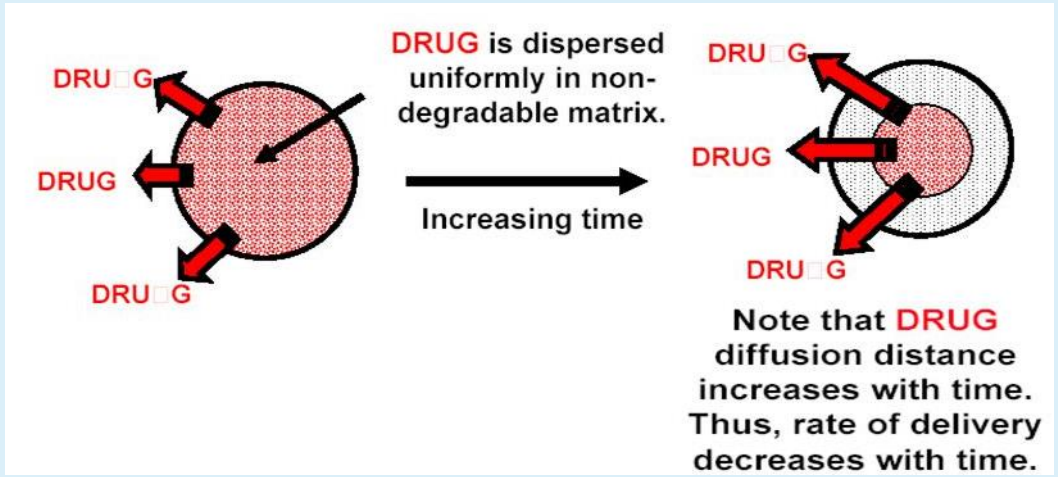
Diffusion Control Release Systems: Matrix Type

- In a matrix or monolithic delivery system the drug is homogenously dissolved or dispersed in an insoluble polymer matrix and
- the rate of release of drug is dependent on the rate of drug diffusion and not on the rate of solid dissolution.
- the release rate of the drug from the matrix system is normally not constant and decreases in time
- the matrix itself is inert and does not dissolve nor degrade in the dissolution medium.
- This means that the dimensions of the matrix do not change during release of the drug.

Diffusion Control Release Systems: Matrix Type

- As the matrix system is immersed in a dissolution medium the drug, present at the surface of the matrix, will dissolve in the dissolution medium.
- Further due to concentration difference, drug will diffuse from the inner layers to the outer layers of the matrix.
- The depletion zone will be formed at the boundary of the matrix which increases in time.
- the drug has to diffuse over a longer distance, the release rate will also decrease with time.





$\frac{dQ}{dt} = k\sqrt{\frac{1}{t}}$

Diffusion Control Release Systems: Matrix Type

- The release of a drug from matrix system under sink conditions was described

  by *Higuchi*

$$Q = \frac{M}{A} = \sqrt{((2C_0 - C_s)DC_s t)}$$

$$\frac{dQ}{dt} = \frac{1}{2}\sqrt{\frac{(2C_0 - C_s)DC_s}{t}}$$

$$\frac{dQ}{dt} = k\sqrt{\frac{1}{t}}$$

Where:

Q = the amount of drug released (M) per surface area (A)
D = the diffusion coefficient of the drug
C_0 = is the initial total drug concentration in the matrix
C_s = the solubility concentration of the drug in the matrix
t = time

- the release rate is inverse proportional to the square root of time. If the release rate is plotted versus the square root of time a straight line is obtained.

Diffusion Control Release Systems: Matrix Type

Advantages:

- Easier to produce than reservoir or encapsulated devices, can deliver high molecular weight compounds.

Disadvantages: Cannot provide zero order release, removal of remaining matrix is necessary for implanted system.

Dissolution Controlled Systems

- Drugs having high aqueous solubility and dissolution rate, shows challenge in controlling their dissolution rate.
- Dissolution-controlled release system are designed by **slowing** the dissolution rate of a drug in the GI medium, incorporating the drug in **an insoluble polymer** and coating drug particles or granules with polymeric materials of varying thickness.
- The rate limiting step for dissolution of a drug is the diffusion across the aqueous boundary layer.

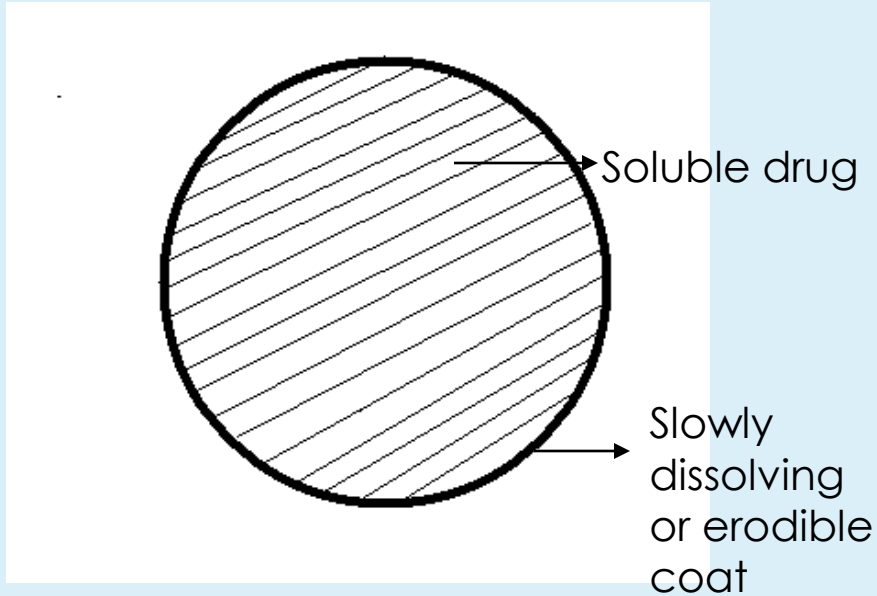
Dissolution Controlled Systems: Reservoir Type

Encapsulation Dissolution Controlled Systems

- The drug particles are coated or encapsulated by microencapsulation techniques with slowly dissolving materials like cellulose, poly ethylene glycols, polymethacrylates, waxes etc. the dissolution rate of coat depends upon the solubility and thickness of the coating.

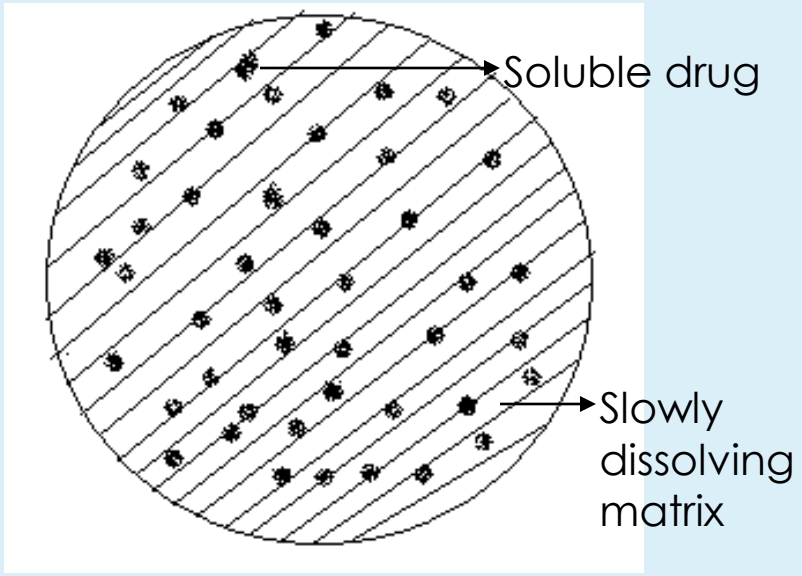
Dissolution Controlled Systems: Encapsulation

- Called as Coating dissolution controlled system.
- Dissolution rate of coat depends upon stability & thickness of coating.
- Masks colour,odour,taste,minimising GI irritation.
- One of the microencapsulation method is used.
- Examples: Ornade spansules, Chlortrimeton Repetabs



Dissolution Controlled Systems: Matrix Type

- Also called as Monolithic dissolution controlled system.
- Controlled dissolution by:
    1. Altering porosity of tablet.
    2. Decreasing its wettebility.
    3. Dissolving at slower rate.
- First order drug release.
- Drug release determined by dissolution rate of polymer.
- Examples: Dimetane extencaps, Dimetapp extentabs.



Dissolution Controlled Systems: Matrix Type

- The basic equation for dissolution of a matrix was described by **Noyes and Whitney**.
- They state that the dissolution rate at which a planar matrix dissolves is proportional to the difference in saturation solubility and the concentration in the dissolution medium.

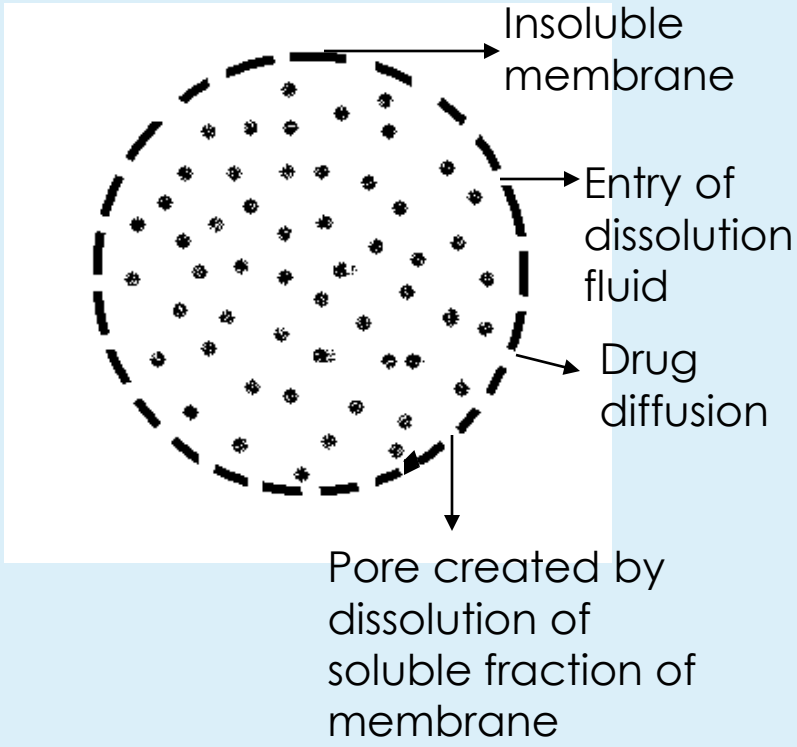
$$dc/dt = kD.A\ (Cs - C\ )$$

$$dc/dt = D/h\ A.\ (Cs - C)$$

dc/dt = Dissolution rate.
k= Dissolution rate constant (1^{st} order).
D = Diffusion coefficient/diffusivity
Cs = Saturation/ maximum drug solubility.
C =Con. Of drug in bulk solution.
Cs-C=concentration gradient.
h =Thickness of diffusion layer.

Dissolution & Diffusion Controlled Release system

- Drug encased in a partially soluble membrane.
- Pores are created due to dissolution of parts of membrane.
- It permits entry of aqueous medium into core & drug dissolution.
- Diffusion of dissolved drug out of system.
- Ex- Ethyl cellulose & PVP mixture dissolves in water & create pores of insoluble ethyl cellulose membrane.



Ion-Exchange Systems

- This system is designed to provide the controlled release of an ionic or ionizable drug.
- Resins are water-insoluble materials containing anionic or cationic groups in repeating positions on the resin chain.
- The drug-charged resin is prepared by mixing the resin with drug solution either by repeated exposure of the resin to the drug in a chromatographic column or by keeping the resin in contact with the drug solution for extended periods of time.
- It is prepared by first **absorbing an ionized drug onto the ion-exchange resin** granules such as codeine base with Amberlite, and
- Then coating the drug resin complex granules with a water permeable polymer,
- e.g. a modified copolymer of polyacrylic and methacrylic ester, and then spray drying the coated granules to produce the polymer coated drug resin preparation
- The drug is released by exchanging with appropriately charged ions in the GIT.

Ion-Exchange Systems

- Ion-exchange systems generally use resins composed of water soluble cross-linked polymers
- These polymers contain salt forming functional groups in repeating position on the polymer chain
- The drug is bound to the resin and released by exchanging with appropriately charged ions in contact with the ion exchange groups

$$Resin^{+} - drug^{-} + X^{-} \longrightarrow resin^{+} - X^{-} + drug^{-}$$

Where X- are ions in the GI tract

THANK YOU