CONTROLLED DRUG DELIVERY SYSTEM

These are drug delivery system in which the drug is in predetermined pattern over a fixed period of time.

- It helps in maintain constant and effective drug level in the body.
- It helps to deliver drug to a particular target by using carrier or chemical derivatives.
- It helps in minimization of undesirable side effects.

TERMINOLOGY / DEFINATIONS

1. Extend Release

When absorption of drug is greater than elemination, release is known as extend release.

2. Prolonged Release

It Releases the active ingredients slowly and work for a longer time. It is a dose of medication over on extend period of time.

3. Sustained Release

It Releases a specific drug at a programmed rate that leads to drug delivery for a prolonged period of time.

4. Controlled Drug delivery

It delivers the drug at pre-determined rate, for a specified period of time.

5. Site specific targetting
It releases the drug at or near the particular site of action. They have extended release characterstics.

6. Receptor targeting
In this system, the target is a particular receptor within an organ or tissue.

7. Fast dissolve drug delivery System [flash]
In this system, solid dosage form dissolve or disintegrate in oral cavity without the help of water or chewing. Fast dissolving is achieved by loose network (zydis, Eli lilly) or with mixture of disintegrating agent and swelling (flash tab, prographarm).

RATIONALE

Main rationale of control drug delivery system is to optimize of biopharmaceutics, pharmacokinetics and pharmacodynamics properties of a drug in a such a way that reduces its side effects and cure desease condition in minimum possible time.

The conventional / traditional drug delivery system lacks many features like dose maintaince, more side effects and site targeting which leads to more patient complance.

A controlled release drug delivery system leads to reduce patient compliance.

An ideal drug delivery system should deliver the drug at a rate dictated by the need of body over a specific period of treatment.

Advantages

- Maintance of drug levels within desired range.
- Less dosing
- Eliminate over dosing
- Prevention of side - effect.
- Reduction in health care cost
- Improved efficancy in treatment
- Reduction in adverse drug effect.
- Improve bioavailability of drugs
- Cure more promptly

Disadvantages

- All drugs are not suitable condidates for controlled release medication.
- Drugs like Riboflavin and ferrous salt, which are not effectively absorbed in lower intestine, are poor condidates.
- Drugs which are have very short half life (< 1 hour) eg. penicillin, furesomide are poor condidates for sustained release formulations.
- Poor in In-vivo In vitro corelation.
- Difficult to optimize the acurate dose and dosing interval.
- Patient variability effects the release rate like GI emptying rate, Residential time etc.

SELECTION OF DRUG CANDIDATES

1. Half life : Drug should have half life of 3-4 hours.

2. Therapeutic Index : Drug should have high therapeutic Index because low therapeutic index are unsuitable for incorporation in control release formulations.

3. Small dose : drug should in small size / dose because big dose is difficult to administrate.

4. Absorption : Absorption of poorly water solouble drug is dissolution rate limited.

APPROACHES TO DESIGN CONTROLL-ED RELEASE FORMULATIONS

1. Diffusion Systems

Diffusion is the movements of drug molecule from higher to lower concentration. In this system, release rate of drug is determined by diffusion through a water insoluble polymer.

Rate of drug is determined by fick's law;

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

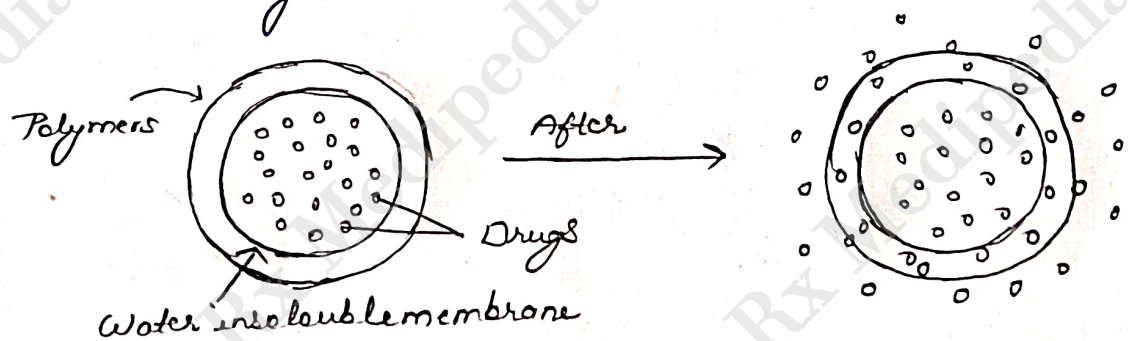
where,

D = diffusion coefficient in area / time

dc/dx = change of concentration "c" with distance

a) Reservoir Systems

It is also called as laminated matrix device. It is a hollow system which is polymer coated. The inner core is surrounded by the water insoluble membrane.



The rate controlling mechanism is that drug will partition into inner membrane and then exchange with fluid surrounding the drug by diffusion.

Commonly used polymers are HPC, ethyl cellulose.

The rate of drug released is calculated,

$$dm/dt = ADk \times \Delta C/l$$

Where,

A = Area

D = diffusion coefficient

k = Partition coefficient of drug b/w the drug core and the membrane

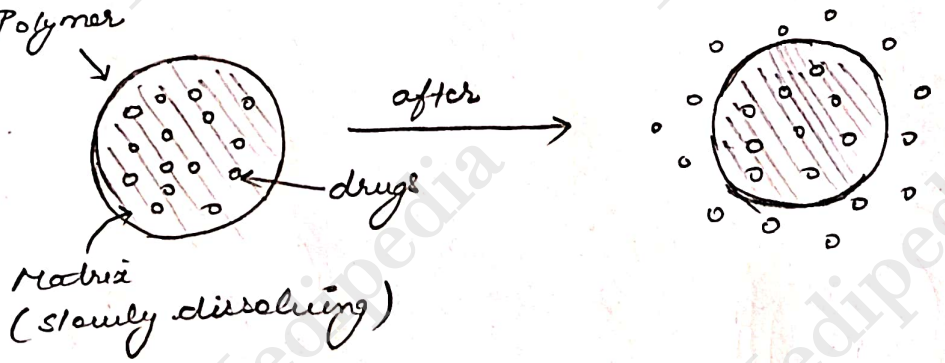
l = Diffusion path length

ΔC = Concentration difference across the membrane

b) Matrix System

It is a homogeneous system in which drug is dispersed in polymer matrix. Rate controlling mechanism is that diffusion occur when drug passes from the polymer matrix into external environment.

Commonly used polymers are methyl cellulose & Carbopol 934.



The rate of drug released is calculated,

$$Q = D\varepsilon/T[2A - \varepsilon Cs]\, Cst^{1/2}$$

Where,

Q = Weight in gms of drug released per unit area of surface at time t

D = Diffusion coefficient of drug in the release medium.

ε = Porosity of the matrix

C_s = Solubility of drug in release medium.

T = Tortuosity of the matrix

A = Concentration of drug in the tablet, as gm/ml

2. Dissolution Systems

Dissolution is the process in which a substance forms a solution. Dissolution process is described by the Noyes-Whitney equation.

$$dC/dt = KD\ A\ (C_s - C) = (D/h)\ A(C_s - C)$$

Where,

dC/dt = Dissolution rate

KD = Dissolution rate constant

A = Total surface area

C_s = Saturation solubility of the solid

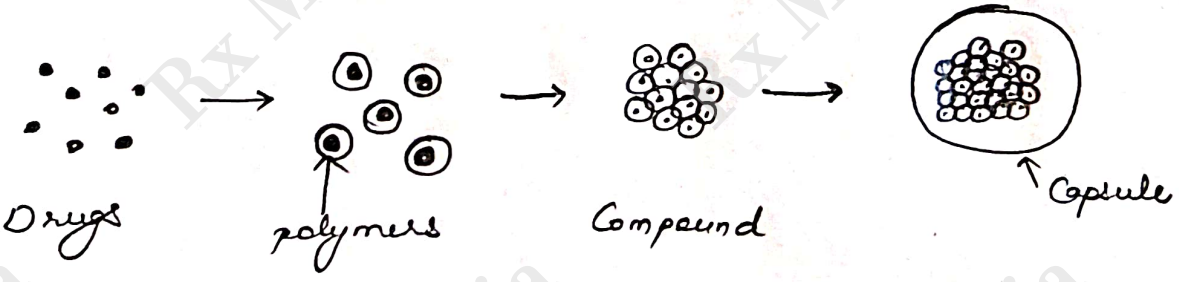
C = Concentration of solute in the bulk solution

D = Diffusion coefficient

h = Thickness of the diffusion layer

a) Encapsulated / Reservoir devices

In this system, granules of drug with slowly soluble polymers is coated in capsules by microencapsulation. Mechanism is managed by decreasing the dissolution rate.



b) Matrix Systems

This system is prepared by compressing the drug with slowly soluble polymer into tablet form. It is also known monolithic dissolution controlled system.

Dissolution occur by,
- Altering porosity of tablet
- decreasing its wet ability
- dissolving at slower rate.

3. Methods using Ion Exchange

The system is designed to provide controlled release of an ionic drug. The system is prepared by first absorbing an ionized drug into the ion exchange resin granules such as codiene base with Amberlite, then after filtration from the alchohalic medium, coating the drug resin complex granules with a water permeable polymer. eg. modified copolymer of polyacrylic
Drug is released by exchanging with charged ions in the GIT. The drug is then diffuse out of resin.

⇒ Two types :

i) Cation exchange → A cationic drug is complexed with a resin containing SO_3^- group.

$$Resin - SO_3^- \, Drug^+ + H^+ \longleftrightarrow Resin - SO_3^- H^+ + Drug^+$$

ii) Anionic exchange → An anionic drug is complexed with a resin containing $N(CH_3)_3^+$ group.

$$Resin - N(CH_3)_3^+ \, Drug^- + Cl^- \longleftrightarrow Resin - N(CH_3)_3^+ Cl^- + Drug^-$$

PHYSIOCHEMICAL & BIOLOGICAL PROP.

PHYSIOCHEMICAL PROPERTIES

1. Aqueous Solubility

Most of drugs are weak acids or weak acids. Drugs with low solubility will be difficult to fit in sustained release mechanism.

For control Drug Delivery System, drug should high water soluble because it absorb quickly.

2. Partition Coefficient

Partition coefficient is the fraction of drug in oil phase and water phase. Drug with high Partition coefficient easily permeate through biological membrane. Drugs that have lower and higher partition coefficient are not suitable for controlled release drug delivery System.

3. Ionization

Drugs which are in ionized form are poor condidate for control Release drug delivery System, because absorption rate of Ionized drugs is 3-4 times less than unionized form.

4. Route of Administration

for control Release drug delivery System, Oral and parentral routes are the most prefered which is followed by transdermal route.

5. Mechonism & Site of Action

Drugs that are absorbed by carrier mediated transport process or through a window are poor candidates for controlled release system, e.g. Vit B.

6. Molecular Size

More than 95% of drugs absorbs by passive diffusion. The upper limit for control release drug delivery systems, of drug molecule size for passive diffusion is 600 dalton.

BIOLOGICAL PROPERTIES

1. Absorption

The desirable quality of oral controlled delivery system is that it should release complete drug and the release drug should be completely absorbed.
Drugs which are absorbed by specialized transport process (carrier mediated) and drug absorption at special sites of GI tract are poor candidates for sustained release products.

2. Distribution

The apparent volume of distribution is one of the important parameter of drugs that describes the magnitude of distribution as well as protein binding within the body. Drugs with high aparent volume of distribution, which influence the rate of elimination of drug, are poor candidates for oral drug delivery System.

3. Metabolism

for control Release drug delivery System, the drugs that are extensively metabolised can be generated as long as the location, rate and extent and metabolism are known and the rate constant are not too large.

4. Therapeutic Index

$$\text{Therapeutic Index} = \frac{TD\,50}{ED\,50}$$

Where,

TD 50 is median toxic dose

ED 50 is median effective dose

Drugs with low therapeutic index are unsuitable for drug incorporation in control Release drug delivery System. A drug is considered to be safe if its therapeutic index value is greater than 10.

5. Size of dose

If ~~it~~ the size of dose is big, it is not suitable for control Release drug formulations.

6. Absorption Window

Certain drugs when administerated orally are absorbed only from a specific part of GI tract. This part is known as 'absorption window'. These kinds of drugs are not suitable for control Release drug delivery System.