Sustain /Controlled / Modified Release Oral Drug Delivery System

- **Controlled drug delivery is one which delivers the drug at a predetermined rate, locally or systemically, for a specified period of time.**

- **Continuous oral delivery of drugs at predictable & reproducible kinetics for predetermined period throughout the course of GIT.**

- To modify the drug release pattern by either increasing or decreasing its rate.

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

Potential Problems Of Conventional Dosage Forms;

1. Lack of temporal delivery

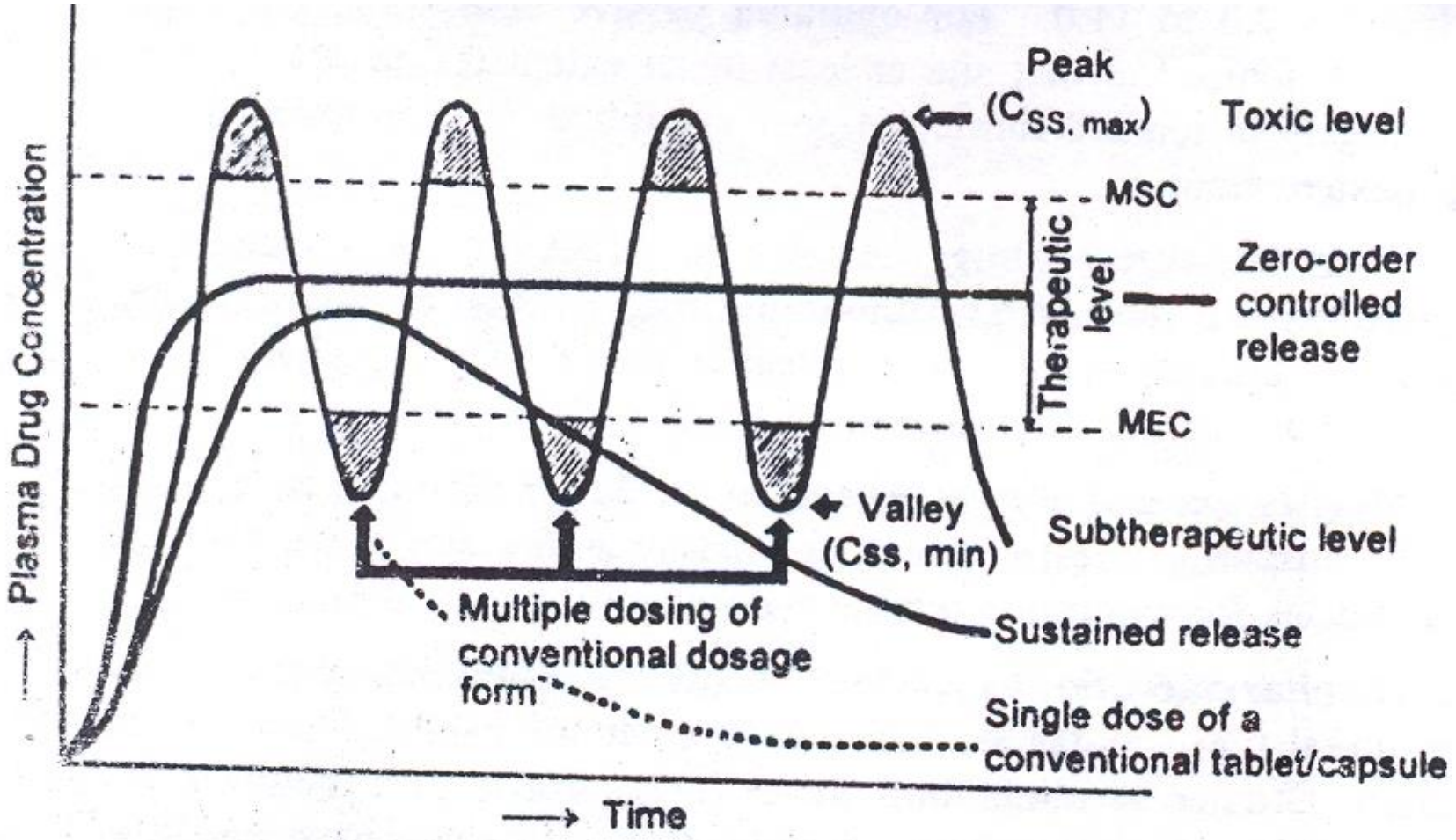
2. Repeated dosage after specific interval. If the interval is not proper there will be large peaks and valleys

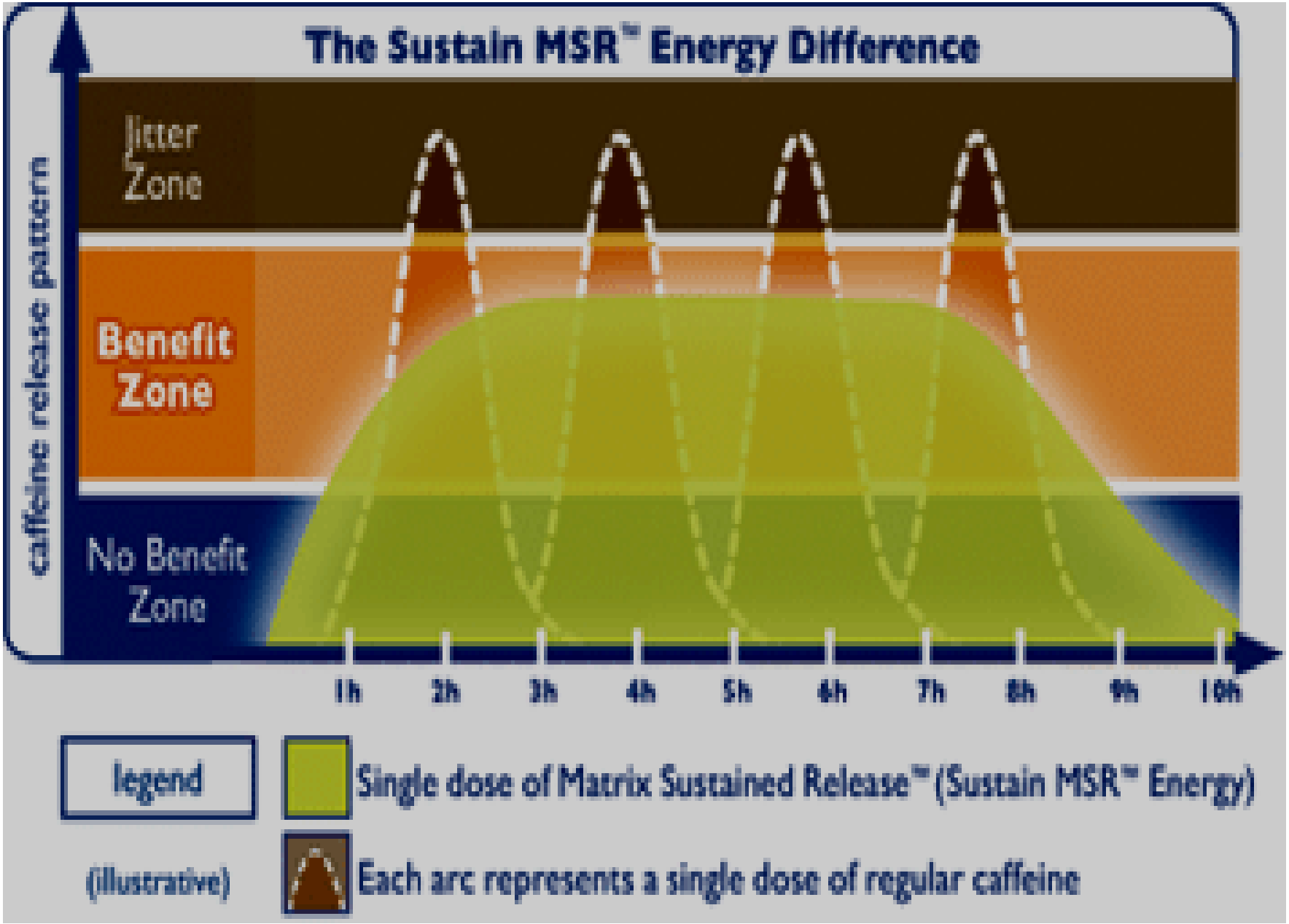
3. Patient non compliance

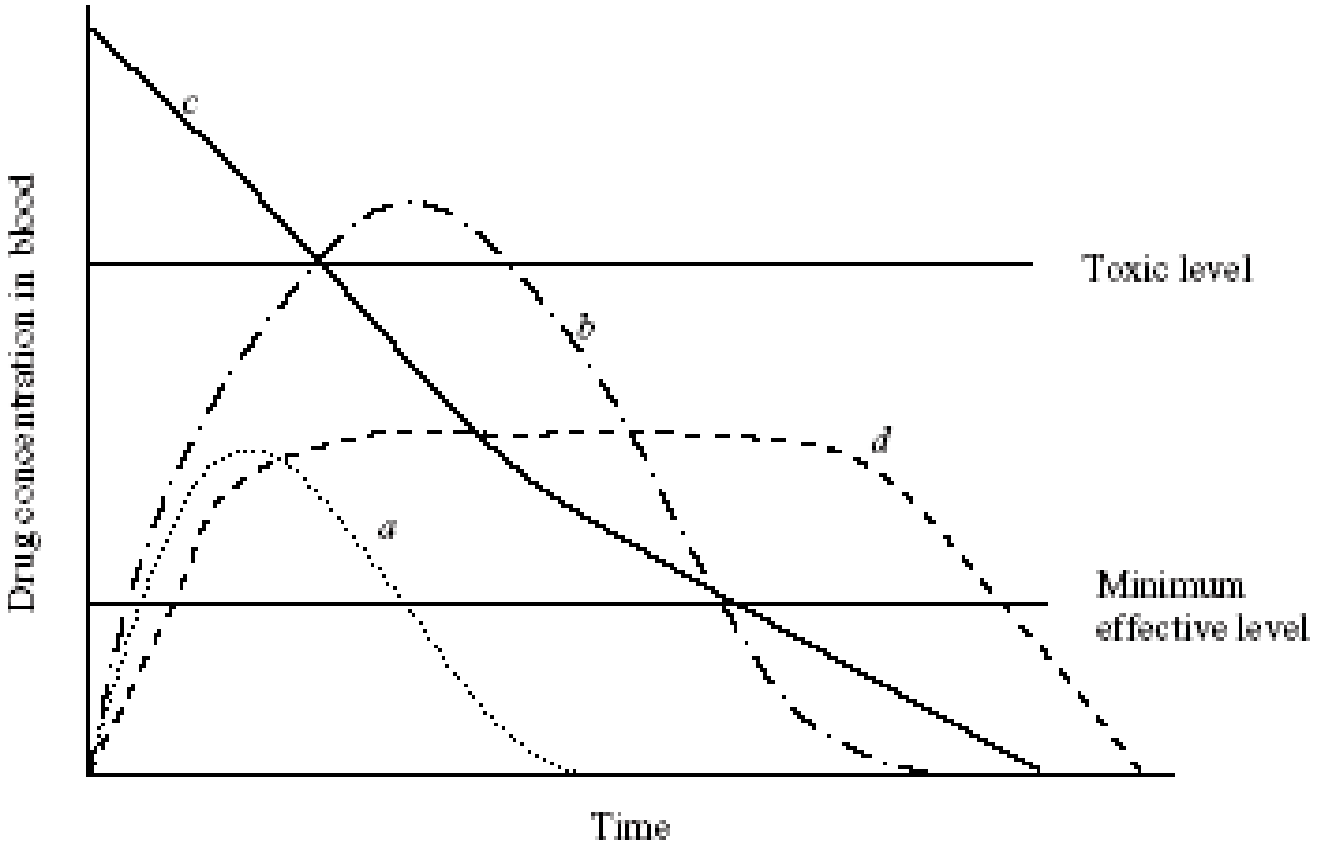
4. Increased untoward effects

Such like problems of conventional dosage form stimulates the researchers to develop modified release dosage form.

Plasma concentration time profile




The Sustain MSR™ Energy Difference
caffeine release pattern
Jitter Zone
Benefit Zone
No Benefit Zone
1h
2h
3h
4h
5h
6h
7h
8h
9h
10h
legend
Single dose of Matrix Sustained Release™ (Sustain MSR™ Energy)
(illustrative)
Each arc represents a single dose of regular caffeine



Theoretical plasma concentration after administration of various dosage forms: (*a*) standard oral dose; (*b*) oral overdose; (*c*) IV injection; (*d*) controlled - release system.

Challenges in Oral Drug Delivery

- **Development of drug delivery system**
  Delivering a drug at therapeutically effective rate to desirable site.
- **Modulation of GI transit time**
  Transportation of drug to target site.
- **Minimization of first pass elimination**

Advantages

- Total dose is low.
- Reduced GI side effects.
- Reduced dosing frequency.
- Better patient acceptance and compliance.
- Less fluctuation at plasma drug levels.
- More uniform drug effect
- Improved efficacy/safety ratio.

Disadvantages

- Dose dumping.
- Reduced potential for accurate dose adjustment.
- Need of additional patient education.
- Stability problem.

Classification:

1. Delayed Release
2. Extended Release
3. Site Specific Targeting
4. Receptor Targeting
5. Fast Dissolve Drug Delivery System (Flash)

Delayed Release:

Example include enteric coated tablets , where a timed release is achieved by barrier coating repeated action tablets or spansules.

Extended Release:

These include any dosage form that maintains therapeutic blood or tissue level of drug for prolong time.

Site Specific Targeting:

In such system the drug delivery is targeted adjacent to or in the diseased organ or tissue.

Receptor Targeting

In such system the target is a particular receptor with in an organ or tissue.

Fast Dissolve Drug Delivery System (Flash)

It is type of solid dosage form that dissolves or disintegrate in the oral cavity without the help of water or chewing. Fast dissolution is achieved by forming loose network (Zydis, Eli Lilly), or by effervescent agent (Oraslav, Cima) or with mixture of disintegrating agent and swelling (Flash Tab, Prographarm) agents.

Design and Fabrication of Oral Controlled Release Systems:

The majority of oral controlled release systems depend;

Dissolution & Diffusion,

or

a combination of both mechanisms,

to generate slow release of drugs into gastrointestinal milieu.

The following techniques are employed in the design and fabrication of oral sustained release dosage forms.

1) Continuous Release Systems

A. Dissolution Controlled Release Systems

i) Matrix Dissolution Controlled Systems

ii) Encapsulation/Coating Dissolution Controlled Systems (Reservoir Devices)

B. Diffusion Controlled Release Systems

i) Matrix Diffusion Controlled Systems

ii) Reservoir Devices or Laminated Matrix Devices

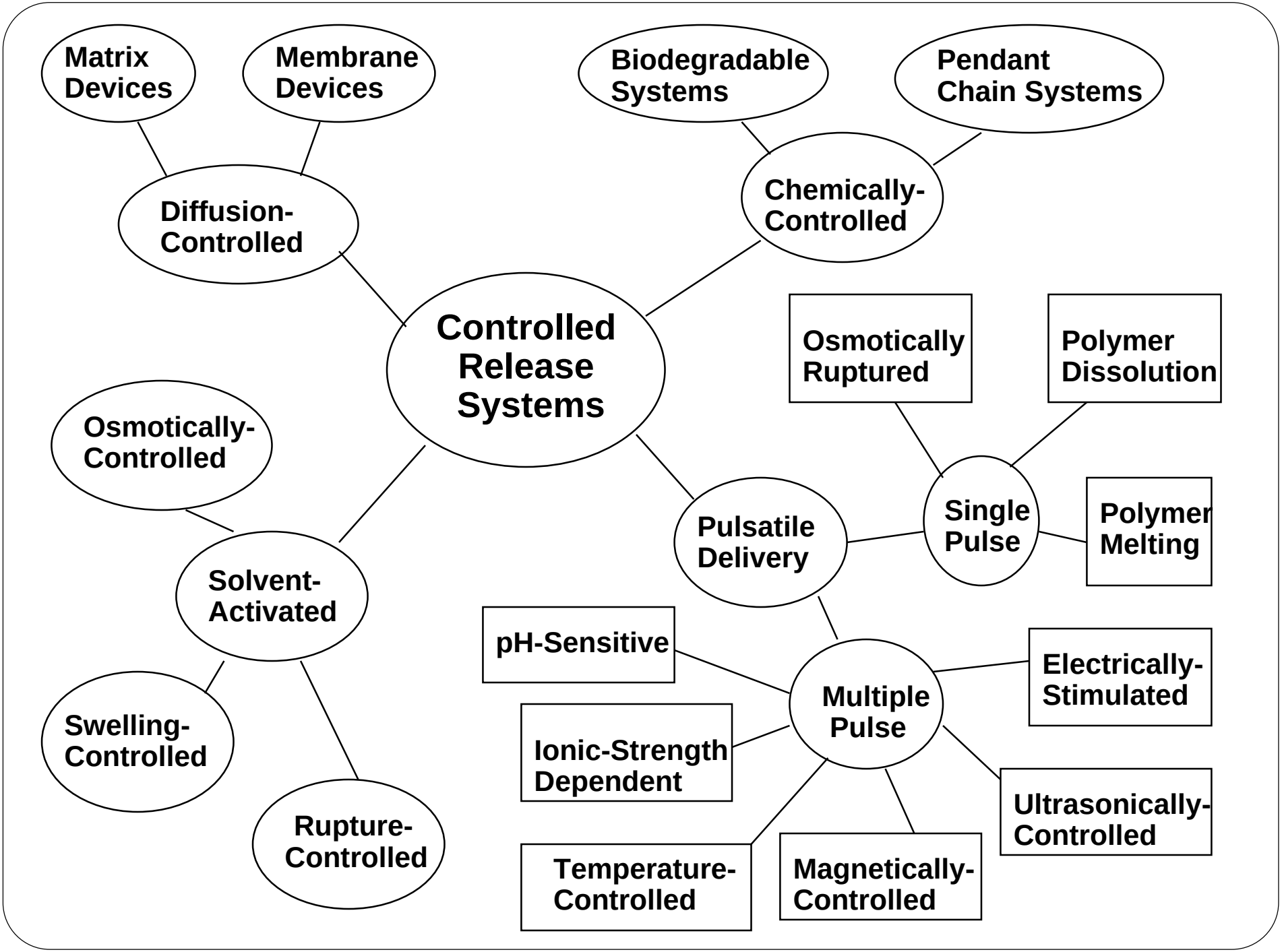
C. Dissolution and Diffusion Controlled Release Systems

D. Ion-Exchange Resin-Drug Complexes

E. pH Dependent Formulations

F. Osmotic Pressure Controlled Systems

G. Hydrodynamic Pressure Controlled Systems


Controlled Release Systems
Diffusion-Controlled
Matrix Devices
Membrane Devices
Chemically-Controlled
Biodegradable Systems
Pendant Chain Systems
Osmotically-Controlled
Solvent-Activated
Swelling-Controlled
Rupture-Controlled
Pulsatile Delivery
Single Pulse
Osmotically Ruptured
Polymer Dissolution
Polymer Melting
Multiple Pulse
pH-Sensitive
Ionic-Strength Dependent
Temperature-Controlled
Magnetically-Controlled
Electrically-Stimulated
Ultrasonically-Controlled

Mechanism aspects of Oral drug delivery formulation.

1. Dissolution : a. Matrix b. Encapsulation
2. Diffusion : a. Matrix b. Reservoir
3. Combination of both dissolution & diffusion.
4. Osmotic Pressure Controlled System.
5. Chemically Controlled Release Systems
   a. Erodible Systems
   b. Drugs Covalently linked with polymers
6. Ion-exchange resin controlled released systems
7. Hydrogels

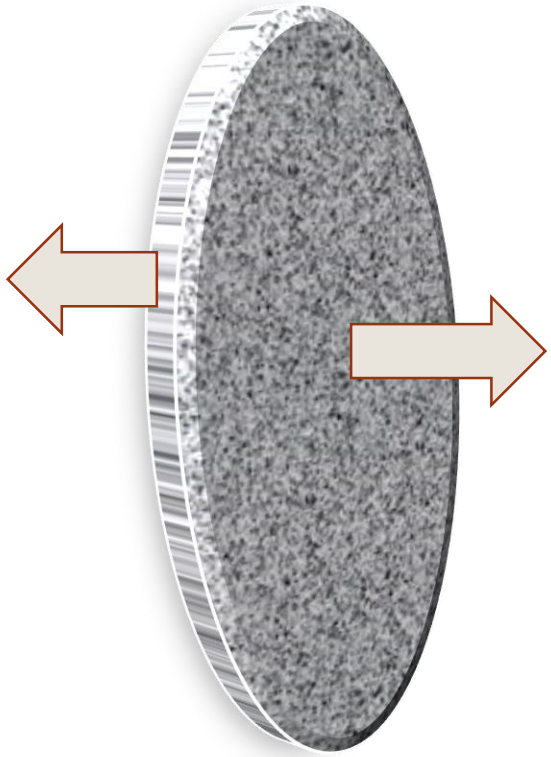
Matrix Type

Also called as Monolith dissolution controlled system since the drug is homogenously dispersed throughout a rate controlling medium waxes (beeswax, carnubawax, hydrogenated caster oil etc) which control drug dissolution by controlling the rate of dissolution;

- Altering porosity of tablet.
- Decreasing its wettebility.
- Dissolving at slower rate.
- Exhibit First order drug release.

Drug release determined by dissolution rate of polymer.

SDM

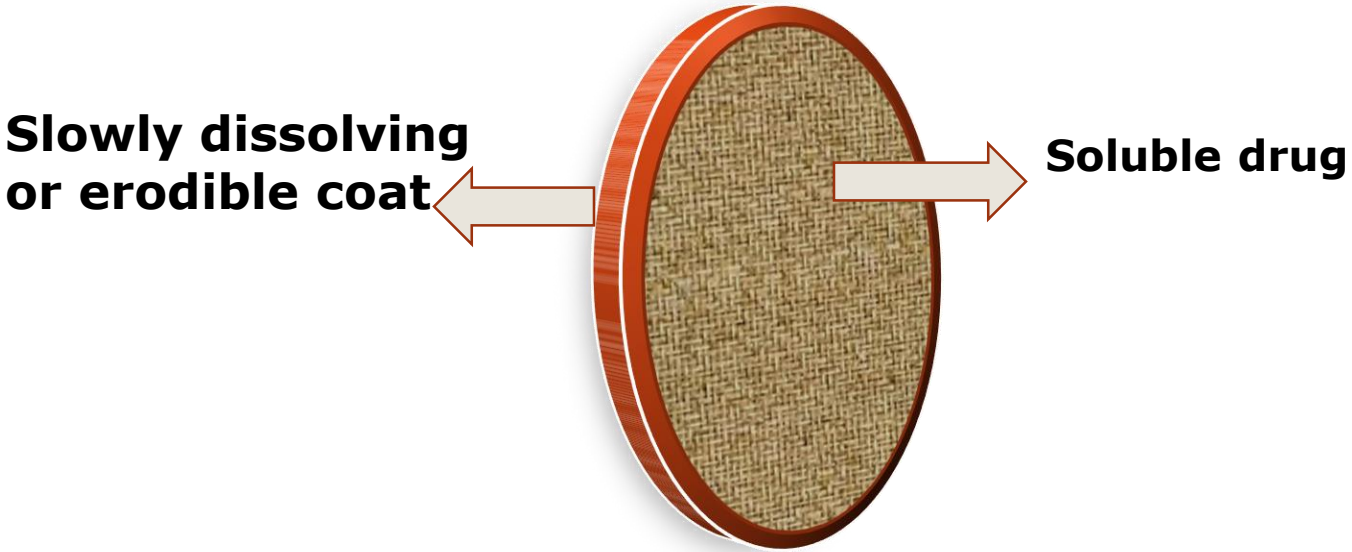


Soluble API mixed with SDM

Encapsulation

Called as Coating Dissolution Controlled System since the drug is encapsulated, with slowly dissolving material like Cellulose, PEG, PMA (polymethylacrylates) & waxes.

Dissolution rate of coat depends upon stability & thickness of coating.



Matrix Diffusion Types

- **Rigid Matrix Diffusion**

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

- **Swellable Matrix Diffusion**

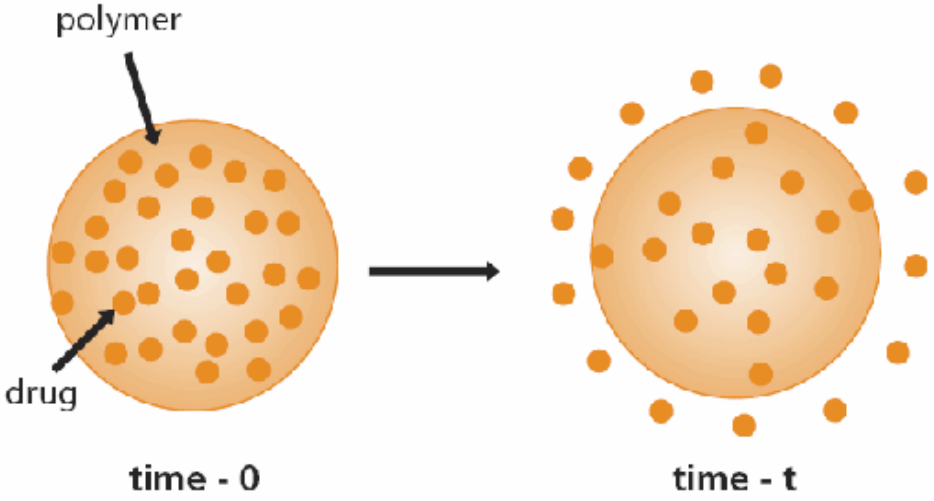
Also called as Glassy hydrogels. Popular for sustaining the release of highly water soluble drugs.

Materials used are hydrophilic gums.

Examples :

Natural:	**Guar gum, Tragacanth.**
Semi-synthetic:	**HPMC, CMC, Xanthum gum.**
Synthetic :	**Polyacrilamides.**

Matrix system



Rate controlling step:

Diffusion of dissolved drug in matrix.

Matrix Diffusion Types

Drug and excipients are mixed with polymers such as Hydroxypropyl methylcellulose (HPMC) and Hydroxypropyl cellulose (HPC) then compressed in to tablet by conventional way.

Release from the tablet takes place by combination of :

- water diffuses into the tablet, swells the polymer and dissolves the drug.
- drug may diffuse out to be absorbed.

Reservoir System

Also called as Laminated matrix device.

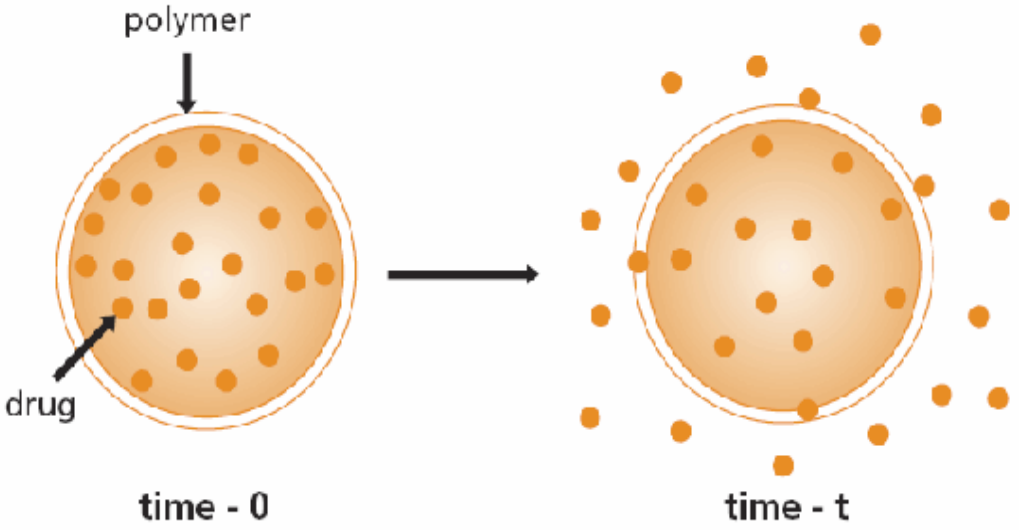
Hollow system containing an inner core surrounded in water insoluble membrane of polymer (HPC, ethyl cellulose & polyvinyl acetate).

Polymer can be applied by coating or micro encapsulation.

Rate controlling mechanism:

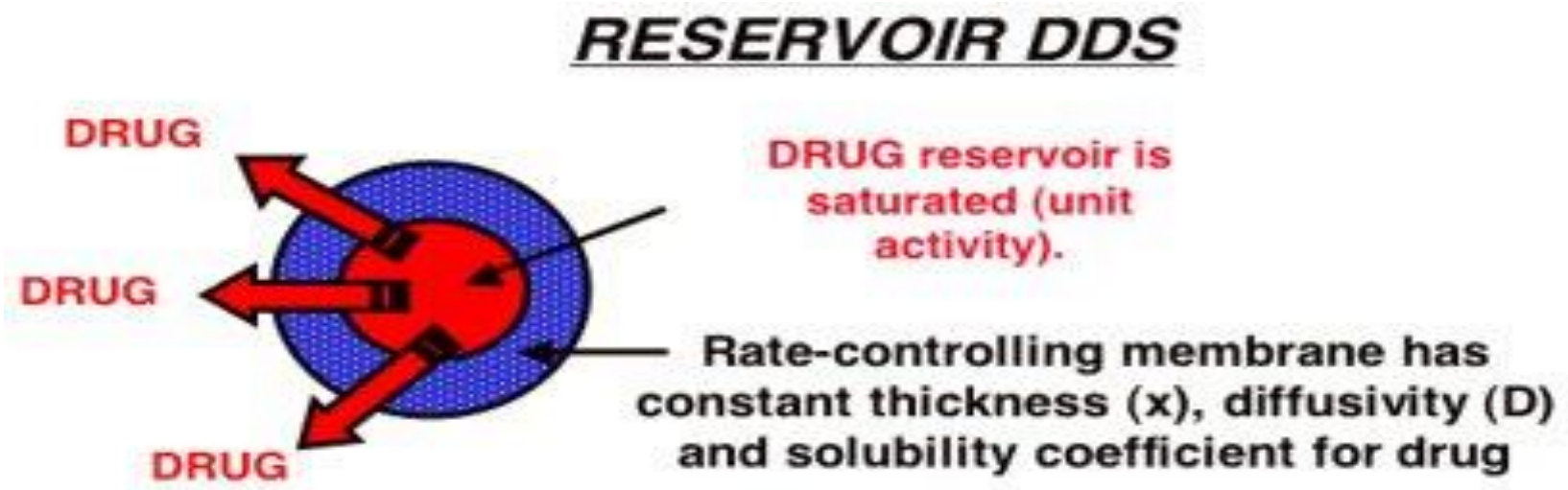
Partitioning into membrane with subsequent release into surrounding fluid by diffusion.

Reservoir System



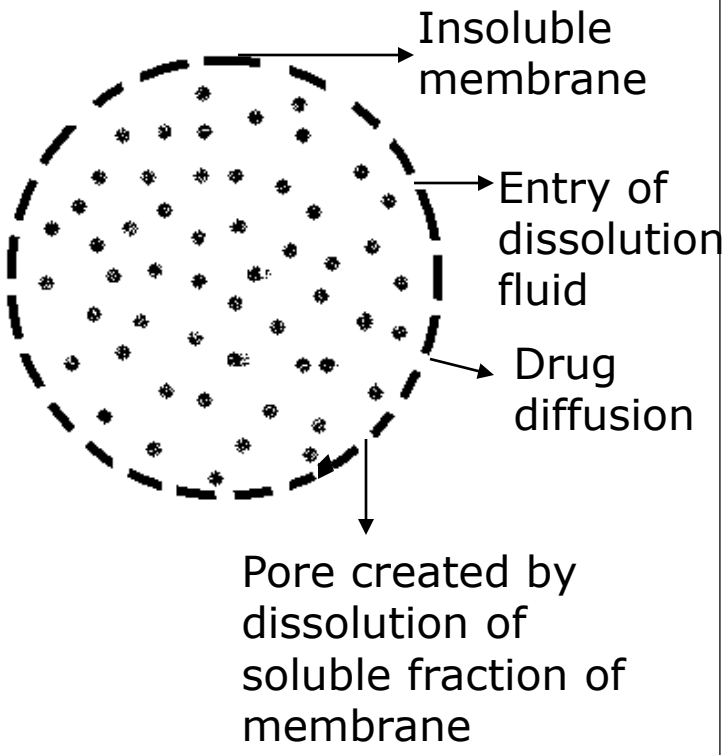
Rate controlling steps :

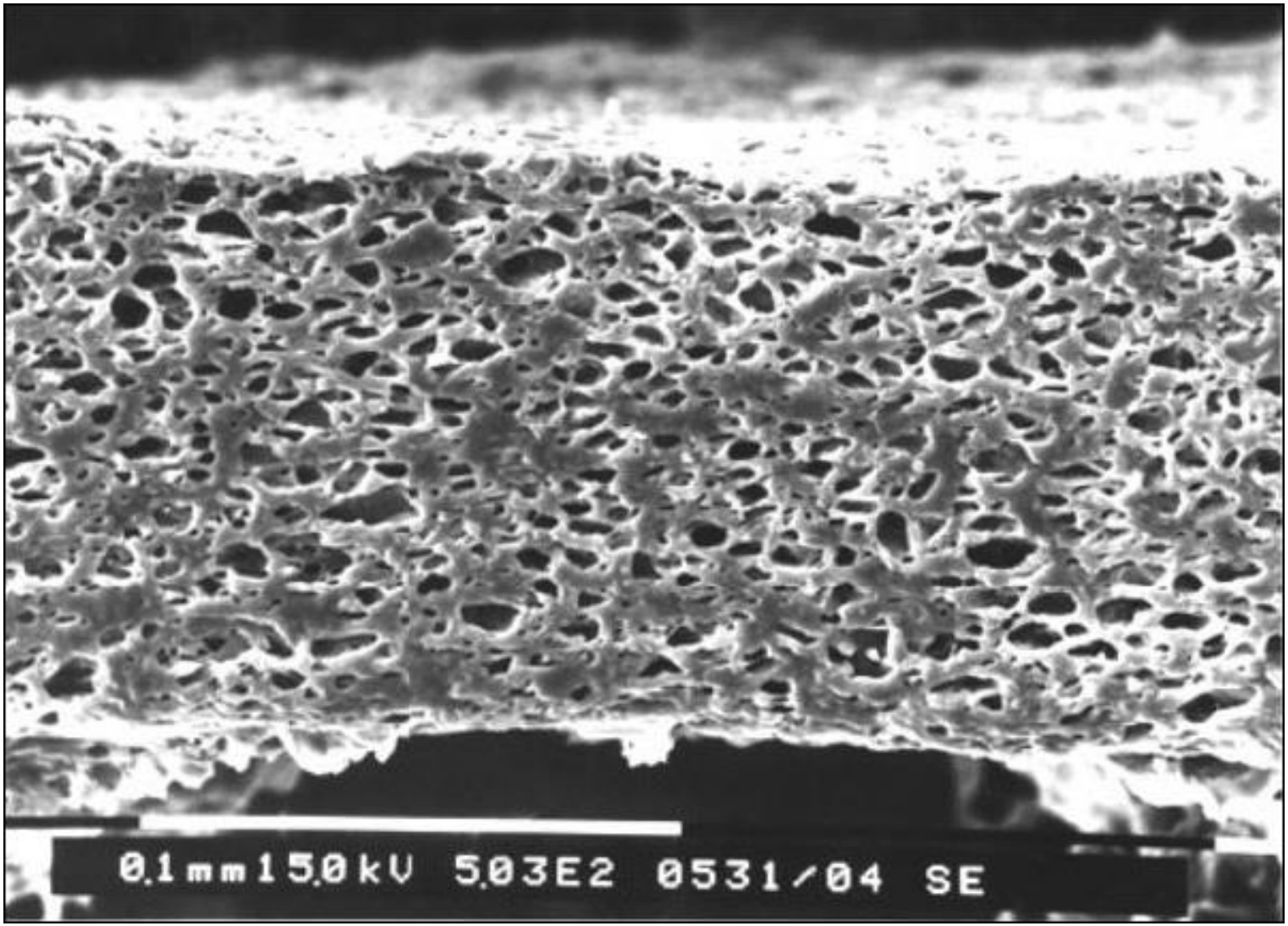
Polymeric content in coating, thickness of coating, hardness of microcapsule.



Dissolution & Diffusion Controlled Release system

- Drug encased in a partially soluble membrane (Ethyl cellulose & PVP mixture)
- Pores are created due to dissolution of soluble parts of membrane.
- It permits entry of aqueous medium into core & drug dissolution take place.
- Diffusion of dissolved drug out of system.

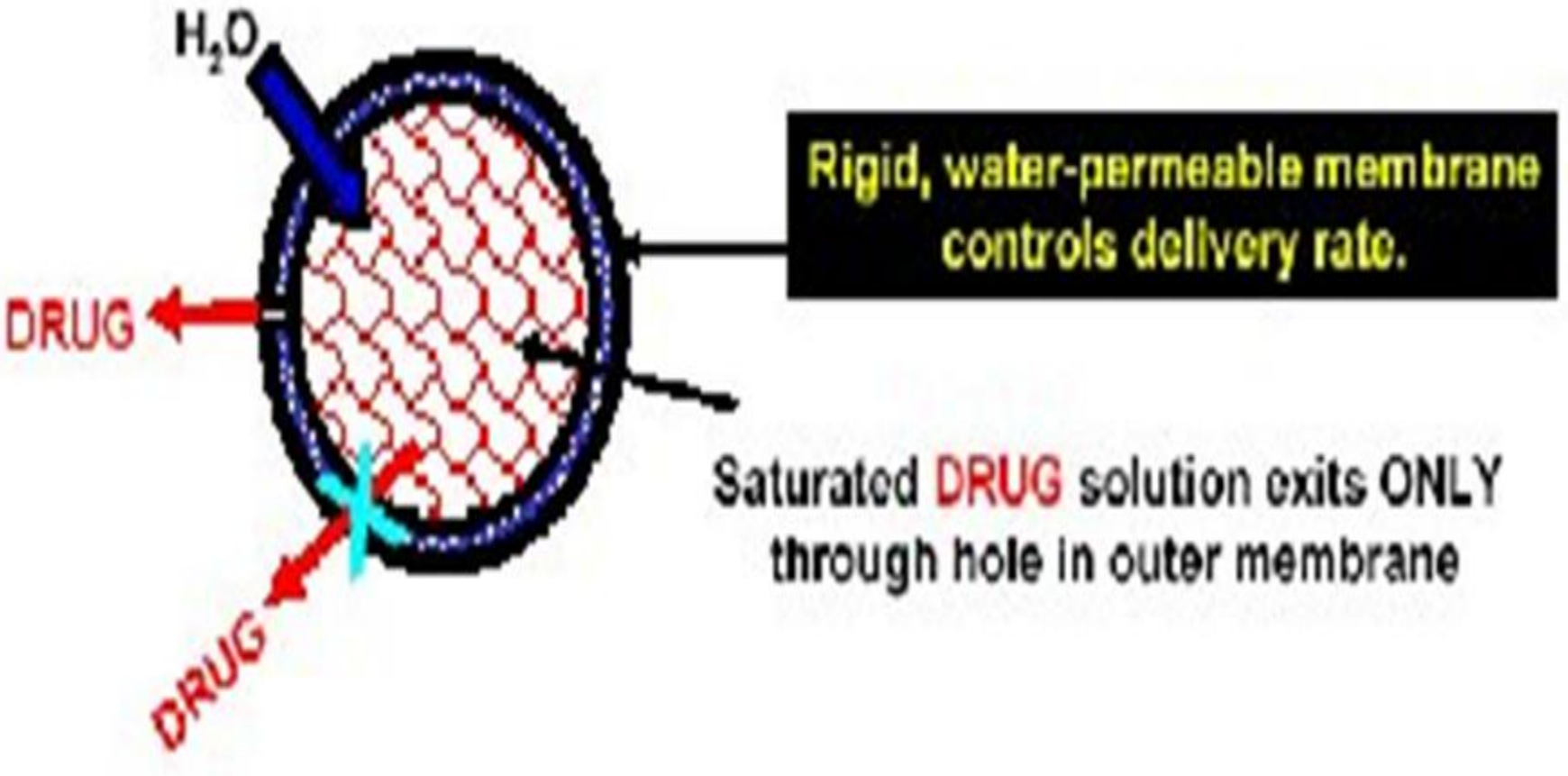



0.1mm 15.0kV 5.03E2 0531/04 SE

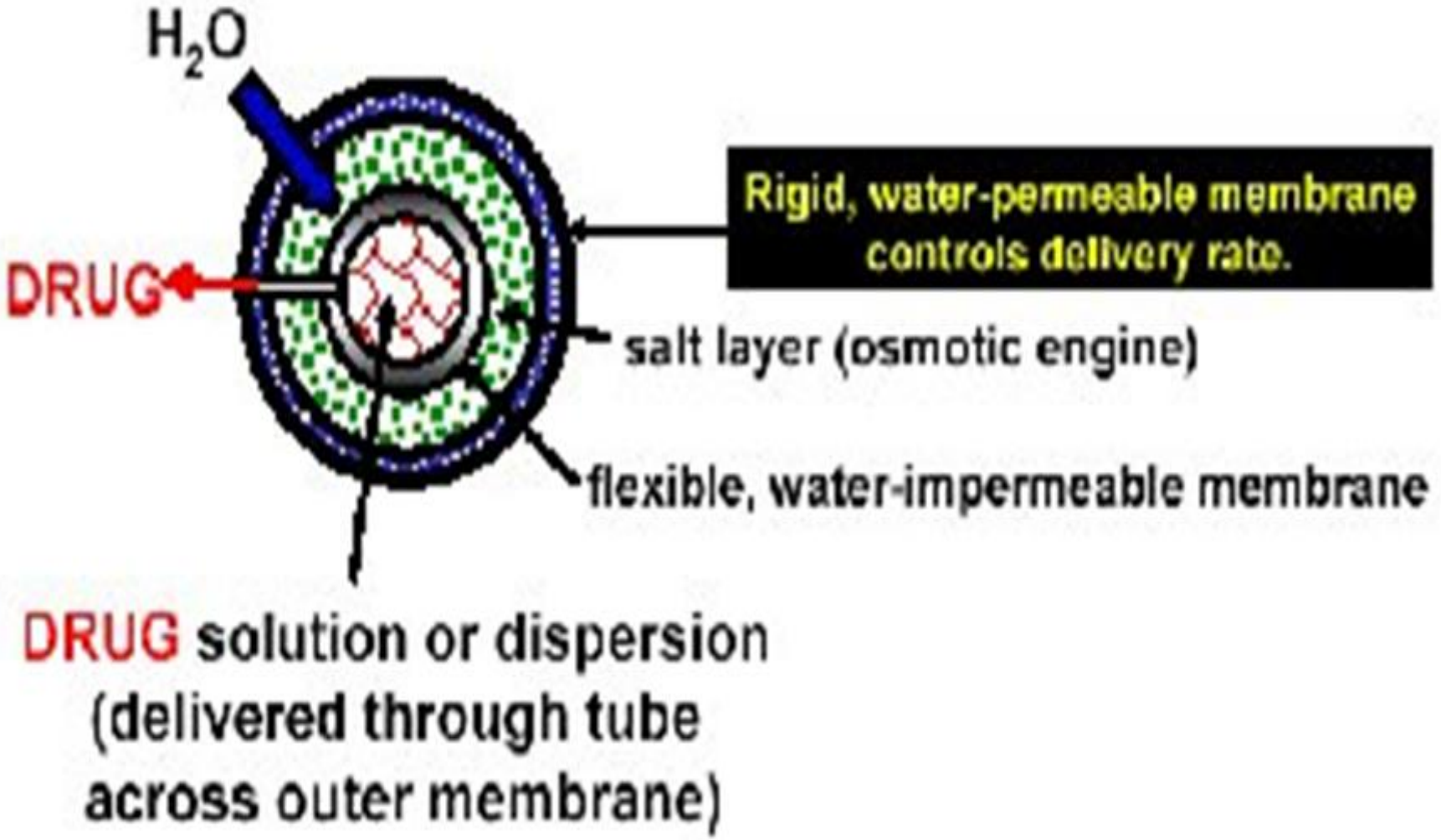
Osmotic Pressure Controlled System

- In this system the Drug may either be osmotically active itself, or combined with an osmotically active salt (e.g., NaCl).
- Surrounded by Semi-permeable membrane which is usually made from Cellulose acetate.
- Drug is pumped out continuously because of osmotic pressure gradient.
- More suitable for hydrophilic drug.
- Provides zero order release.

Osmotic Pressure Controlled System



Osmotic Pressure Controlled System



Chemically Controlled Released Systems

In this system the drug is either mixed or chemically combine with biodegradable polymer that change their chemical structure, when exposed to biological fluids.

These polymers are designed in such a way that they degrade into biologically safe and progressively smaller moieties as a result of hydrolysis of the polymer chains and thus releasing API.

It is of two types;

- **Erodible Systems**
- **Pendent Chain System**

Chemically controlled released Systems

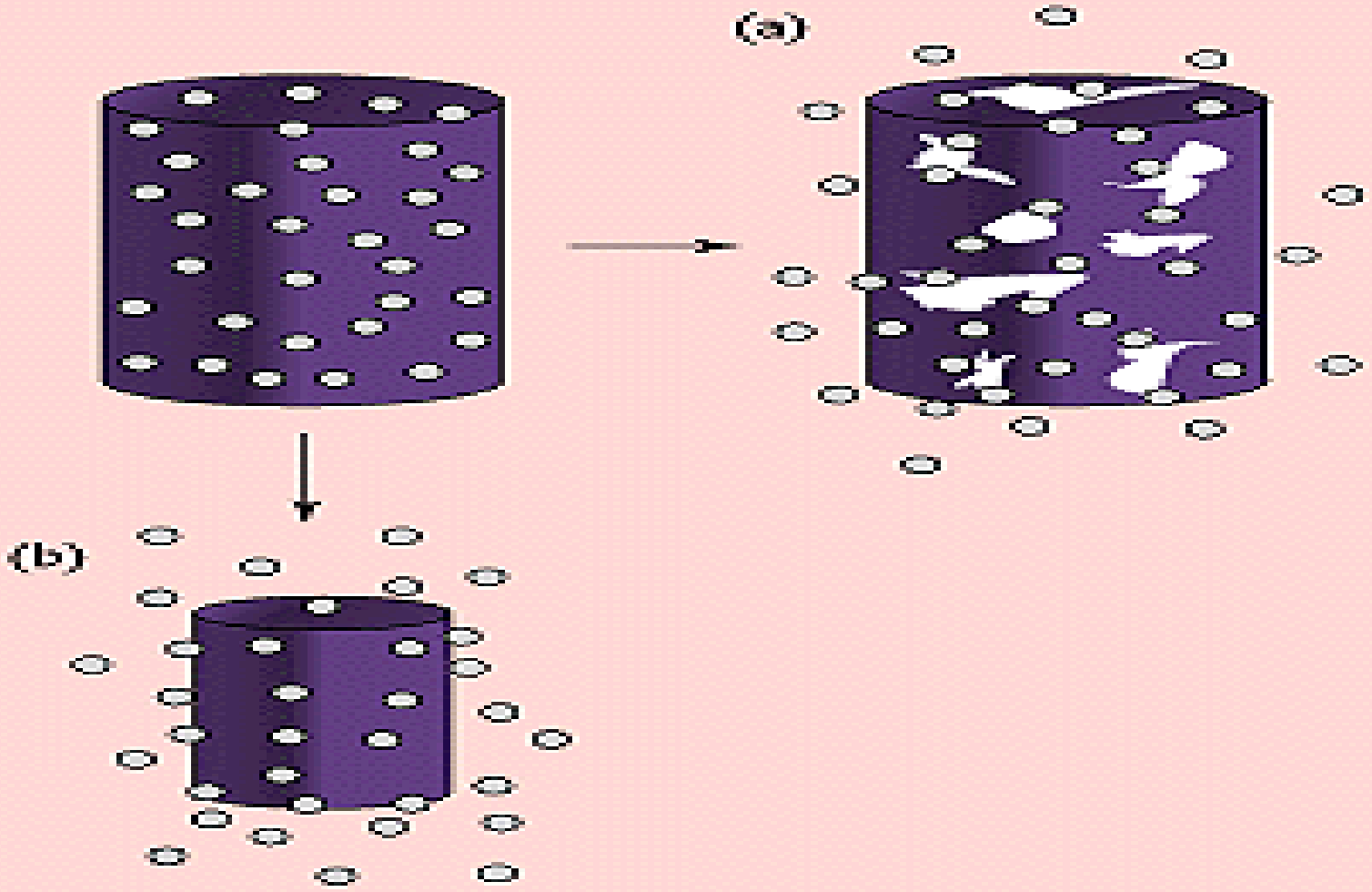
Erodible Systems

Two types;

Bulk Erosion: Polymer degradation may occur through bulk hydrolysis.

Surface Erosion: Degradation occur at the surface of the polymers e.g. Polyorthoesters & Polyanhydrides , resulting a release rate is proportional to the surface area of the delivery system.

Chemically controlled released Systems



Drug delivery from (a) bulk-eroding (b) surface-eroding biodegradable systems

Chemically Controlled Released Systems

Pendent Chain System

Consist of linear homo or copolymers with drug attached to its backbone chains. e.g. Hydroxy propyl methyacrylamide etc.

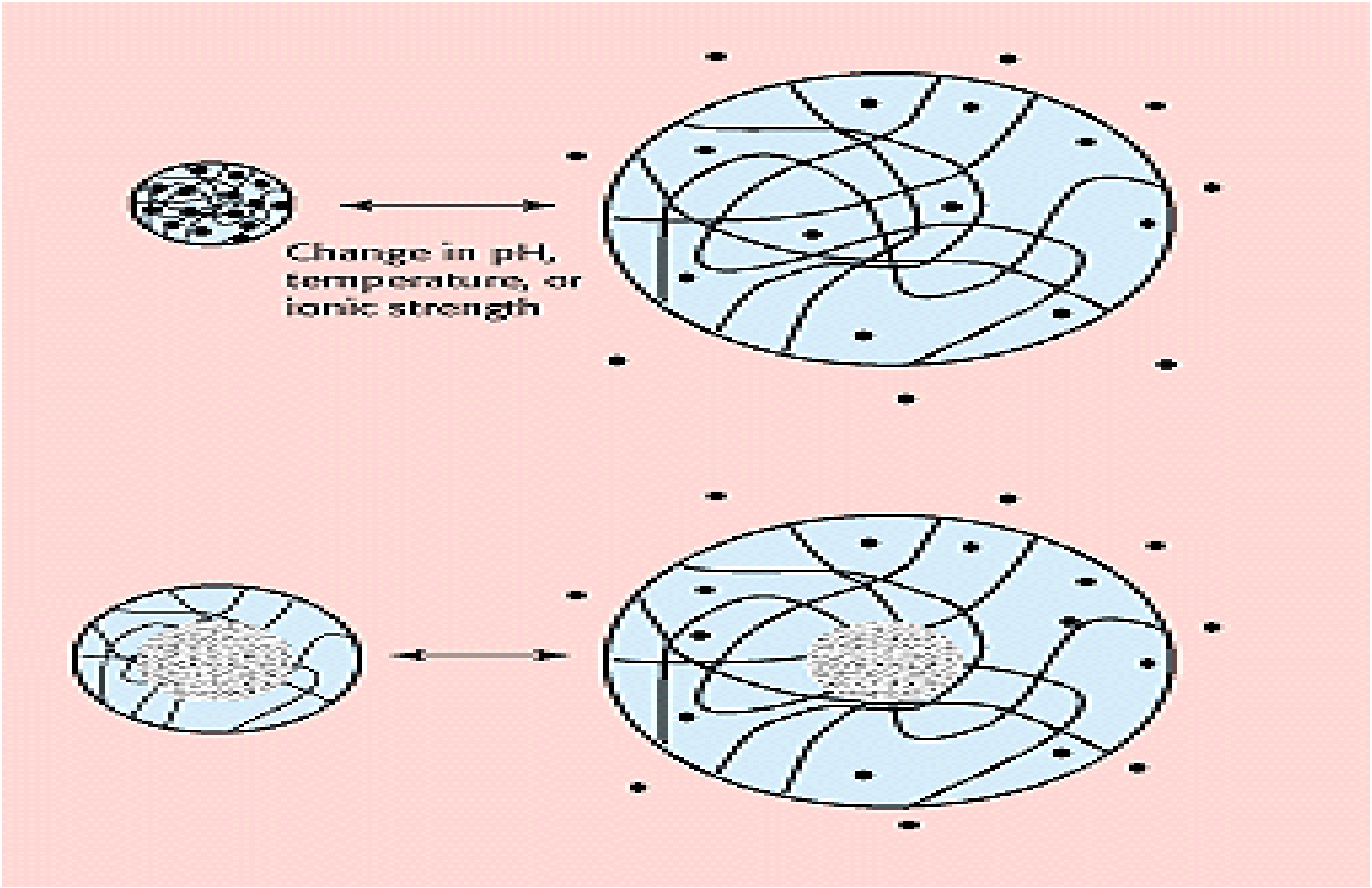
- ✓ Release drug by hydrolysis or enzymatic degradation of the linkages
- ✓ Follows zero order kinetics, cleavage of the drug is rate determining step.

Hydrogels

Three dimensional structures composed of primarily hydrophilic polymers having chemical or physical cross links which provides a network structure to hydrogels.

Insoluble because of network structure and provides desirable protection of liable drugs, peptides and proteins

Hydrogels



Drug delivery from matrix swelling-controlled release systems

Ion-Exchange Resins Controlled Release Systems

Such system provide control release of an ionic (ionisable) drug.

Ionisable drug is absorbed on ion-exchange resins granules and then granules are coated with water permeable polymers using spray drying technique.

H^+ Cl^- in the gastric fluid are exchange with cationic and anionic drugs from the ion-exchange resins.

Characteristics of Drugs Unsuitable for Peroral Sustained Release

Characteristics	Drugs
Not effectively absorbed in the lower intestine	Riboflavin, Ferrous Sulfate
Absorbed and extracted rapidly (short biologic half life i.e. < 1Hr)	Penicillin G, Furosemide
Long biologic half life i.e. > 12 Hr	Diazepam
Large doses required (> 1G)	Sulfonamides, Sucralfate
Drug with low therapeutic index	Digitoxin, Warferrin, Phenobarbital
Precise dosage to individual is required	Anticoagulants
No clear advantage for sustained release	Griseofulvin
If the pharmacological activity of the active compound is not related to its blood levels.	

Kinetics

Mathematical models are used to evaluate kinetics and mechanism of drug release from the tablets.

1. **Zero Order Release Model**
2. **First Oder Release Model**
3. **Hixson-Crowell Release Model**
4. **Higuchi Release Model**
5. **Korsmeyer-Peppas Release Model**

The model that give highest Regration Value "r^2" is considered as the best fit of the release data.

Zero Order Release Kinetics

Release kinetics independent of concentration of drugs in the dosage form is described as Zero Order Release Kinetics. Equation for Zero order release is;

$$Q_t = Q_o + K_o t$$

Where

Q_t = initial amount of drug

Q_o = cumulative amount of drug at time "t"

K_o = Zero order release constant

t = time in hours

First Order Release kinetics

Release kinetics dependent on the concentration of drugs in the dosage form is described as First Order Release Kinetics. Equation for First Order release is;

$$\log Q_t = \log Q_o + K_o t/2.303$$

Where

Q_t= initial amount of drug

Q_o = cumulative amount of drug at time "t"

K_o = First order release constant

t = time in hours

Hexson-Crowell Release Model

Describes drug release by dissolution and with changes in surface area and diameter of particles or tablets;

Its equation is;

$$\sqrt[3]{Q_o} - \sqrt[3]{Q_t} = K_{HC}.t$$

Where

Q_t= initial amount of drug

Q_o = cumulative amount of drug at time "t"

K_{HC} = Hexson-Crowell release constant

t = time in hours

Higuchi Release Model

Model suggests that the drug is release by diffusion.

$$Q = K_H t^{1/2}$$

Where

Q = cumulative amount of drug at time "**t**"

K_H = Higuchi release constant

t = time in hours

Korsmeyer-Pappas Release Model

Release kinetics dependent on the concentration of drugs in the dosage form

$$F = (M_t / M) = K_m t^n$$

Where

F = Fraction of drug release at time "**t**"

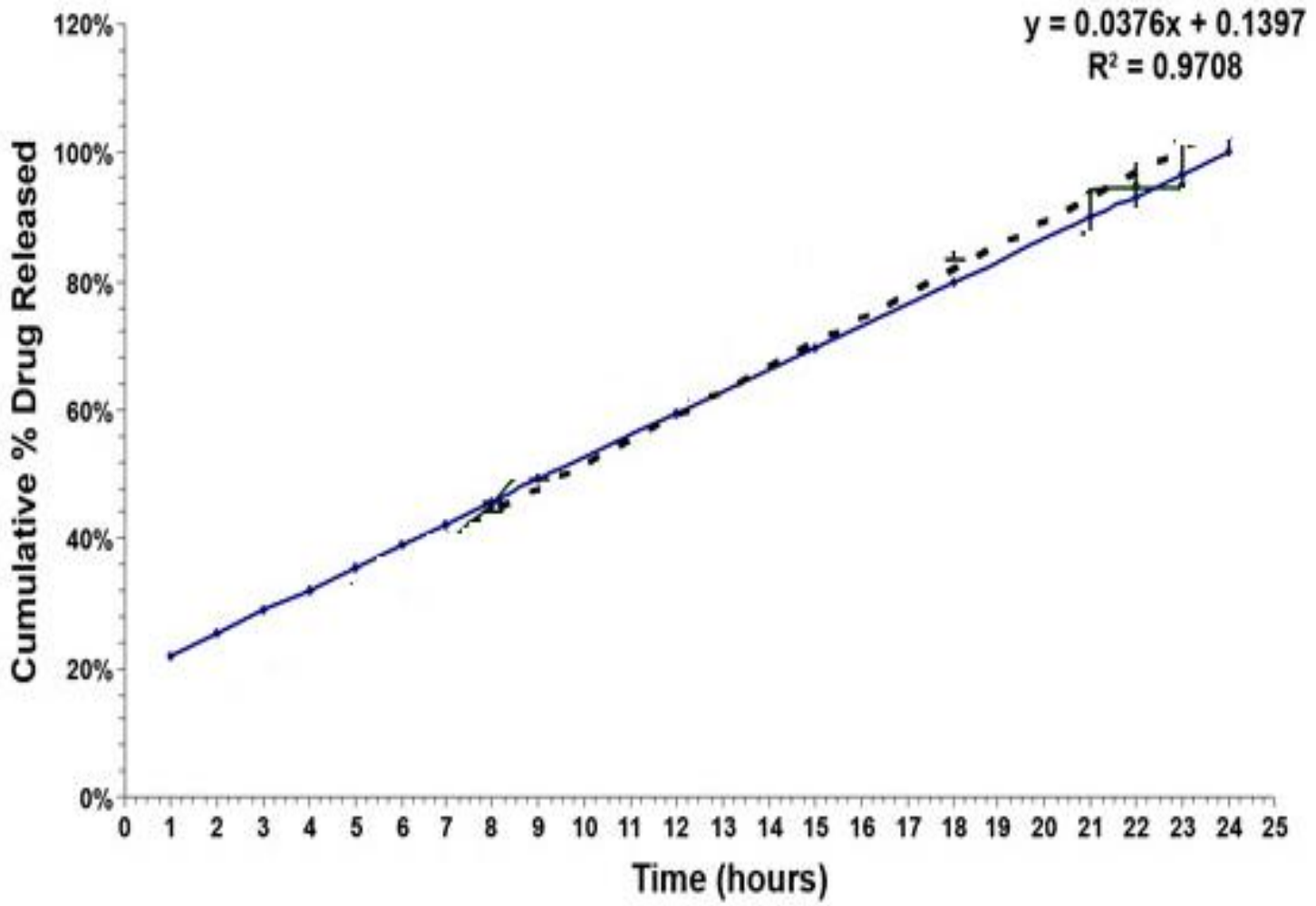
$\mathbf{M_t}$ = Amount of drug release at time "**t**"

M = total amount of drug in dosage form

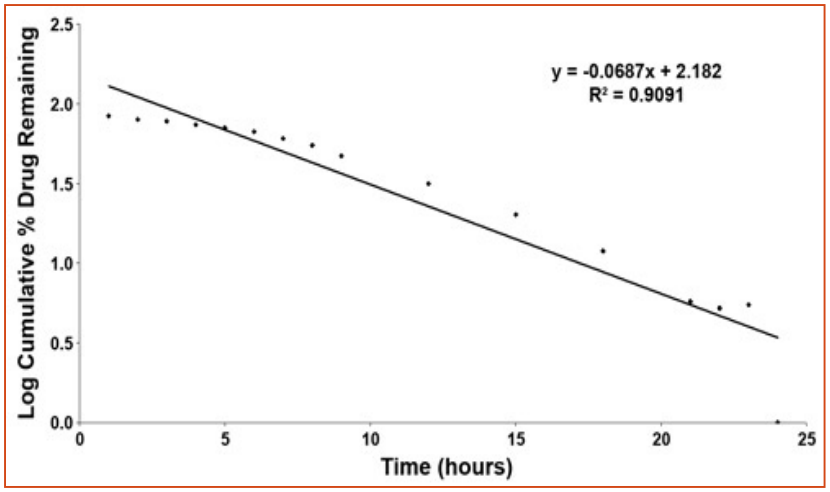
$\mathbf{K_m}$ = Kinetic constant

n = Diffusion or release exponent

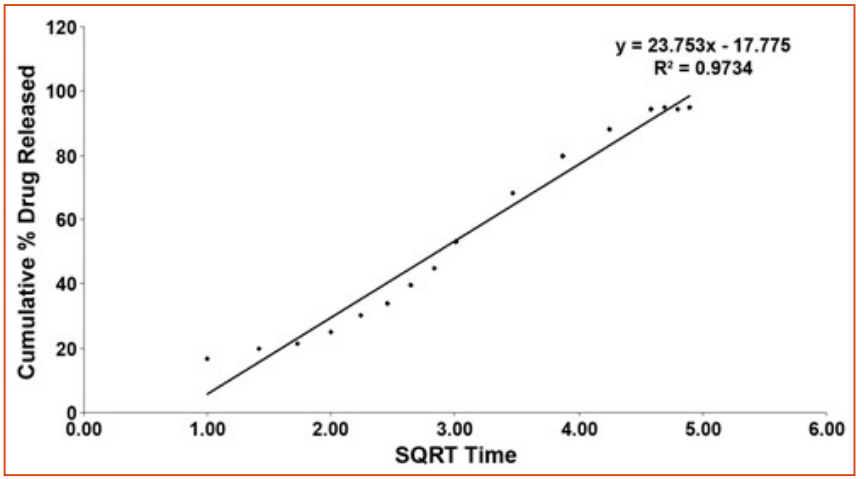
t = time in hours



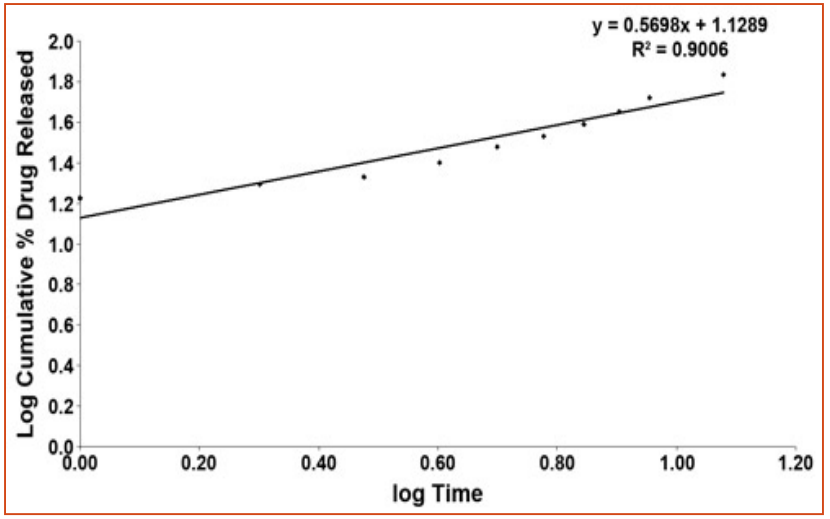
Zero Order Kinetics



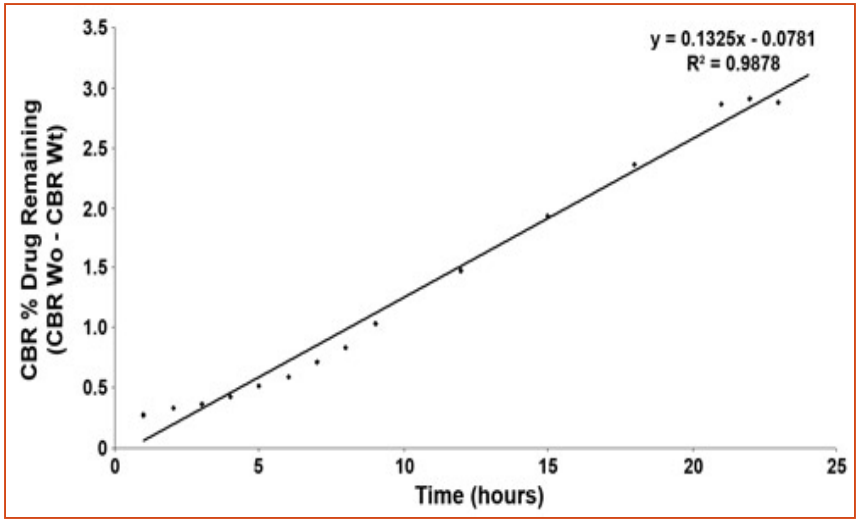
First Order Kinetics



Higuchi Model Kinetics



Korsmeyer –Peppas Kinetics



Hexson-Crowell Kinetics

Design of Sustained Release Dosage Forms

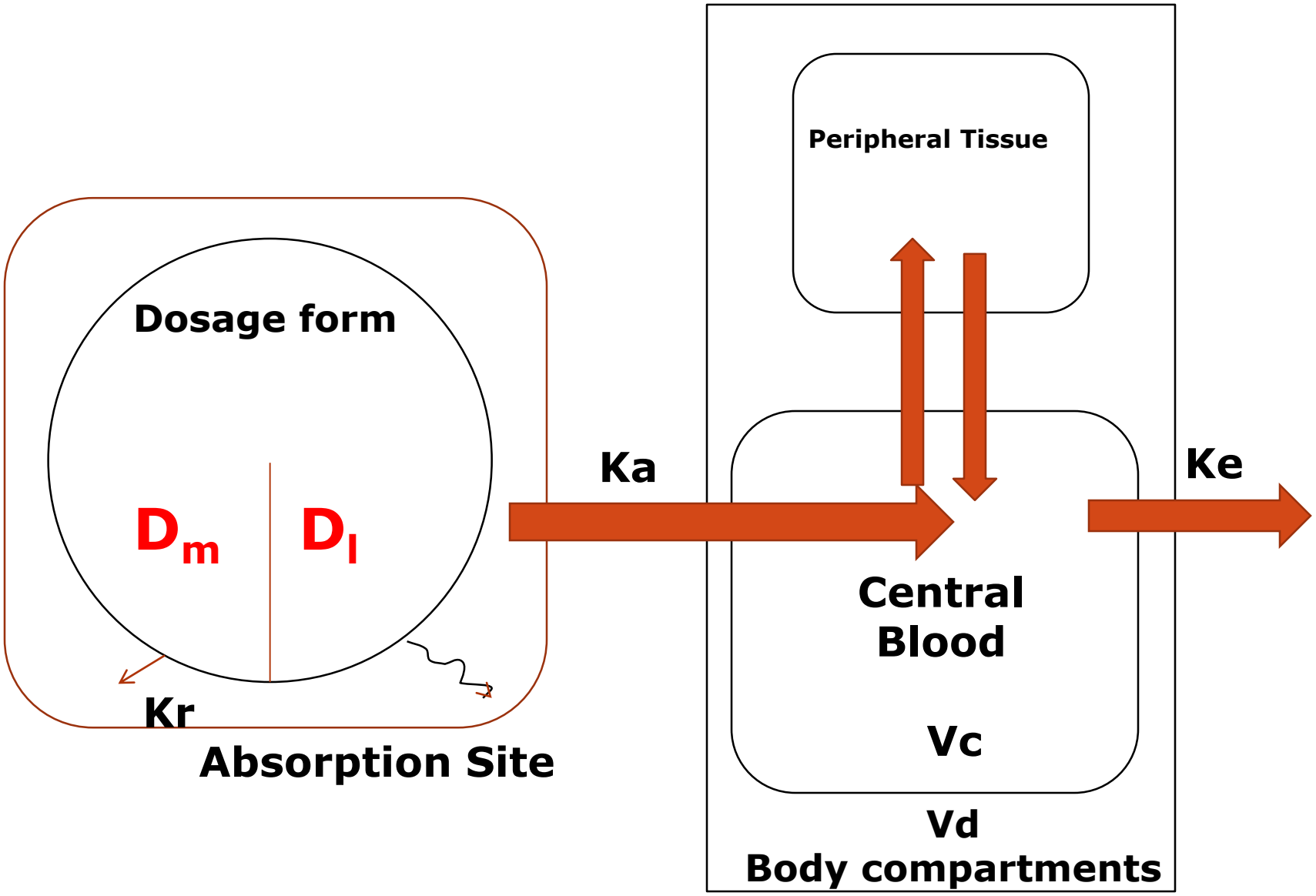
Objective: To deliver drug at a rate necessary to achieve and maintain a constant drug blood level. This is can be done by attempting to obtain zero order release from dosage forms i.e. drug release from dosage form is independent of the amount of drug in the delivery system.

Generally sustain release system do not attain this type of release and try to mimic zero order release by providing drug in slow first order fashion as shown by following equation.

$$\text{Rate in} = \text{Rate out} = K.C_d.V_d$$

Where, C_d = Desired drug level, V_d = Volume of distribution

K = elimination rate constant



Pharmacokinetic model of an ideal peroral sustained release

Factors Influencing Design of Sustained Release Dosage Forms:

A. Pharmaceutics: This refers to the development / manufacturing of an efficient delivery system in which the drug has maximum physiological stability and optimum bioavailability.

B. Biopharmaceutics / Pharmacokinetics: This involves the study of absorption, distribution, metabolism and excretion of the drug, before and after reaching the target site and evaluation of the relationship between delivery system and therapeutic response.

C. Pharmacodynamics / Clinical Pharmacology: It is the study of the mechanism of action and clinical efficacy of a drug administered in dosage form in terms of onset, intensity and duration of pharmacological activity.

Drug Properties Influencing the Design of Sustained Release Drug Delivery System are classified as:

A. Physicochemical Properties of the Drug

i) Aqueous Solubility: A drug with good aqueous solubility, especially if pH independent, serves as a good candidates.

ii) Partition Coefficient: Between the time a drug is administered and is eliminated from the body, it must diffuse through a variety of biological membranes. The ability of drug particles to penetrate through these membranes is given by Partition coefficient.

iii) Drug stability: Drug for sustain release should not have a high degradation rate in GI track. Drugs with stability problems are poor candidates.

iv) Protein Binding: Most part of the blood proteins are re-circulated and are not eliminated, drug-protein binding can serve as a depot. In general charged compounds have a greater tendency to bind a protein. e.g. 95% PPB drugs are Diazepam, Dicoumarol, Novobiocin.

v) Dose size: For oral dosage form a dose size of 0.5 to 1.0 gm is considered maximum. Higher doses have to be given as liquids. Drugs with low therapeutic index need to be given additional core if dose size is high.

B. Biological Properties of the Drug:

i) Absorption: The rate-limiting step in drug delivery from a sustained release product is release, from the dosage form rather than absorption.

A high absorption rate is advantageous for sustain drug release.

The rate, extent and uniformity of absorption is an important factor, as here $K_r <<< K_a$.

ii) Distribution: It not only lowers the concentration of circulating drug but it also can be rate limiting in its equilibration with blood and extracellular fluid.

The V_d and the ratio of drug in tissue to that of plasma at steady state is an important parameters to be considered in determining the release rate.

iii) Metabolism: Metabolism to other active form can also be considered as sustained effect.

The extent of metabolism should be identical and predictable when the drug is administered by different routes.

If a drug, upon chronic administration, is capable of either inducing or inhibiting enzyme synthesis, it will be poor candidate.

iv) Elimination Half Life: Smaller the $t_{½}$, larger the amount of drug to be incorporated in the sustained release dosage form.

Drug with the half-life in the range of 2 to 4 hours make good candidate for such a system e.g. Propranolol.

Drugs with long half-life need not be presented in such a formulation e.g. Amlodipine.

v) Side Effect: The incident of side effects can be minimized by controlling the concentration at which the drug exists in plasma at any given time.

Hence sustained release formulation appears to offer a solution to this problem.

Designing approach

Dosage form modification

Principle involved in modifying drug release;

Embedded matrix

- Drug dispersed in matrix
- Drug dissolved in matrix

Barrier

- Diffusion of drug
- Permeation of barrier
- Erosion of barrier

Polymers used are of three types:

a. Insoluble and inert e.g. polyethylene, ethyl cellulose, PVC, Methyl acrylate-methyl acrylate co-polymer etc.
b. Insoluble and erodible e.g. carnauba wax, stearly alcohol, stearic acid and PEGs etc . Castor wax, PEG monostearate and triglycerides etc
c. Hydrophilic e.g. methyl cellulose, HEC, HPMC, Sodium CMC, sodium alginate.

Methods of dispersion of drug in polymers:

1. Solvent evaporation
2. Fusion
3. Dry blend