CONTROLLED DRUG DELIVERY SYSTEM

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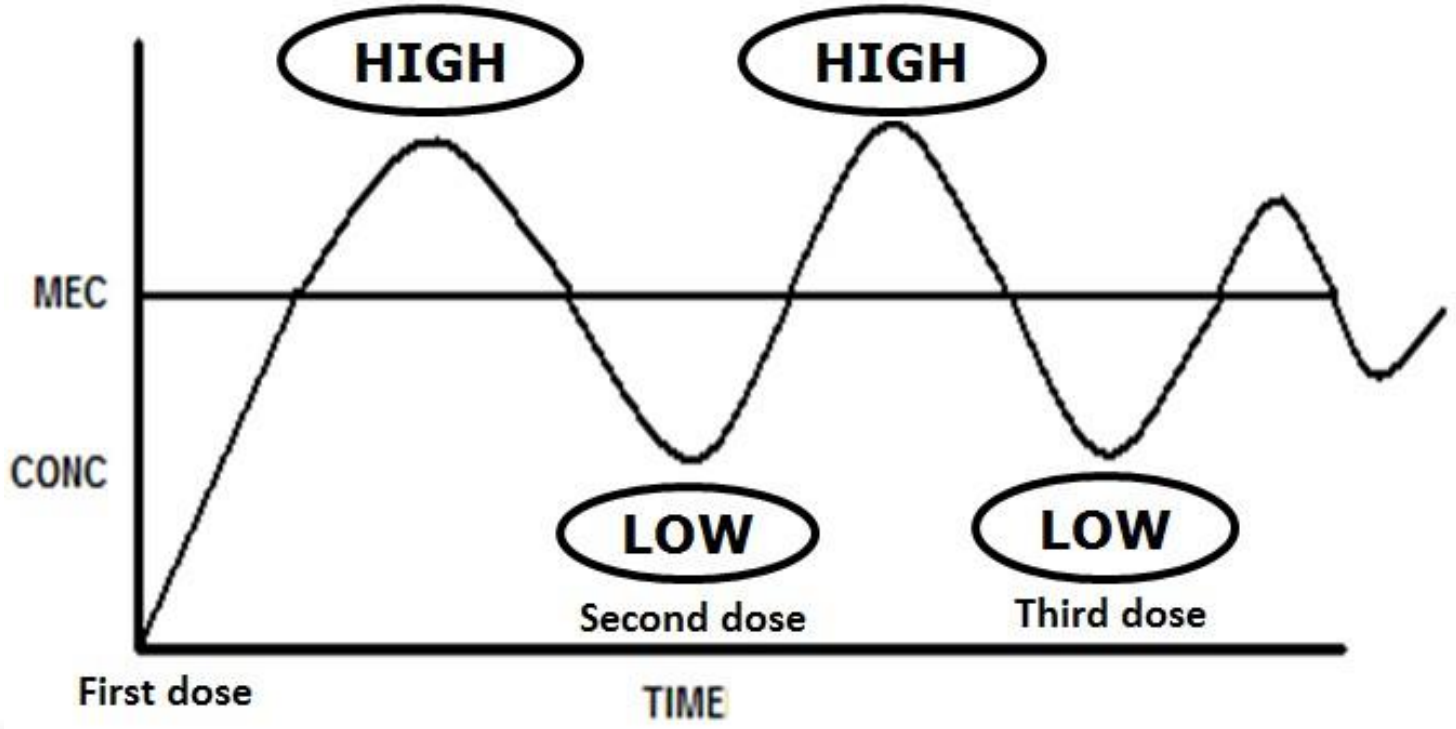
Introduction

- The term “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 has lead to various new techniques of delivering the drugs for maximum patient compliance at minimal dose and least side effects.
- Generations of dosage forms
  - ✓ 1st gen. – Conventional (unmodified) release of drug
  - ✓ 2nd gen.– Controlled release of drug (CR)
  - ✓ 3rd gen. – Targeted distribution drug delivery systems

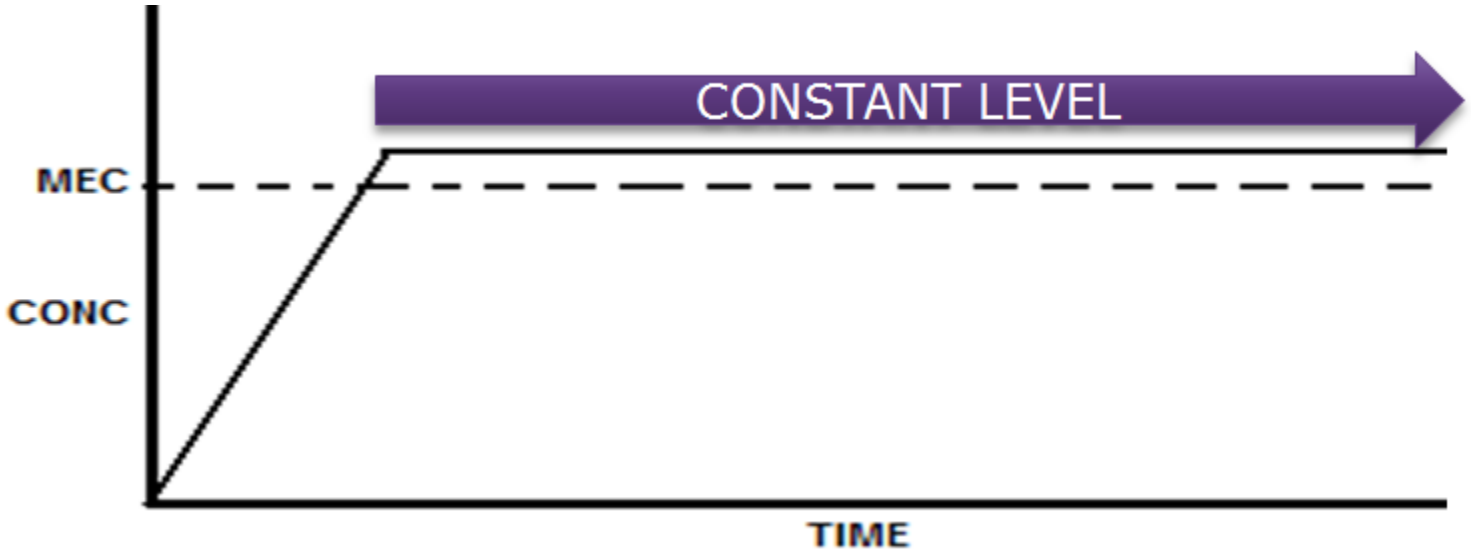
Conventional drug delivery system

- In the conventional therapy aliquot quantities of drugs are introduced into the system at specified intervals of time with the result that there is considerable **fluctuation in drug concentration level** as indicated in the figure.



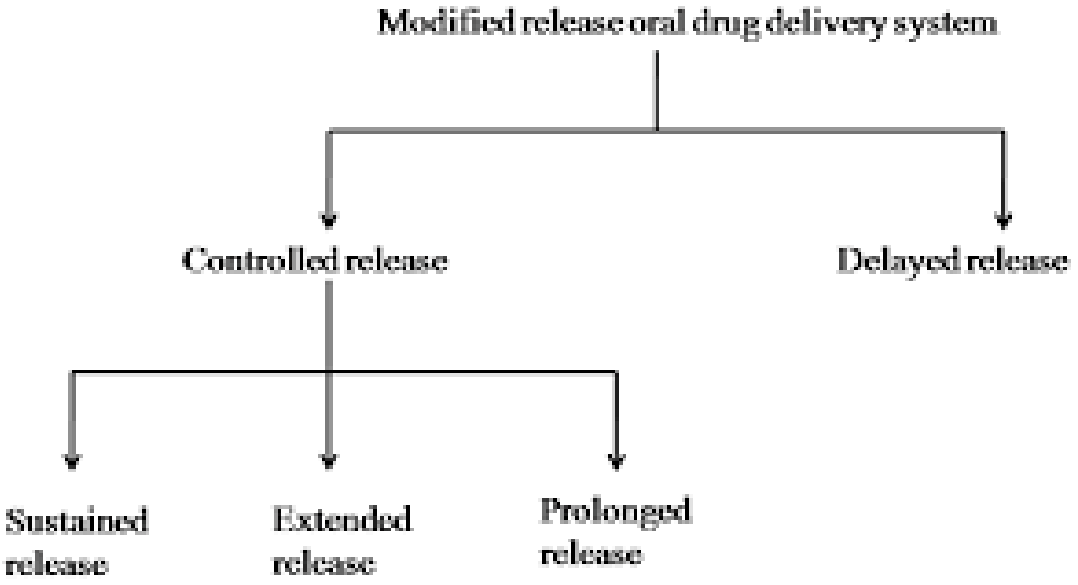
Ideal dosage regimen

- However, an ideal dosage regimen would be one, in which the concentration of the drug, nearly coinciding with minimum effective concentration (M.E.C.), is maintained at a **constant level** throughout the treatment period. Such a situation can be graphically represented by the following figure



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

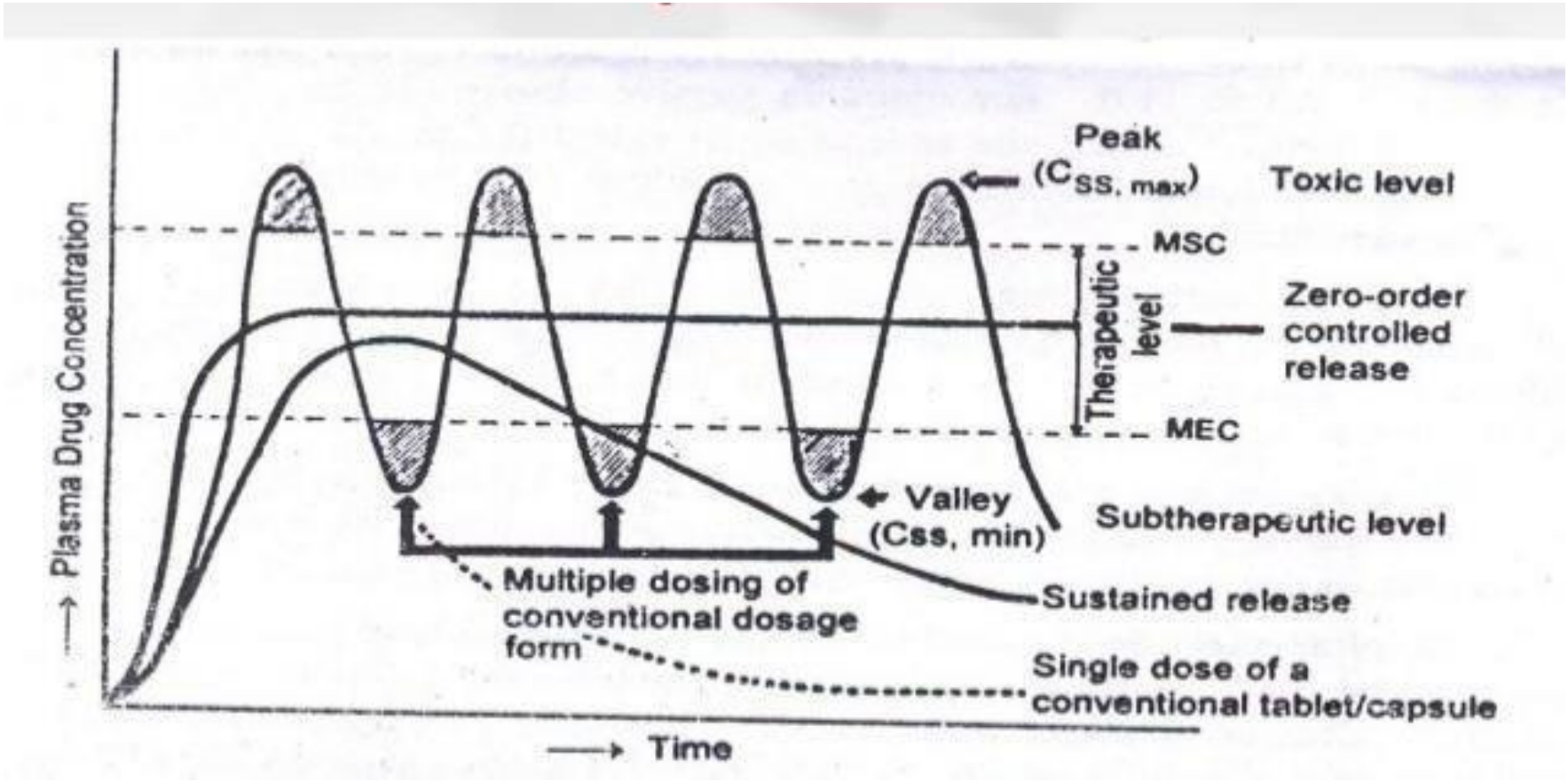


DEFINITION

- **CONTROLLED RELEASE DRUG DELIVERY:** Drug delivery system that are designed to release the drug at predetermined rate, locally or systemically according to the need of the body and disease states for a specified period of time.
- It follows ***zero order release***
- **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.
- It follows ***first order release***

- **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

Comparison of Drug Release Profile



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.

Rationale

- 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 *in-vivo* environment in which drug release take place.
- This is usually concerned with maximum drug availability by attempting to achieve a maximum rate and extent of drug absorption.
- However, ***control of drug action*** through formulation also implies controlling bioavailability to reduce drug absorption rates.

Concept

- It is based on two considerations *i.e.*, release rate & dose consideration

A. Release rate consideration:

- **Immediate release conventional dosage form**

Dosage form $\xrightarrow{K_r}$ Drug in absorption site $\xrightarrow{K_a}$ Drug to target site $\xrightarrow{K_e}$ Drug elimination

- **Non immediate release dosage form (SR/CR)**

Dosage form $\xrightarrow{K_r}$ Drug to target site $\xrightarrow{K_e}$ Drug elimination

Here, K_r = 1st order release rate constant
K_a = 1st order absorption rate constant

K_e = 1st order elimination rate constant

- The above criteria *i.e.*, ***(K_r>K_a)*** is in case of ***immediate release,*** where as in ***non immediate (K_r<K_a)*** *i.e.*, release is rate limiting step.
- So that effort for developing modified release formulation must be directed primarily altering the release rate.
- Rate should be independent of drug release from dosage form over time.
- The release rate should follow zero order kinetics

$$\mathbf{K_r = rate\ in = rate\ out = K_e V_d . C_d}$$

Where, K_e = overall elimination (first order kinetics).

V_d = total volume of distribution.

C_d = desired drug concentration.

B. Dose consideration:

- To achieve the therapeutic level & sustained release of drug for a given period of time from the dosage the formulation is designed in two parts

a) Initial (primary/loading) dose

b) Maintenance dose

there for the total dose 'W' can be.

$$W = D_i + D_m$$

- In a system, the therapeutic dose release follows zero order process for specified time period then,

$$W = D_i + K_0 \text{ r. } T_d$$

Where, T_d = time desired for sustained release from one dose.

- If maintenance dose begins to release the drug during dosing t=0 then,

$$\mathbf{W = D_i + K_0\, r\, T_d - K_0\, r\, T_p}$$

Where, T_p = time of peak drug level.

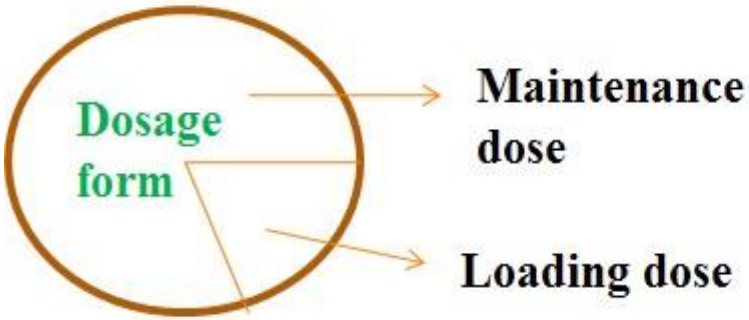
- However a constant drug can be obtained by suitable combination of D_i & D_m that release the drug by first order process, then

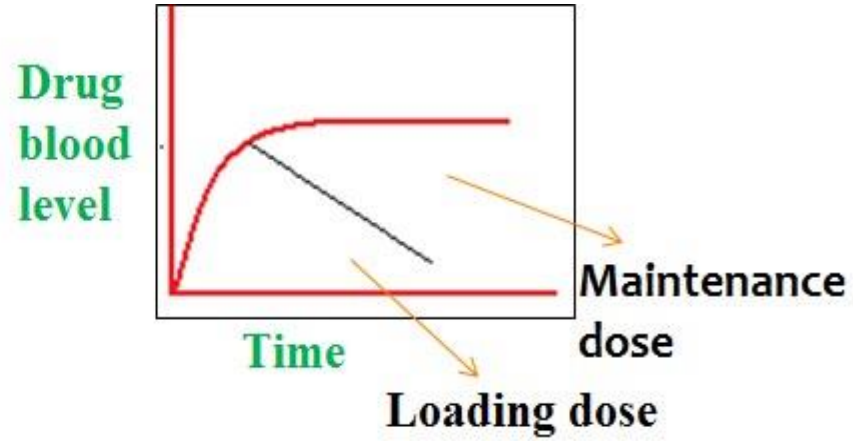
$$\mathbf{W = D_i + (K_e\, C_d\, / K_r)\, V_d}$$

Controlled Drug Delivery System

CR dosage form may contain:

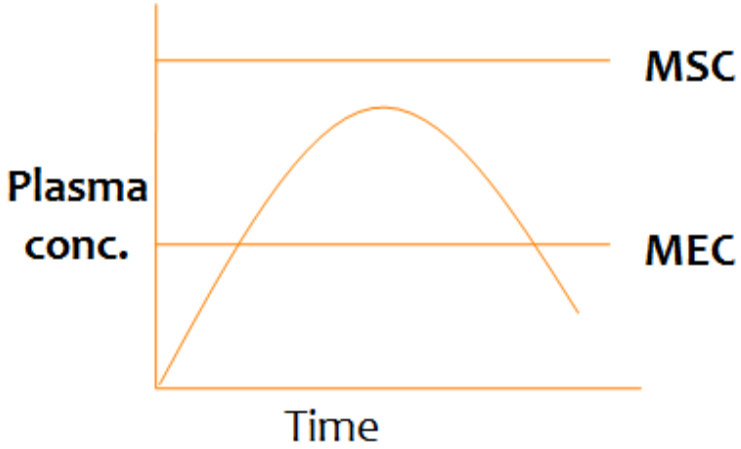
- ✓ **Loading dose:** Release the drug immediately after administration and follows first order kinetics.
- ✓ **Maintenance dose:** Release the drug slowly and maintain the therapeutic level for extended period of time. It follows zero order kinetics.

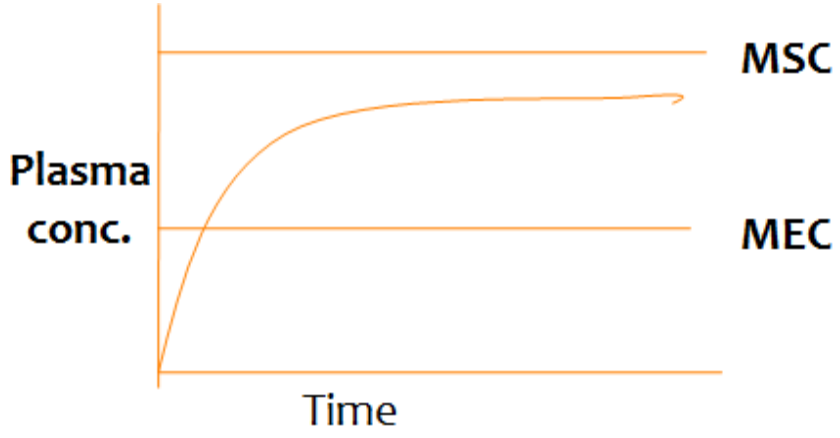




Difference between SR & CR

SR	CR
1)Slow release of drug over extended period of time.	1)Maintain a constant drug level in blood or tissue.
2)Non site specific.	2)Site specific.
3)They show first order.	3)They show zero order.
4)Release of drug is conc. dependent.	4)Release of drug is conc. independent.
5)Non predictable & reproducible.	5)Predictable & reproducible.
6)Plot	6)Plot





MSC= Maximum Safe Conc. & MEC = Minimum Effective Conc.

Advantages

- **Improved** patient **convenience and compliance** due to less frequent drug administration.
- Reduction in fluctuation in steady-state level and therefore **better control of disease condition.**
- **Increased safety margin** of high potency drug due to better control of plasma levels.
- **Maximum utilization of drug** enabling reduction in total amount of dose administered.
- **Reduction in health care cost** through improved therapy, shorter treatment period.

- **Less frequency of dosing** and reduction in personnel time to dispense, administer monitor patients.
- **Better control of drug absorption**
- **Reduction in adverse effects** (both systemic and local), especially for potent drugs, in sensitive patients.
- **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.
- **Constant blood levels** achieve desired effect and this effect is maintained for an intended period of time.

- Drug susceptible to enzymatic inactivation or by bacterial decomposition can be protected by encapsulation in polymer system suitable for SR.

Disadvantages

- **Decreased systemic availability** in comparison to immediate release conventional dosage forms; this may be due to incomplete release, increased first-pass metabolism, increased instability, insufficient residence time for complete release, site specific absorption, pH dependent solubility etc.
- **Poor *in-vivo* to *in-vitro* correlation.**
- **Possibility of dose dumping** due to food, physiologic or formulation variable or chewing or grinding of oral formulation by the patient and thus increased risk of toxicity.
- **Retrieval of drug is difficult** in case of toxicity, poisoning or hypersensitivity reaction.

- The physician has **less flexibility** in adjusting dosage regimens. This is fixed by the dosage form design. (**half tablet can’t be given**)
- Controlled release forms are designed for the normal population *i.e.*, on the basis of average drug biologic half-life’s. Consequently disease states that alter drug disposition, significant patient variation and **so forth are not accommodated.**
- Economics factors must also be assessed, since **more costly processes and equipment** are involved in manufacturing many sustained release forms.
- 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 sustained release dosage forms. E.g. diazepam

Ideal characteristics of drug/Ideal drug selection criteria

- Drugs which have **half life** between **2-8 hrs.**
- Drugs which have **therapeutic index greater than 10.**
- Drugs which undergo **least first pass metabolism**.
- Substances should have **good aqueous solubility**.
- **Dose size** should be **0.5-1.0 gm.**

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, Larger amount of drug required.
Toxic concentration	Apart the value of MTC And MEC safer the dosage form

Factors affecting the design of CRDDS

1. Biological properties

i. Absorption

ii. Distribution

iii. Metabolism

iv. Biological half life (excretion)

v. Margin of safety

vi. Therapeutic window

vii. Absorption window

viii. Patients physiology

2. Physiological factors

i. Dosage size

ii. Partition coefficient & molecular weight

iii. Drug stability

iv. Molecular size & diffusivity

v. Pka

vi. Aqueous Solubility

vii. Drug stability

viii. Protein binding

1. **Biological Factors**

i. 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 into controlled release system. Absorption= dissolution
- The characteristics of absorption of a drug can be greatly effects its suitability for controlled 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 wil

probably be poor candidates for controlling systems. The rate, extent and uniformity of absorption of a drug are important factors considered while formulation of controlled release formulation. As the rate limiting step in drug delivery from a controlled-release system is its release from a dosage form, rather than absorption.

- If we assume that transit time of drug 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 controlled release formulation. An another important criteria is the through absorption of drug in GIT tract.
- Drug like Kanamycin and gentamycin shows absorption at different sites, Riboflavin like drug absorbed effectively by carrier transport and

at upper part of GIT that make it preparation in CDDS difficult.

- As the rate limiting step in drug delivery from a controlled-release system is its release from a dosage form, rather than absorption. Rapid rate of absorption of drug, relative to its release is essential if the system is to be successful.
- **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 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

$$V_d = \text{dose}/C_0$$

Where:

C_0= initial drug concentration immediately after an IV bolus injection

- In case of two compartment model.

$$V_{ss} = (1+K_{12}/K_{21})/V_1$$

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 those instance where steady state drug concentration in both compartment has been reached. At any other time it tends to overestimate or underestimate.

- To avoid uncertainty characteristic in the apparent volume of distribution as an estimation of the amount of drug in the body. The T/P ratio is used.
- The amount of drug in the body can be calculated by T/P ratio as given below.

$$T/P = K_{12} (K_{21}-\beta)$$

Where:

β = slow deposition constant

T= amount of drug in peripheral

iii. Metabolism:

- There are two areas of concern relative to metabolism that significantly restrict controlled release formulation.
- If drug upon chronic administration is capable of either inducing or inhibiting the enzyme synthesis it will be poor candidate for controlled release formulation because of difficulty of maintaining uniform blood levels of drugs.
- If there is a variable blood level of drug through a first-pass effect, this also will make preparation of controlled release product difficult.
- Drug that are significantly metabolized before absorption, either in lumen of intestine, can show decreased bio-availability 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 enzyme. Process device at specific period, allowing more complete conversion of the drug to its metabolite.

iv. 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 ($t_{1/2}$).
- Therapeutic compounds with 2-8 hrs half life are excellent candidates for controlled 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. More than 8 hours are also generally not used in sustaining forms, since their effect is already sustained.
- E.g.; Digoxin, Warfarin, Phenytoin etc.

v. Margin of safety:

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

$$TI = \frac{LD_{50}}{ED_{50}}$$

- 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.

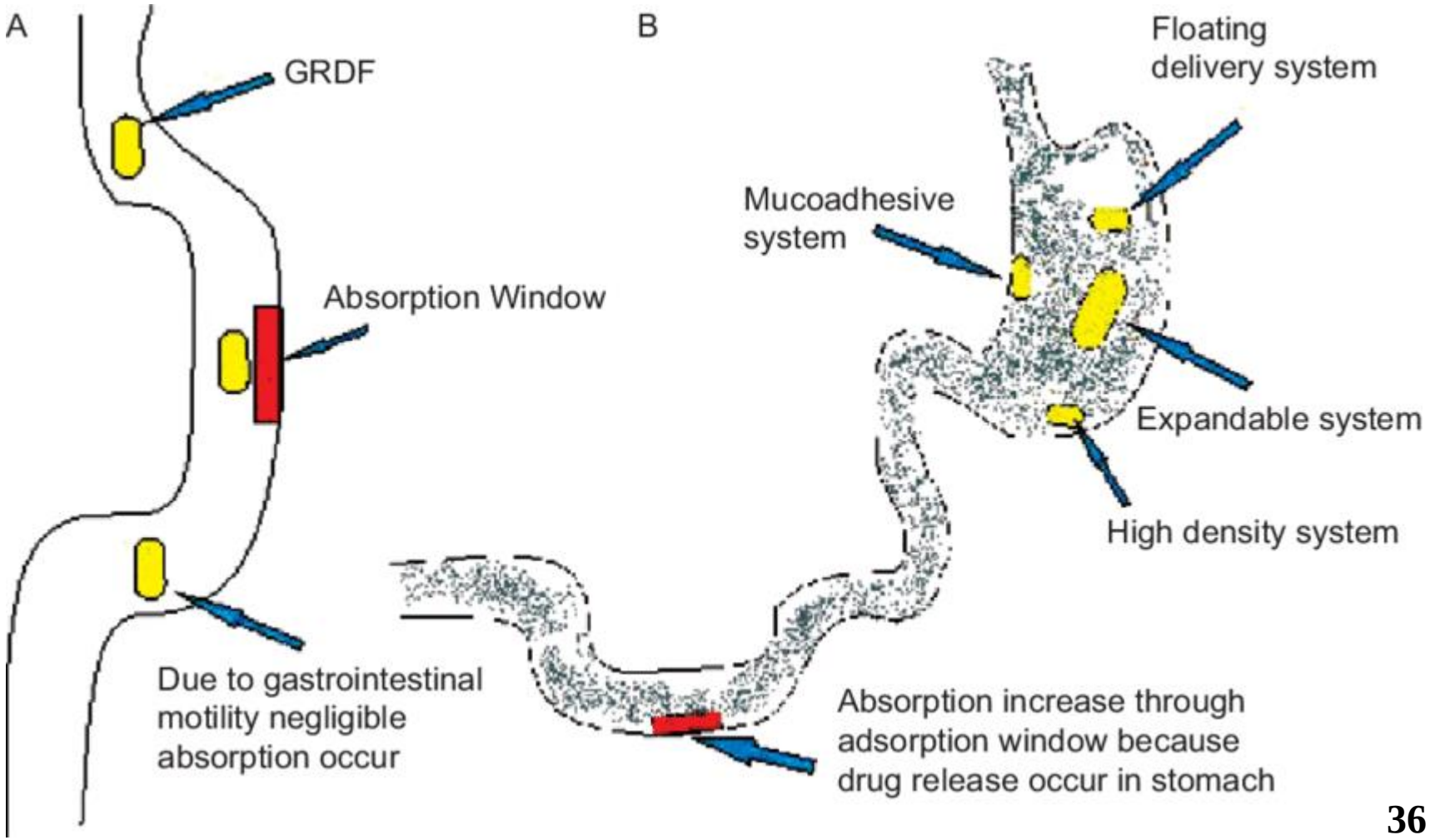
vi. Therapeutic window:

- The drugs with narrow therapeutic index are not suitable for CRDDS.
- If the delivery system failed to control release, it would cause dose dumping and ultimate toxicity

vii. Absorption window:

- The drugs which show absorption from the specific segment in GIT, are a poor candidate for CRDDS.

- Drugs which absorbed throughout the GIT are good candidates for controlled release



viii. Patient physiology:

- The physiological condition of the patient like gastric emptying rate, residential time, and GI diseases influence the release of the drug from the dosage form directly or indirectly.

2. Physiological Factors

i. Dosage size

- For those drugs requiring large conventional doses the volume of controlled 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. So 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 controlled release dosage forms.
- If an oral product has a dose size greater that 500 mg it is a poor candidate for controlled release system. Since addition of sustaining

dose and possibly the sustaining mechanism will, in most cases generates a substantial volume product that is unacceptably large.

ii. Partition coefficient and molecular weight

- 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 lipid in nature, therefore 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 is 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 with values on the order of 10.8 being most common for drugs with molecular weight greater than 500.

- Thus high molecular weight drugs or polymeric drugs should be expected to display very slow release kinetics in controlled release device using diffusion through polymer membrane.
- 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.

$$K=C_o/C_s$$

Where, C_o= Equilibrium concentration in organic phase.

C_s= Equilibrium concentration in aqueous phase.

- 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.

- Drugs with extremely high partition coefficient are very oil soluble and penetrates into various membranes very easily.
- 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

iii. Drug Stability

- The stability of drug in environment to which it is exposed is another physicochemical factor to be considered in design at 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 form. 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 under go extensive Gut–Wall metabolism have decreased the bioavailability.
- When these drugs are administered from a controlled dosage form to achieve better bioavailability at different routes for drug administration should be chosen Eg. Nitroglycerine
- The presence of metabolizing enzymes at the site or pathway can be utilized.

v. Molecular size & 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

$$\text{Log } D = - S_v \log v + K_v = - S_m \log M + K_m$$

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.

vi. Pka (dissociation constant)

- Presenting drug in an unchanged form is advantageous 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 Pka range for acidic drug whose ionization is pH sensitive is around 3.0-7.5 and Pka range for basic drug whose ionization is pH sensitive around 7.0-11.0 are ideal for the optimum positive absorption

vii. Aqueous Solubility:

- Most of the active pharmaceutical moiety (API) are weakly acidic or basic in nature that affect the water solubility of API. Weak water soluble drugs are difficult to design the controlled release formulations. High aqueous solubility drug show burst release followed by a rapid increment in plasma drug concentration. These types of drugs are a good candidate for CRDDS. The pH dependent solubility also creates a problem in formulating CRDDS. BCS class-III & IV drugs are not a suitable candidate for this type of formulations

vii. Drug stability:

- Drugs that are stable in acid/base, enzymatic degradation and other gastric fluids are good candidates for CRDDS. 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.

viii. 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 CRDDS because the protein binding increases the biological half-life. So there is no need to sustain the drug release

Oral Controlled Drug Delivery

1. Diffusion-controlled drug release
    a) Reservoir devices
    b) Matrix devices
2. Dissolution-controlled drug release
    a) Encapsulation dissolution control
    b) Matrix dissolution control
3. Dissolution and diffusion controlled drug release
4. Ion exchange resins-drug complexes
5. Osmotic controlled drug release
6. Altered density formulation
7. Delayed release system
    a) Intestinal release system
    b) Colonic release system

Diffusion Controlled System

- Basically diffusion process shows the movement of drug molecules from a region of a higher concentration to lower concentration.
- 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'

- Diffusion systems are characterized by release rate of drug which is dependent on its diffusion through inert water insoluble membrane barrier.

- There are basically two types of diffusion devices.

a) Reservoir Type:

- In the system, a water insoluble polymeric material encloses a core of drug which controls release rate.
- Drug will partition into the membrane and exchange with the fluid surrounding the particle or tablet.
- Additional drug will enter the polymer, diffuse to the periphery and exchange with the surrounding media.
- The polymers commonly used in such devices are Ethyl cellulose and Poly-vinyl acetate.

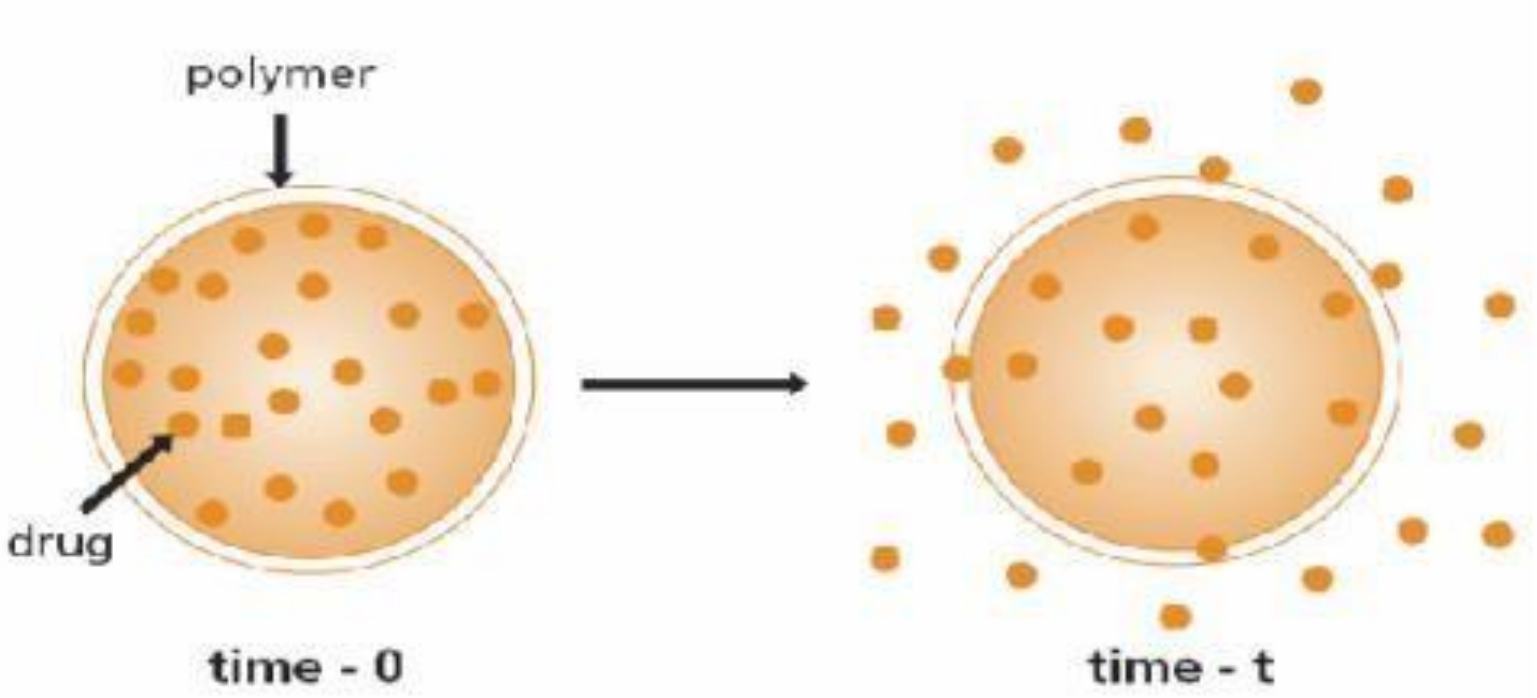


Fig 1: Schematic Representation of Reservoir Diffusion Controlled Drug Delivery Device

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

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

Where, A = Area,

D = Diffusion coefficient,

K = Partition coefficient of the drug between the drug core and the membrane,

ℓ = Diffusion path length and

ΔC= Concentration difference across the membrane.

- **Advantage:** By this system **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.

b) Matrix Type:

- A solid drug is homogenously dispersed in an insoluble matrix and the rate of release of drug is dependent on the rate of drug diffusion and not on the rate of solid dissolution.
- **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.

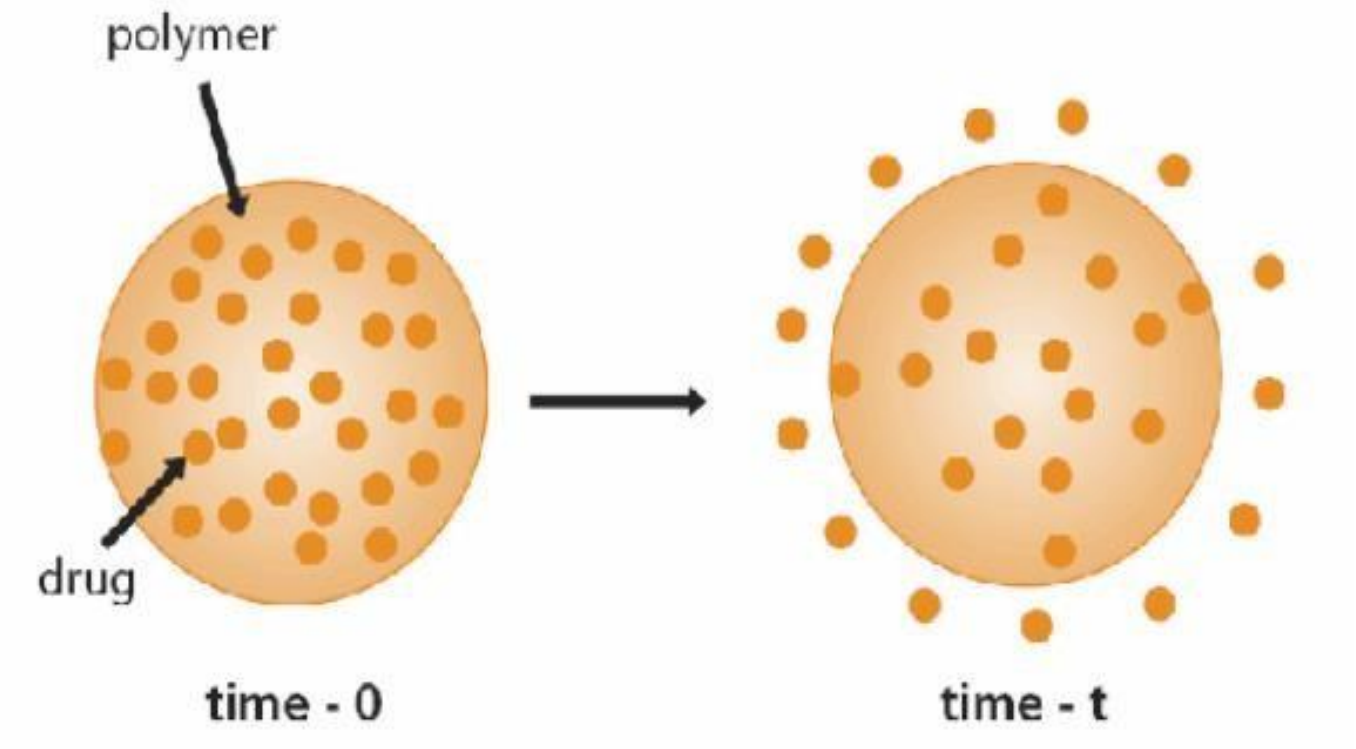


Fig 2: Schematic Representation of Monolithic (matrix) Diffusion Controlled Drug Delivery Device

Diffusion Controlled Drug Release

Reservoir devices

Product	Active ingrediant
Nico 400 capsule	Nicotinic acid
Nitro Bid capsule	Nitroglycerin
Measurin capsule	Acetyl salicylic acid
Bronkodyl capsule	Theophylline

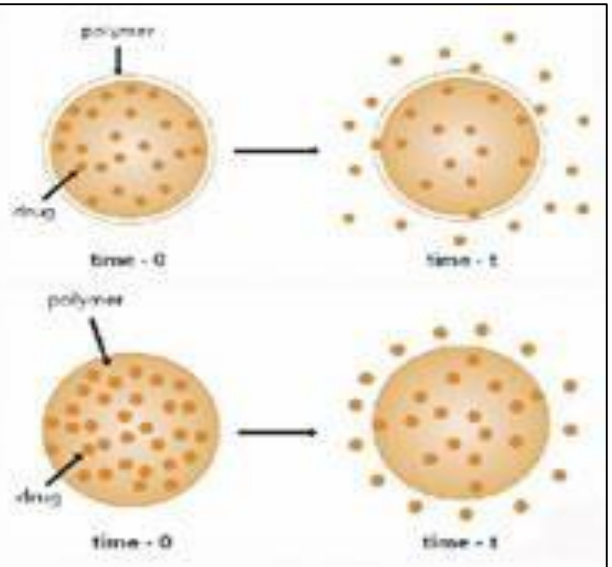
Matrix devices

Product	Active ingrediant
Ferro gradumet tablet	Ferrous fumarate
Procan tablet	Procainamide HCl
Desoxyn tablet	Methamphetamine HCl

Diffusion Controlled Drug Release

Rate Controlling factors

1. Reservoir systems (membrane controlled)
2. Monolithic (matrix) systems



Diffusion Controlled Drug Release

- **Polymeric content in coating**
- **Thickness of coating**
- **Hardness of microcapsule**

- **Diffusion of dissolved drug through the matrix**

Dissolution Controlled Systems

- Drugs having high aqueous solubility and dissolution rate, shows challenge in controlling their dissolution rate.
- Dissolution-controlled release can be obtained 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.
- The solubility of the drug provides source of energy for drug release, which is countered by stagnant-fluid diffusional boundary layer.

- The rate of dissolution (dm/dt) can be approximated by

$$\frac{dm}{dt} = \frac{ADS}{h}$$

Where, S = Aqueous solubility of the drug.

A = Surface area of the dissolving particle or tablet.

D = Diffusivity of the drug and

h = Thickness of the boundary layer.

a) 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.

- Those with the thinnest layers will provide the initial dose.
- The maintenance of drug levels at later times will be achieved from those with thicker coating.

b) Matrix Dissolution Controlled Systems:

- In matrix systems the drug is homogeneously dispersed throughout a rate controlling medium.
- Waxes such as beeswax, carnauba wax, hydrogenated castor oil etc are used which control drug dissolution by controlling rate of dissolution, fluid penetration into the matrix by altering the porosity of tablet, decreasing its wettability or by itself getting dissolved at a slower rate.
- The drug release is often **first order** from such matrices.

- The wax embedded drug is generally prepared by dispersing the drug in molten wax and solidifying and granulating the same.

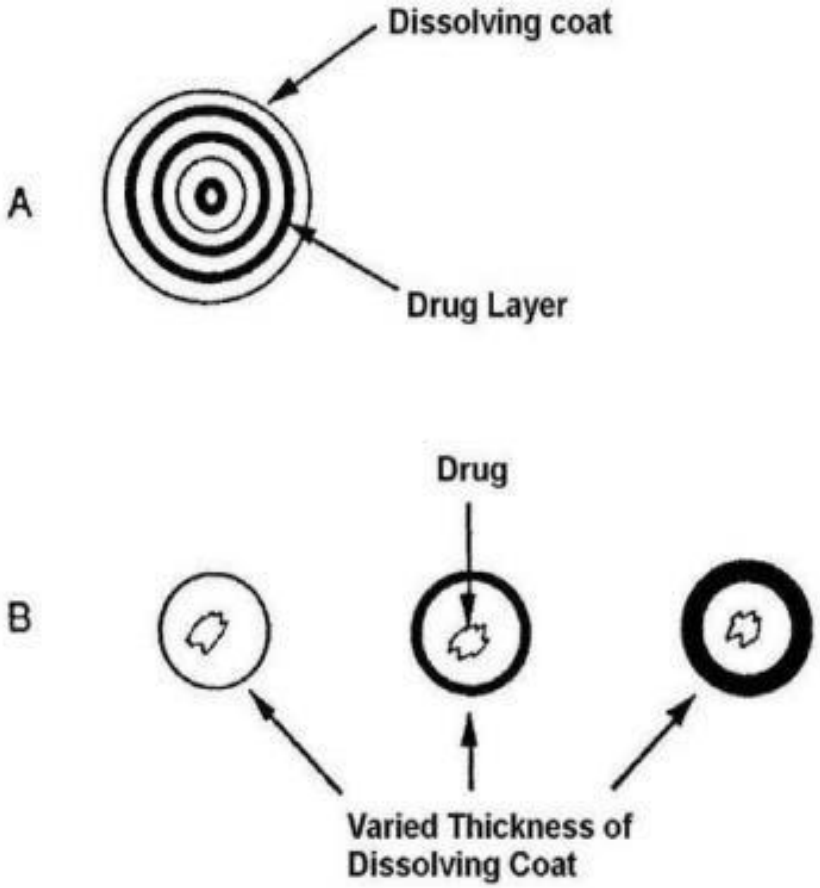


Fig 3: Encapsulation Dissolution Controlled Systems

Dissolution Controlled Drug Release

Encapsulation dissolution control

Product	Active ingrediant
Benzedrine	Amphetamine sulphate
Thorazine	Chlorpheniramine HCl
Diamox	Acetazolamide
Ferro sequels	Ferrous fumarate

Matrix dissolution control

Product	Active ingredient
Quinidex	Quinidine sulphate
Nicobid	Nicotinic acid
Chlor trimeton	Chlorpheniramine maleate

Dissolution Controlled Drug Release

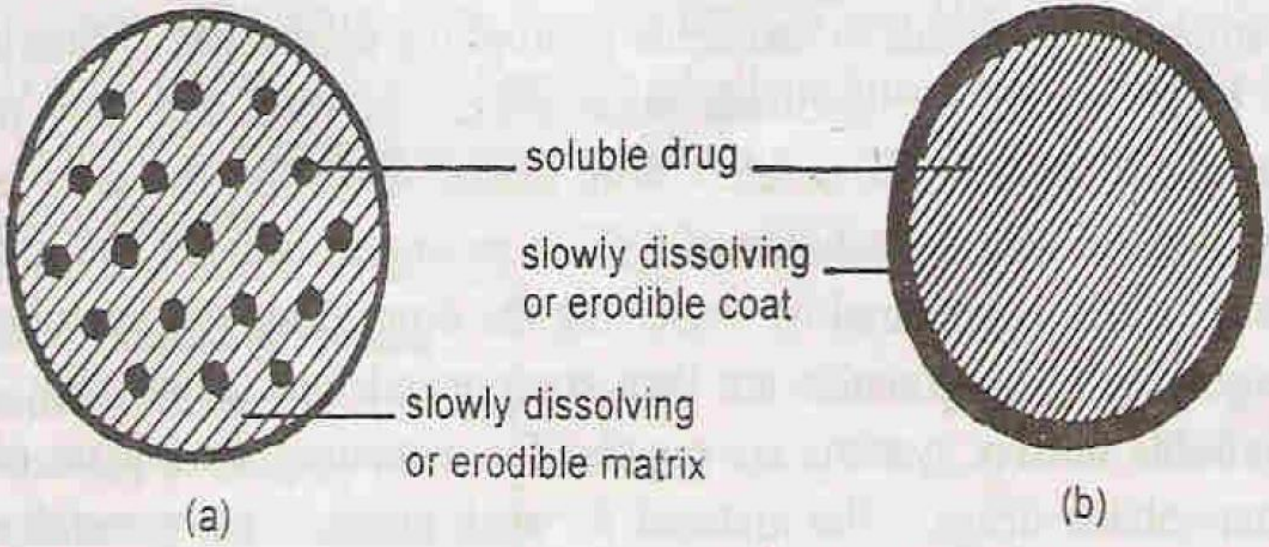


Fig. 15.6 Schematic representation of dissolution controlled release systems —(a) matrix system, and (b) coated/encapsulated system

Rate Controlling factors

- **Dissolution of dispersed drug through medium**
- **Solubility & thickness of coat**

Dissolution and Diffusion Controlled Release Systems

- The drug core is enclosed in a partially soluble membrane.
- Pores are thus created due to dissolution of parts of the membrane which permit entry of aqueous medium into the core and hence drug dissolution and diffusion of dissolved drug out of the system.
- An example of obtaining such a coating is using a mixture of ethyl cellulose with poly vinyl pyrrolidine or methylcellulose

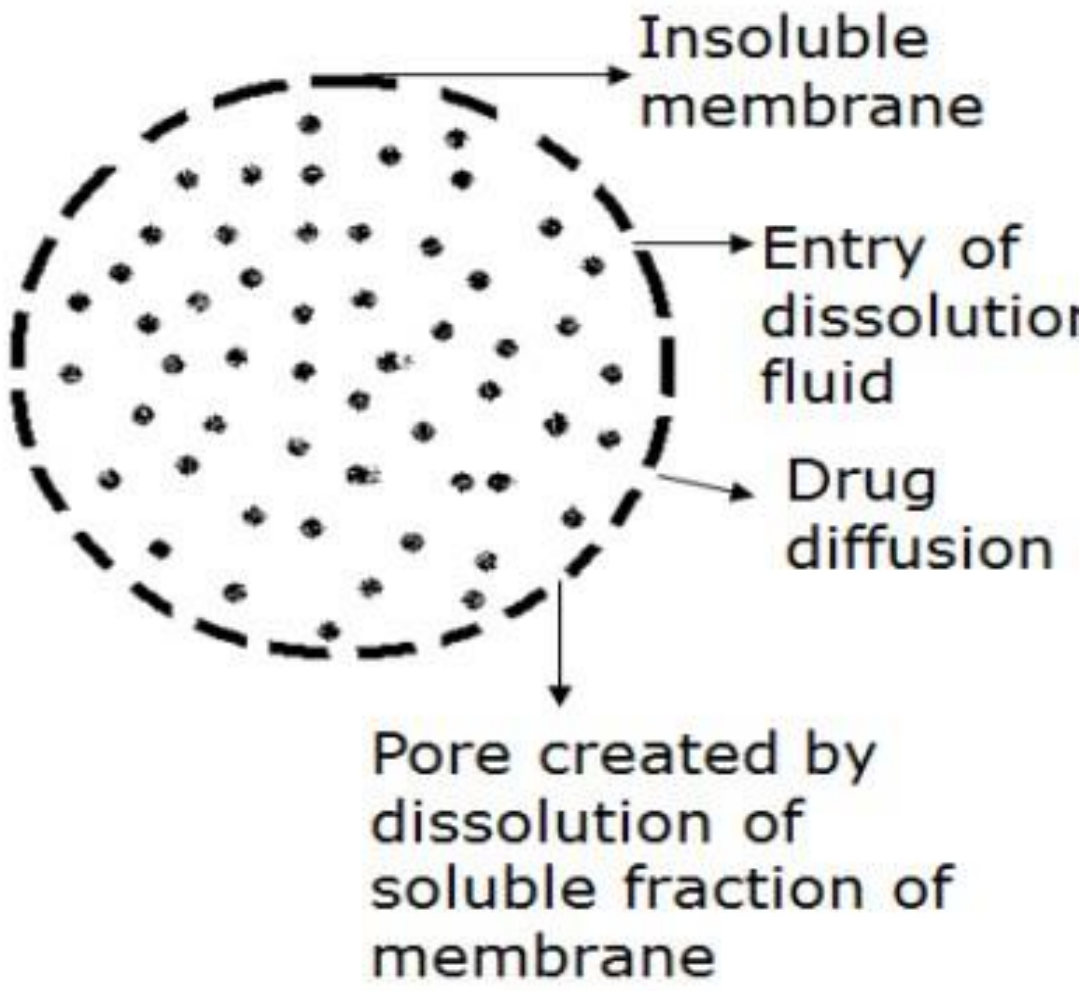
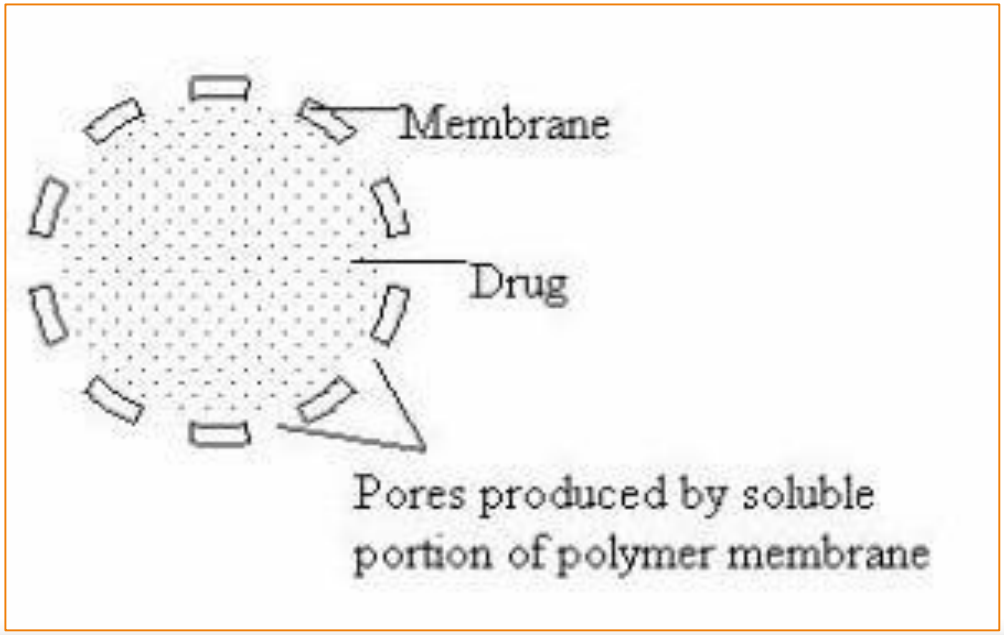


Fig 4: Dissolution and Diffusion Controlled Release System

Dissolution and Diffusion Controlled Drug Release

- Drug core is enclosed with a partially soluble membrane.
- Dissolution of part of membrane allows for diffusion of contained drug through pores in the polymer coat.



Rate Controlling factor

- **Fraction of soluble polymer in the coat**

Water Penetration Controlled Systems

- In water penetration controlled delivery systems, rate control is obtained by the penetration of water into the system. They are

a) Swelling Controlled Systems

- Swelling controlled release systems are initially dry and when placed in the body absorbs water or other body fluids and swells.
- Swelling increases the aqueous solvent content within the formulation as well as the polymer mesh size, enabling the drug to diffuse through the swollen network into the external environment.

b) Osmotically Controlled Release Systems

- These systems are fabricated by encapsulating an osmotic drug core

containing an osmotically active drug (or a combination of an osmotically inactive drug with an osmotically active salt e.g. NaCl) within a semi permeable membrane made from biocompatible polymer, e.g. cellulose acetate.

- A gradient of osmotic pressure is then created, under which the drug solutes are continuously pumped out of tablet through small delivery orifice in tablet coating over a prolonged period of time through the delivery orifice.
- This type of drug system dispenses drug solutes continuously at a zero order rate.
- Release of drug is independent on the environment of the system.

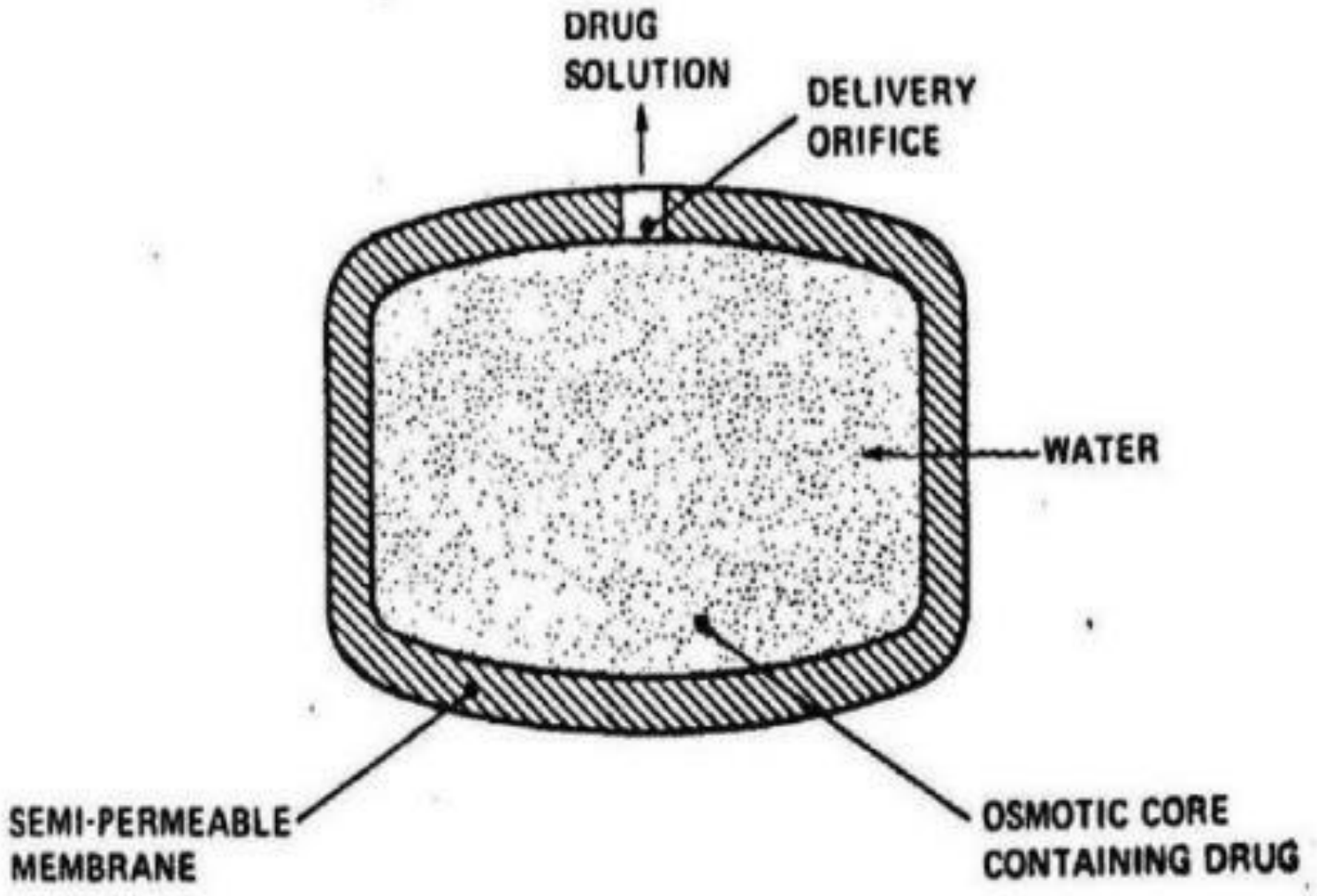


Fig 5: Osmotically Controlled Release System

Osmotic Controlled Drug Release

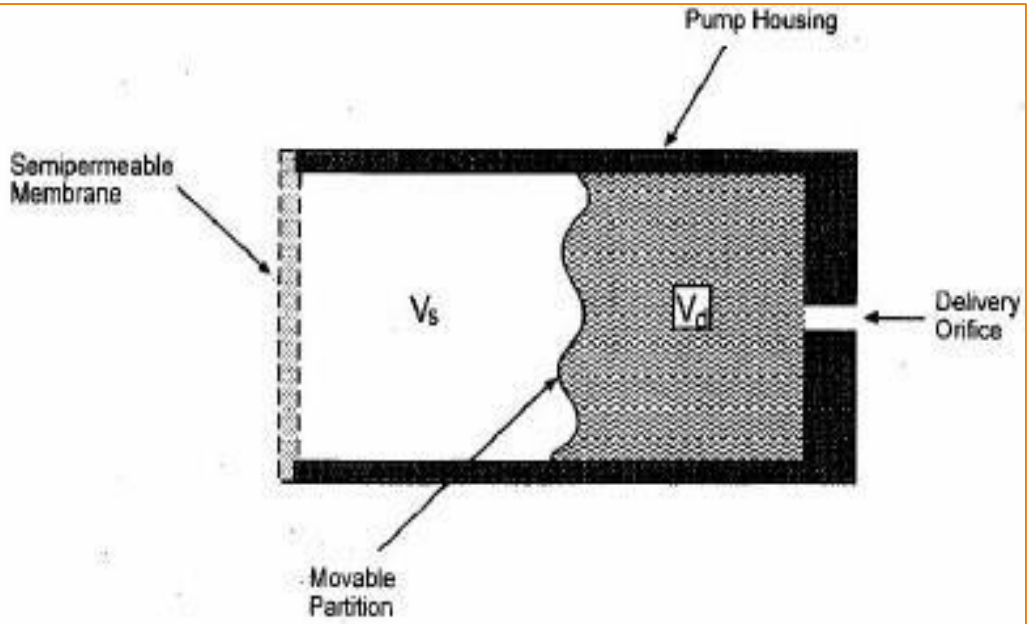


Figure 2 Schematic representation of a generic osmotic pump.

Rate Controlling factor

- **Orifice diameter**
- **Membrane area**
- **Membrane thickness**
- **Membrane permeability**
- **Drug solubility**

Methods using Ion Exchange

- This system is designed to provide the controlled release of an ionic or ionizable drug.
- It is prepared by first absorbing an ionized drug onto the ion-exchange resin granules such as codeine base with Amberlite and then after filtration from the alcoholic medium, 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.

- The drug is then diffuse out of the resin.

Where X^- are ions in the GI tract

- The rate of diffusion control by: the **area of diffusion**, **diffusion path length** and **rigidity of resin**.
- Thus, drug release depends on the ionic environment (pH, electrolyte conc.) and the properties of resin.
- **Advantage:** For those drugs which are highly susceptible to degradation by enzymatic processes since it offers a protective mechanism by temporarily altering the substrate.

- **Limitation:** The release rate is proportional to the conc. of the ions present in the vicinity of administration site. So variable diet, water intake & intestinal contents affects the release rate of drug.
- They are mainly of 2 types - cation exchange and anion exchange resin.

a) Cationic Drugs

- A cationic drug forms a complex with an anionic ion-exchange resin e.g. a resin with a SO_3^- group.
- In the GI tract hydrogen ion (H^+) in the gastrointestinal fluid penetrates the system and activates the release of cationic drug from the drug resin complex.

b) Anionic Drugs

- An anionic drug forms a complex with a cationic ion exchange resin, e.g. a resin with a $[N(CH_3)_3^+]$ group.
- In the GI tract, the Chloride ion (Cl^-) in the gastrointestinal fluid penetrates the system and activates the release of anionic drug from the drug resin complex.

Ion Exchange Resins-Drug Complexes

$$Resin^{+}\text{-}Drug^{-} + X^{-} \longrightarrow Resin^{+}\text{-}X^{-} + Drug^{-}$$

$$Resin^{-}\text{-}Drug^{+} + Y^{+} \longrightarrow Resin^{-}\text{-}Y^{+} + Drug^{+}$$

Product	Active ingredient
Biphetamine capsule	Amphetamine
Tussionex capsule/ tablet	Hydrocodone phenyl toloxamine
Ionamin capsule	Phenteramine

Chemically Controlled Release Systems

- Chemically controlled release systems are the systems that change their chemical structure, when exposed to biological fluid.
- Mostly, biodegradable polymers are designed to degrade as a result of hydrolysis of the polymer chains into biologically safe and progressively smaller moieties.
- It is of two types and they are **Erodible systems** and **Pendent chain system**

(i) Erodible Systems:

- In erodible systems, the mechanism of drug release occurs by erosion.
- Erosion may be two types and they are

- **Bulk Erosion process:** Polymer degradation may occur through bulk hydrolysis

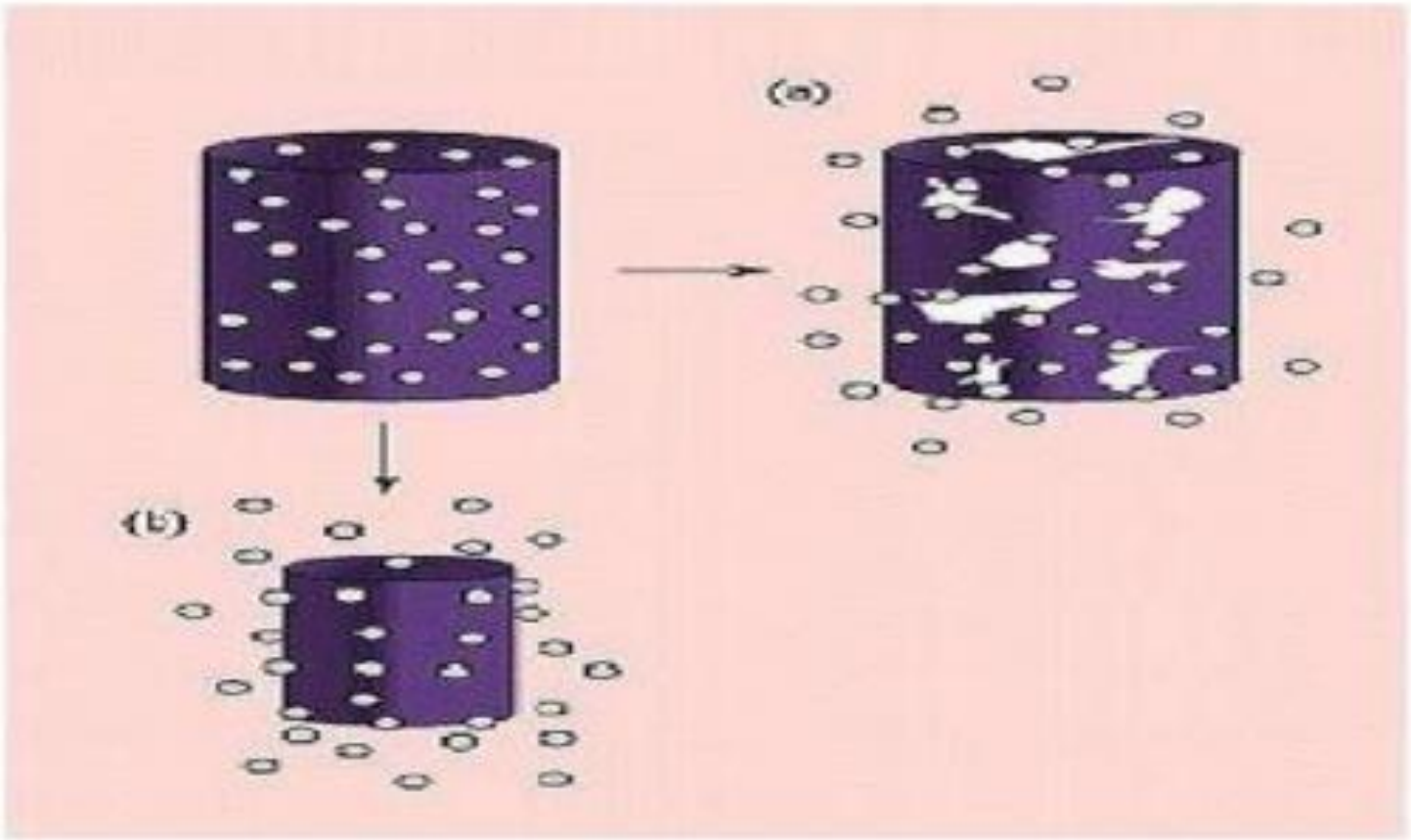
✓ When the polymer is exposed to water, hydrolysis occurs

✓ Hydrolysis degrades the large polymers into smaller biocompatible compounds

✓ These small compound diffuse out of the matrix through the voids caused by swelling

✓ Loss of the small compounds accelerates the formation of voids thus the exit of drug molecules

✓ e.g. poly lactide, polyglycolic acid



"a" indicates bulk erosion
"b" indicates surface erosion

Fig 6: Bulk Erosion and Surface Erosion

- **Surface Erosion process:** Polymers like polyorthoesters and polyanhydrides etc degradation occurs only at the surface of the polymer, resulting in a release rate that is proportional to the surface area of the delivery system.

✓ When the polymer is exposed to water hydrolysis occurs

✓ Hydrolysis degrades the large polymers into smaller biocompatible compounds

✓ These small compound diffuse from the interface of the polymer

✓ Loss of the small compounds leads to drug loss

✓ Note these polymers do not swell.

✓ e.g polyanhydrides

(ii) Pendent Chain System

- Pendent chain systems consist of linear homo or copolymers with the drug attached to the backbone chains.
- The drug is released from the polymer by hydrolysis or enzymatic degradation of the linkages.
- **Zero order** can be obtained and the cleavage of the drug is the rate controlling mechanism.
- Example for polymers used in pendent chain systems like n-(2-hydroxy propyl)methacrylamide etc.

pH– Independent Formulations

- The gastrointestinal tract present some unusual features for the oral route of drug administration with relatively brief transit time through the gastrointestinal tract, which control the length of prolongation, further the chemical environment throughout the length of gastrointestinal tract is limitation on dosage form design.
- Since most drugs are either weak acids or weak bases, the release from controlled release formulations is pH dependent.
- However, buffers such as salts of amino acids, citric acid, phthalic acid phosphoric acid or tartaric acid can be added to formulation, to help to maintain a constant pH thereby rendering pH independent drug release.

- A buffered controlled release formulation is prepared by mixing a basic or acidic drug with one or more buffering agent, granulating with appropriate pharmaceutical excipients and coating with gastrointestinal fluid permeable film forming polymer.
- When gastrointestinal fluid permeates through the membrane, the buffering agents adjust the fluid inside to suitable constant pH thereby rendering a constant rate of drug.

Hydrogels

- Hydrogels are water swollen three dimensional structures composed of primarily hydrophilic polymers.
- They are insoluble because of chemical or physical cross-links.
- The physical cross-links include crystallites, entanglements or weak associations like hydrogen bonds or vander waals forces.
- These cross-links provide the physical integrity and network structure.
- Hydrogels provide desirable protection of labile drugs, peptides and proteins.

Altered Density Formulations

- It is reasonable to expect that unless a delivery system remains in the vicinity of the absorption site until most, if not all of it would have limited utility.
- Therefore, several approaches have been developed to prolong the residence time of drug delivery system in the gastrointestinal tract like High density approach and Low density approach.

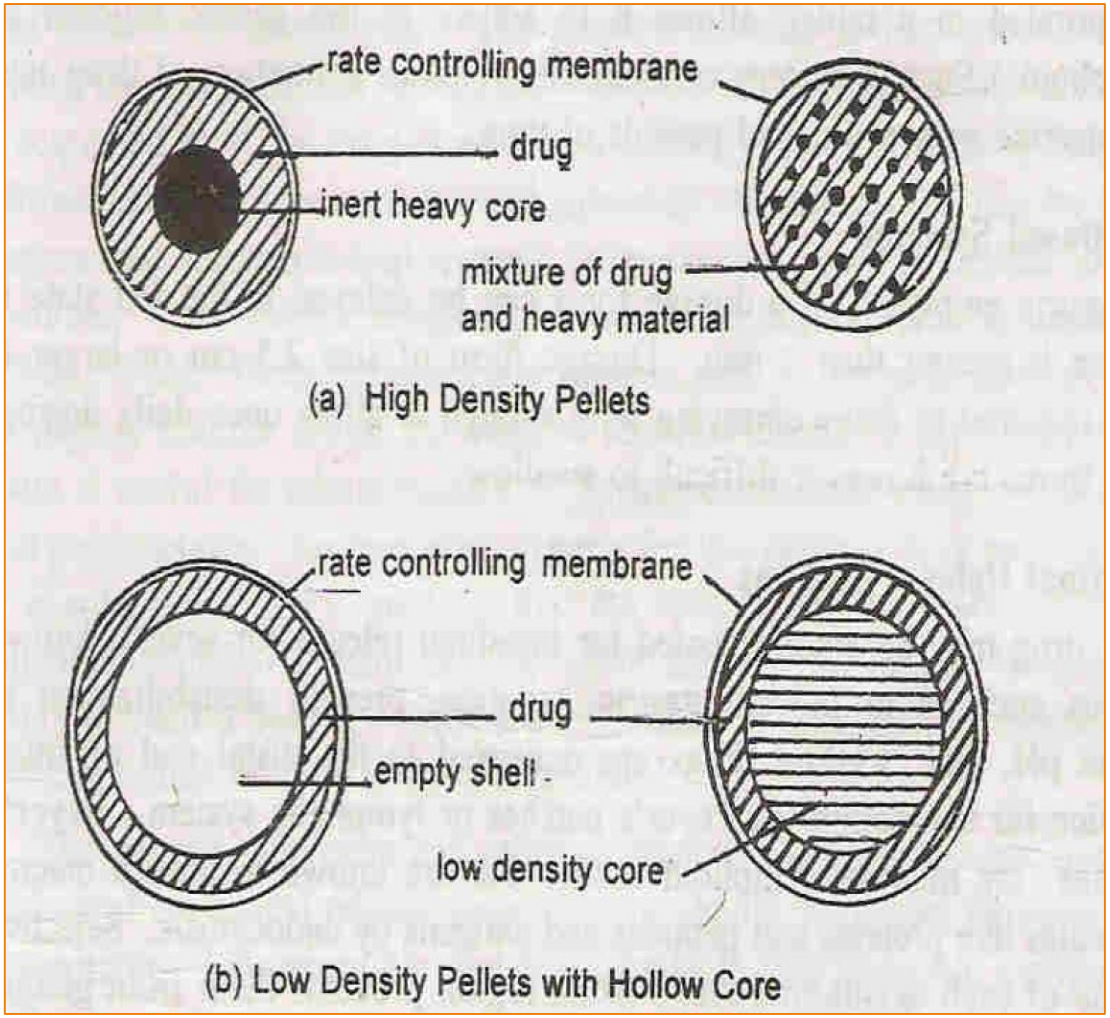
a) High Density Approach

- In this approach the density of the pellets must exceed that of normal stomach content and should therefore be at least 1-4 gm/cm^3.

b) Low Density Approach

- Globular shells which have an apparent density lower than that of gastric fluid can be used as a carrier of drug for sustained release purpose.

Altered Density



- Drug can be mixed with heavy inert material.
- The weighted pellet can be covered with a diffusion controlled membrane.

- Globular shells can be used as a carrier.
- The coating of mixture of drug and polymers is given to the undercoat of the shell.

Evaluation of CR Tablets

- Appearance
- Friability
- Hardness
- Thickness
- Weight variation
- Tablet density
- Drug content
- *In vitro* drug release
- *In vivo* study
- Stability study
- Bio adhesion or mucoadhesion test
- *IVIVC*
- Floating capability
- Kinetic modelling

Evaluation of CR Pellets

- Friability
- Weight variation
- Drug content
- Floating capability
- *In vitro* drug release
- Kinetic modelling
- *In vivo* study
- Expiry date determination and stability studies
- Bio adhesion or mucoadhesion test
- IVIVC

Evaluation of CR Capsules

- Weight variation
- Drug content
- *In vivo* study
- *In vitro* drug release
- Stability study

Evaluation

- Drug release is evaluated based on drug dissolution from dosage form at different time intervals.
- Specified in monograph.
- Various test apparatus and procedures – USP, Chapter <724>.

Two types

1. *In vitro* evaluation
2. *In vivo* evaluation

***In vitro* evaluation:**

- Acquire guidelines for formulation of dosage form during development stage before clinical trials.
- Kinetics or rate of drug release from the dosage form can be measured in simulated gastric and intestinal fluids.
- Necessary to ensure batch to batch uniformity in production of a proven dosage form.
- Obtain *in vitro/in vivo* correlation

- *In vitro* quality control tests include:

1. Rotating basket (apparatus 1)
2. Paddle (apparatus 2)
3. Modified disintegration testing apparatus (apparatus 3)

- At a specified time intervals measurement of drug is made in simulated gastric fluid / intestinal fluid.
- 2 hrs in gastric fluid and 6 hrs in intestinal fluid

Data is analysed to see

- Dose dumping *i.e.*, Maintenance dose is released before the period is completed.
- Dose that is unavailable (is not released in G.I.T).
- Release of loading dose.
- Unit to unit variation, predictability of release properties.
- Sensitivity of the drug to the process variables
- Composition of the simulated fluid
- Rate of agitation
- Stability of the formulation
- Ultimately does the observed profile fit expectations.

Other apparatus specific for CR evaluations

- Rotating bottle
- Stationary basket / rotating filter
- Sartorius absorption and solubility simulator
- Column-type flow through assembly

1. **Rotating bottle method:**

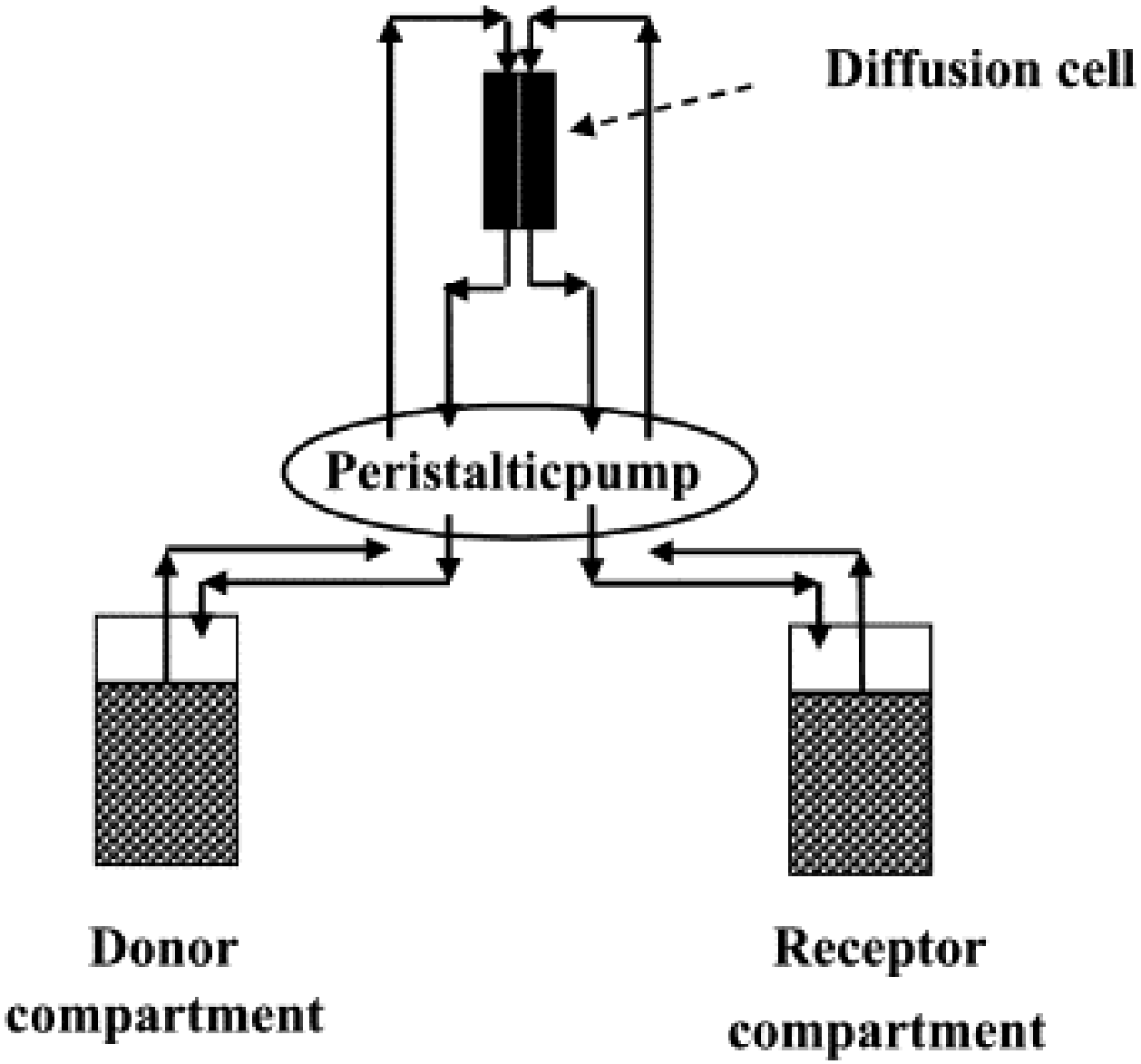
- Samples are tested in 90 ml bottles containing 60 ml of fluid which are rotated end over end in a 37º C bath at 40 rpm.

2. **Sartorius device**

- Includes an artificial lipid membrane which separates the dissolution chamber from simulated plasma compartment in which the drug concentration are measured or dialysis membrane may be used.

Advantages:

- Measure release profile of disintegrating dosage units such as powder materials, suspensions, granular materials, if permeability is properly defined.



Sartorius device

3. Column flow through apparatus

- Drug is confined to a relatively small chamber in a highly permeable membrane filters.
- Dissolution fluid might be re-circulated continuously from the reservoir allowing measurement of cumulative release profile.
- Duration of testing 6-12 h.

Media used:

- Simulated gastric fluid or pH 1.2
- Simulated intestinal fluid pH 7.2
- Temperature 37 ºC
- If required bile salts, pancreatin and pepsin can be added.

Example

Specifications for Aspirin Extended-release Tablets

Time (hr)	Amount Dissolved
1	Between 15% and 40%
2	Between 25% and 60%
4	Between 35% and 75%
8	Not less than 70 %

In vivo evaluation

- A clinical trial, testing the availability of the drug being used in the form prepared by noting its effect versus time.
- Preliminary *in vivo* testing of formulation carried out in a limited number of carefully selected subjects based on

✓ Similar body built, size, occupation, diet, activity and gender.

✓ A single dose administered and effect measured over time (24 h)

✓ Test may or may not be blind and cross over design.

Application of CRDDS

Application of CRDDS in following drug delivery system

- Oral controlled drug delivery system
- Gastro Retentive DDS
- Ocular drug delivery system
- Transdermal drug delivery system
- Intestinal drug delivery system
- Colonic drug delivery system

Marketed product

Tablets		
Composition	**Product name**	**Manufacturer**
Carbamazepine	Zen retard	Intas
Diclofenac sodium	Dic-SR	Deep pharma limited
Diclofenac sodium	Nac-SR	Systopic
Diclofenac sodium	Voveran-SR	Ciba- Geigy
Nifedipine	Depine retard	Cadila health care
Theophylline	Theo PA	Welcome
Capsules		
Diazepam	Elcoin	Ranbaxy
Diclofenac sodium	Diclotal CR	Blue cross
Indomethacin	Indoflam TR	Recon
Nitroglycerine	Angispan	Lyka
Transdermal		
Nitroglycerine	Nitroderm TTS	Ciba-Geigy
Nicotine	Nicotine patch	Ciba-Geigy

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Thank You