CONTROLLED-SUSTAINED DRUG DELIVERY SYSTEMS

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An ideal drug delivery system must have two prerequisites:

- It would be a single dose for the duration of treatment, whether it be for days or weeks as with infection or for the lifetime of the patient as in hypertension or diabetes.

- It should deliver the active entity directly to the site of action, thereby minimizing or eliminating side effects. This may necessitate delivery to specific receptors or to localization to cells or to specific areas of the body.

Terminology:

Sustained Release Drug Delivery Systems:

Sustained release constitutes any dosage form that provides medication over an extended time to maintain therapeutic blood or tissue levels of the drug.

Controlled Release Drug Delivery Systems:

controlled release system is able to provide some actual therapeutic control, whether this be of a temporal nature, spatial nature, or both. The system attempts to control drug concentrations in the target issue.

Repeat-Action drug delivery systems:

Repeat-action tablets are an alternative method of sustained release in which multiple doses of drug are contained within a dosage form, and each dose is released at a periodic interval.

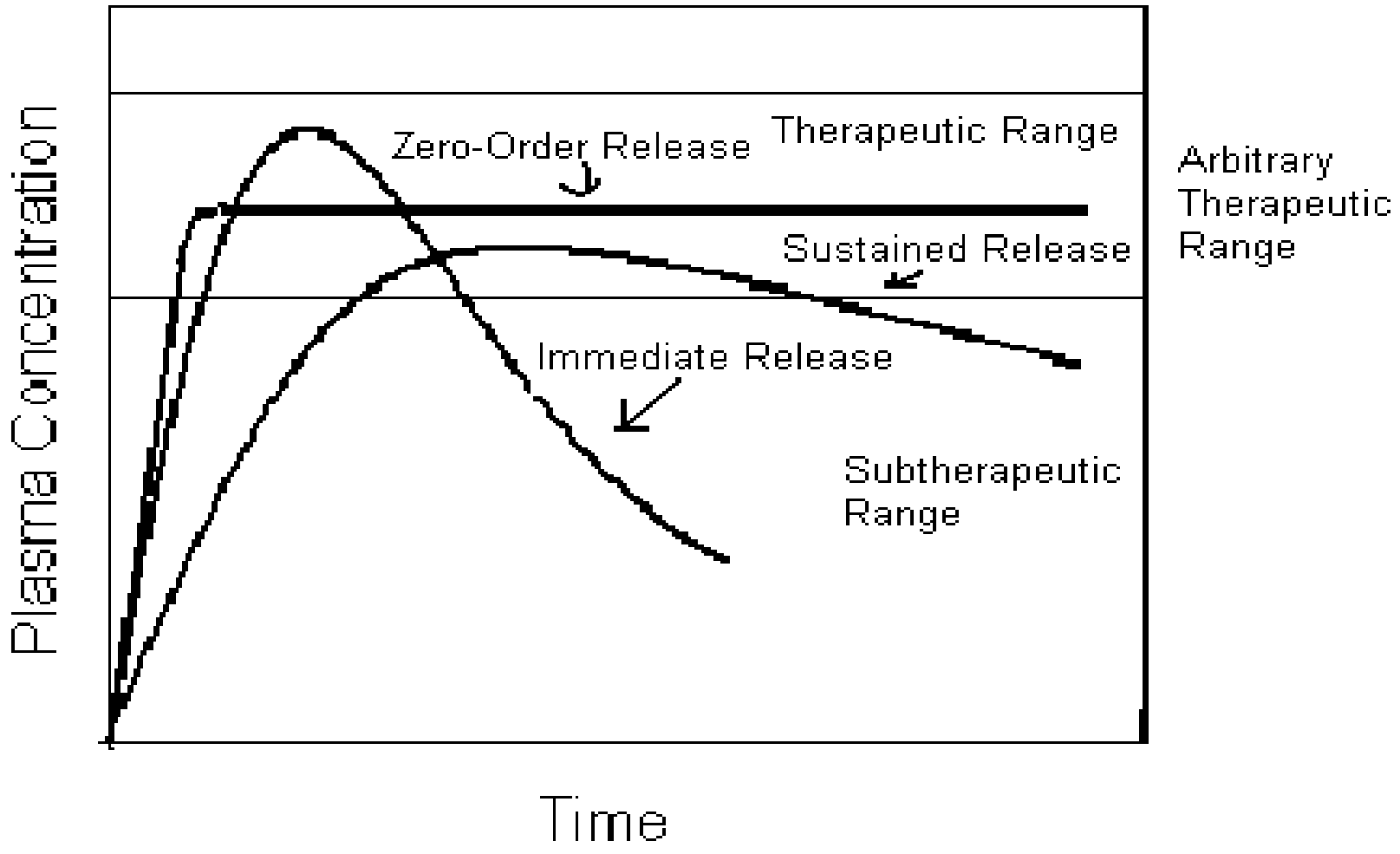
Delayed Release Drug Delivery Systems:

Delayed release systems may not be sustaining but these dosage forms maintains the drug within the dosage form for some time before release.

Targetted Delivery Systems

- *Site-specific systems* and *targeted delivery systems* are those which regulates the release to the specific site or target at a controlled manner so as to improvise the therapeutic efficacy.

- Concept of SR/CRDDS:



Drug level versus time profile showing differences between zero-order controlled release, slow first-order sustained release , and release from a conventional tablet or capsule.

Advantages of Controlled Release Systems:

- Decreased incidence and/or intensity of adverse effects and toxicity.
- Better drug utilization.
- Controlled rate of release.
- More uniform blood concentrations.
- Improved patient compliance.
- Reduced dosing frequency.
- More consistent and prolonged therapeutic effect.
- A great selectivity of pharmacological activity.

Disadvantages of Controlled Release Systems:

- Increased variability among dosage units.
- Stability problems.
- Toxicity due to dose dumping.
- Increased cost.
- More rapid development of tolerance.
- Need for additional patient education and counseling.

Characteristics of Drugs Suitable For Controlled Release:

- Exhibit moderate rates of absorption and excretion.
- Uniform absorption throughout the GIT.
- Administered in relatively small doses.
- Possess a good margin of safety.
- For the treatment of chronic therapy.

Characteristics of Drugs Unsuitable For Controlled Release:

- Not effectively absorbed in lower intestine (Riboflavin).
- Absorbed and excreted rapidly; short biological half lives,<1hr (penicillin G, Furosemide).
- Long biological half lives >12hr (Diazepam, Phenytoin).
- Large doses required, 1g (sulphonamides).
- Drugs with low therapeutic index (phenobarbital, Digoxin)
- Precise dosage titrated to individuals required (Anticoagulants, cardiac glycosides).
- No clear advantage for sustained release formulation (Griseofulvin).

Physicochemical Properties Of A Drug Influencing Drug Product Design and Performance:

- **Aqueous solubility:**

  Tetracycline dissolves to a greater extent in the stomach than in the intestine, although it is best absorbed in the intestine. Hence, poor candidates for controlled release systems, unless the system is capable of retaining the drug in the stomach and gradually releasing it to the small intestine or unless the solubility is made higher and independent of the external environment by encapsulating the drug with an acid.

- **Partition Coefficient and Molecular Size:**

  Drugs with extremely high partition coefficient (very oil soluble) readily penetrate the membranes but are unable to proceed further and vice versa with drugs with very low partition coefficient (excessive aqueous solubility).

- **Drug Stability:**

  Controlled release of Nitroglycerin.

- **Protein Binding:**

  Many drugs bind to plasma proteins. Drug protein binding can serve as depot for the drug producing a prolonged release profiles, especially if a high degree of drug binding occurs.

Biological Factors Influencing Design and Performance of Controlled Release Systems:

- **Absorption:**

  Aminoglycosides such as gentamycin and kanamycin.

  Riboflavin is absorbed by an active transport process in the upper part of the GIT.

- **Distribution:**

  The distribution of drugs into tissues can be one important factor in the overall drug elimination kinetics, since it not only lowers the concentration of circulating drug but it also can be rate-limiting in its equilibration with blood and extracellular fluid.

- **Metabolism:**

  Hydralazine is metabolized by the intestinal wall and/or the liver during absorption, although it is well absorbed.

  In contrast, Bromocriptine is incompletely absorbed, the poor bioavailability of which is further reduced by first pass metabolism in the liver resulting in an absolute bioavailability of only 6%.

- **Duration of Action:**

  For a drug with very short half-life, the desired rate of release will be quite large.

- **Side Effects:**

  A controlled release form of levodopa, lowered the incidence of drug induced dyskinesis and the patients able to tolerate a larger daily dose of the drug.

- **Margin of Safety:**

  Drugs with narrow therapeutic index gives precise drug release patterns so that the plasma concentration achieved is within the therapeutically safe and effective range.

- **Role of Disease State:**

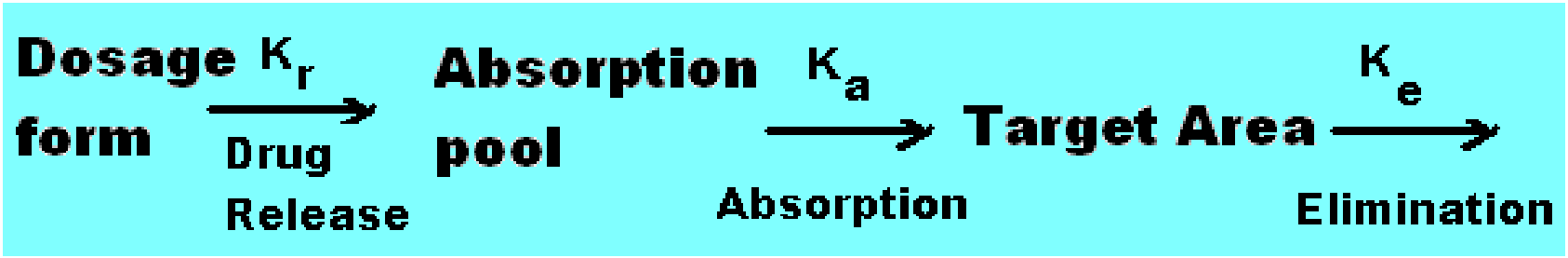
  Controlled release Aspirin tablets in the proper dosage provided and maintained blood levels at therapeutic concentration over 8-10hrs, a duration that was about twice as long as that provided by conventional tablets.

- **Role of Circadian Rhythm:**

  Several biological processes and disease states shown to be influenced by circadian rythms. As a result,the response to certain drugs also follows cicadian rythms.

  Digitalis glycosides, antianginal, diuretics, Psychoactive drugs such as amphetamines, Barbiturates, carbamazepine, ethyl alcohol and chlordiazepoxide.

Design principle of sustained release dosage forms for release rate and dose considerations:



- K_r^o = Rate In = Rate Out = $K_e.C_d.V_d$
- $W = D_i + D_m$
- $W = D_i + K_r^o T_d$
- $W = D_i + K_r^o T_d - K_r^o T_p$
- $W = D_i + (K_e C_d / K_r) V_d$
- $W = D_i + (K_e C_d / K_r) V_d – D_m K_e T_p$

ORAL CONTROLLED RELEASE SYSTEMS:

Controlled Release Systems:

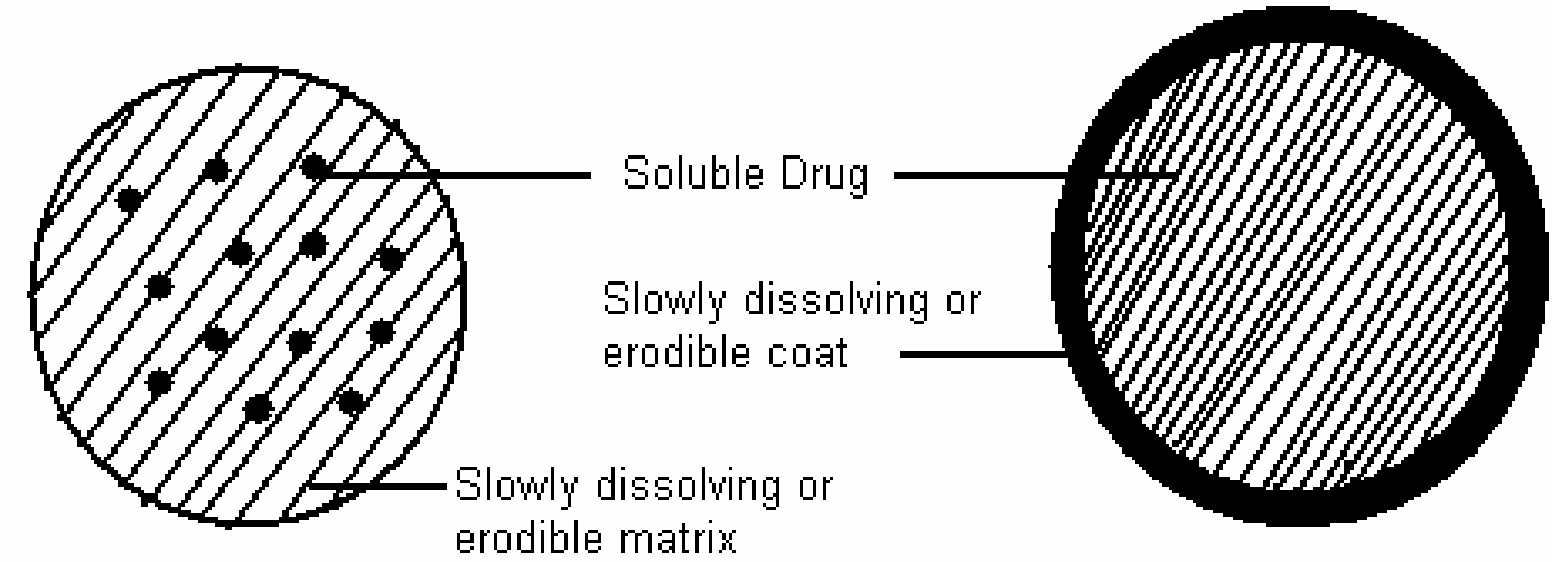
- Dissolution Controlled release systems
- Diffusion Controlled release systems
- Dissolution-Diffusion Controlled release systems
- Ion-exchange resin-drug complexes
- Slow dissolving salts and complexes
- pH-dependent formulations
- Osmotic pressure controlled systems
- Hydrodynamic pressure controlled systems

Delayed Transit and Continuous Release Systems:

- Altered density systems
- Mucoadhesive Systems
- Size-based Systems

Dissolution-Controlled Systems:

Dissolution-controlled systems can be made to be sustaining in several different ways. By altering layers of drug with rate-controlling coats, a pulsed delivery can be achieved.



Schematic representation of dissolution controlled release systems

(a) Matrix Systems, and (b) Coated/encapsulated System

$$dc/dt = K_D A(C_S - C) = D/h\ A(C_S - C)$$

Where,

dc/dt = dissolution rate

K_D = dissolution rate constant

D = diffusion coefficient

C_s = saturation solubility of the solid

C = concentration of solute in the bulk solution

$$W_o^{1/3} - W^{1/3} = K_D t$$

Where,

K_D=Cube-root dissolution rate constant

W_o & W =Initial weight and the weight of the amount remaining at time t, respectively

Diffusional Systems:

Diffusional systems are characterized by the release rate of a drug being dependent on its diffusion through an inert membrane barrier.

Two types of Diffusional systems are recognized:

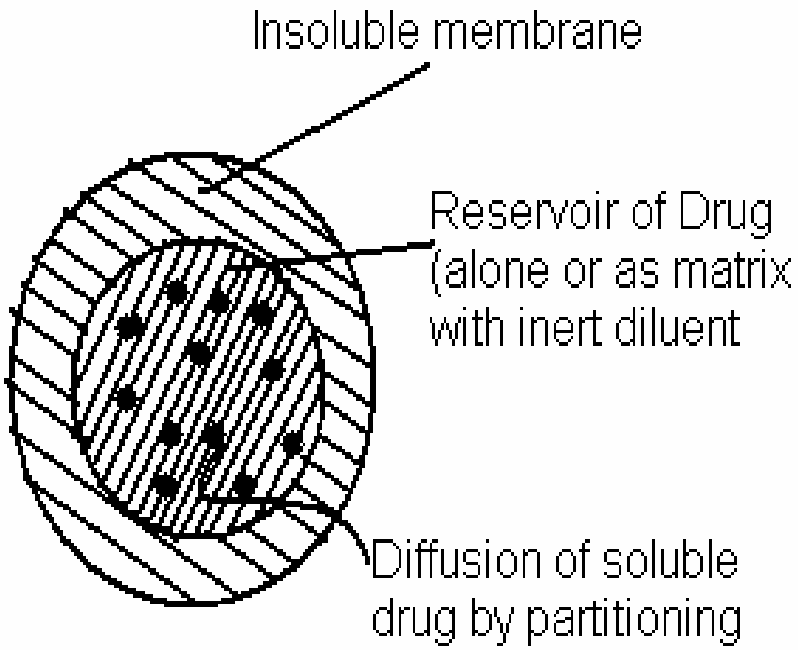
- **Reservoir Devices**
- **Matrix Devices**

Reservoir devices:

- Reservoir devices, as the name implies, are characterized by a core of drug, the reservoir, surrounded by a polymeric membrane.
- The nature of membrane determines the rate of release of drug from the system.
- The process of diffusion is generally described by Fick's law which states that the amount of drug passing across a unit area is proportional to the concentration difference across that plane.

Rate Controlling Step:

Polymeric content in coating,
Thickness of coating,
Hardness of microcapsule



Drug release by Diffusion across the insoluble membrane of the reservoir device

$$J = - D.dC/dX$$

Where,

J = flux (amount /area- time)

D = diffusion coefficient of the drug in the membrane (area/time)

dC/dX = rate of change in the concentration C relative to distance X in the membrane.

NOTE: **D** is a reflection of drug molecule's ability to diffuse through the solvent and is dependent on such factors as molecular size &charge.

$dM_t/dt = ADK\Delta C/d$

where,

M_t = mass of drug released after time t.

dM_t/dt = steady-state release at time t.

A = surface area of the device.

A true Controlled–Release system with a zero-order release rate can be possible only if all of the variables on the right side of the above equation remain constant.

Advantages of Reservoir Diffusional Systems:

- Zero-order delivery is possible.
- Release rate variable with polymer type.

Disadvantages of Reservoir Diffusional Systems:

- System must be removed from implant sites.
- Difficult to deliver high molecular weight compounds.
- Generally increased cost per dosage unit.
- Potential toxicity if system fails

Matrix Devices:

- A matrix device, as the name implies, consist of drug dispersed homogenously through out a polymer matrix.

- The equation which described the rate of release of drugs dispersed in an inert matrix system, have been derived by Higuchi.

- The following equation can be written based on it

$$dM/dh = C_o dh - C_s/2$$

where,

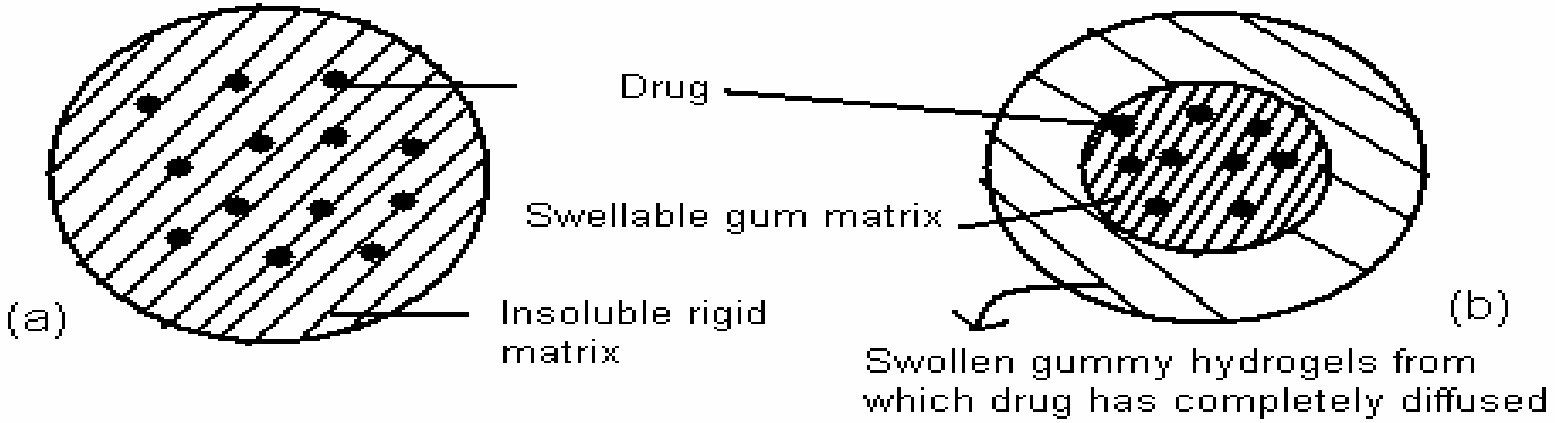
dM = change in the amount of drug released per unit area.

dh = change in the thickness of the zone of matrix that has been depleted of drug .

C_o = total amount of drug in a unit volume of the matrix.

C_s = saturated concentration of drug within the matrix.

Rate Controlling Step:
Diffusion of dissolved drug through the matrix



Diffusion Controlled Devices

(a) Rigid matrix, and (b) Swellable matrix

- From diffusion theory,

$$dM = D_m C_s / h.dt$$

Where,

D_m= diffusion coefficient in the matrix

$$M = kt^{1/2}$$

Where,

k = constant

Advantages of Matrix Diffusion Systems:

- Easier to produce than reservoir devices.
- Can deliver high molecular weight compounds.

Disadvantages of Matrix Diffusion Systems:

- Cannot obtained zero-order release .
- Removal of remaining matrix is necessary for implanted systems.

Bioerrodible and Combination Diffusion and Dissolution Systems:

$$M_t/M = 1 - (1 - k_o t/C_o a)^n$$

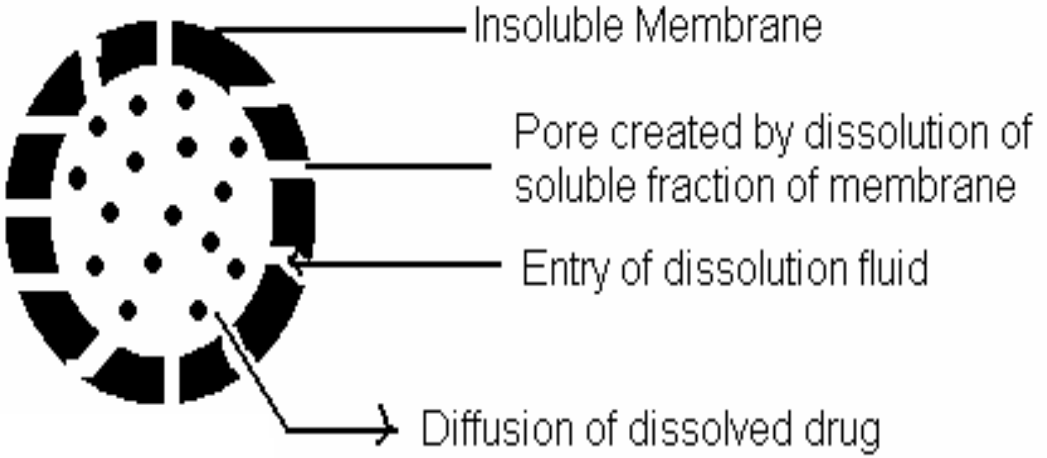
Where,

n =1, for a slab

n = 2, for a cylinder

n = 3, for a sphere

Rate Controlling Factor:
Fraction of soluble polymer in the coat



Dissolution and Diffusion Controlled Systems

Advantages of Bioerrodible Matrix Systems:

- Easier to produce than reservoir devices.
- Can deliver high molecular weight compounds.
- Removal from implant sites not necessary.

Disadvantages of Bioerrodible Matrix Systems:

- Difficult to control kinetics owing to multiple processes of release.
- Potential toxicity of degraded polymer must be considered.

Ion-exchange systems:

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

$$\text{Resin}^{+} - \text{drug}^{-} + X^{-} \rightarrow \text{resin}^{+} - X^{-} + \text{drug}^{-}$$

$$\text{Resin}^{-} - \text{drug}^{+} + Y^{+} \rightarrow \text{resin}^{-} - Y^{+} + \text{drug}^{+}$$

Osmotically Controlled Systems:

In this systems, osmotic pressure provides the driving force to generate controlled release of drug.

The rate of flow, dV/dt, of water into the device can be represented as

$$\frac{dV}{dt} = \frac{Ak}{h}(\Delta\pi - \Delta P)$$

Where,

k = membrane permeability

A = area of the membrane

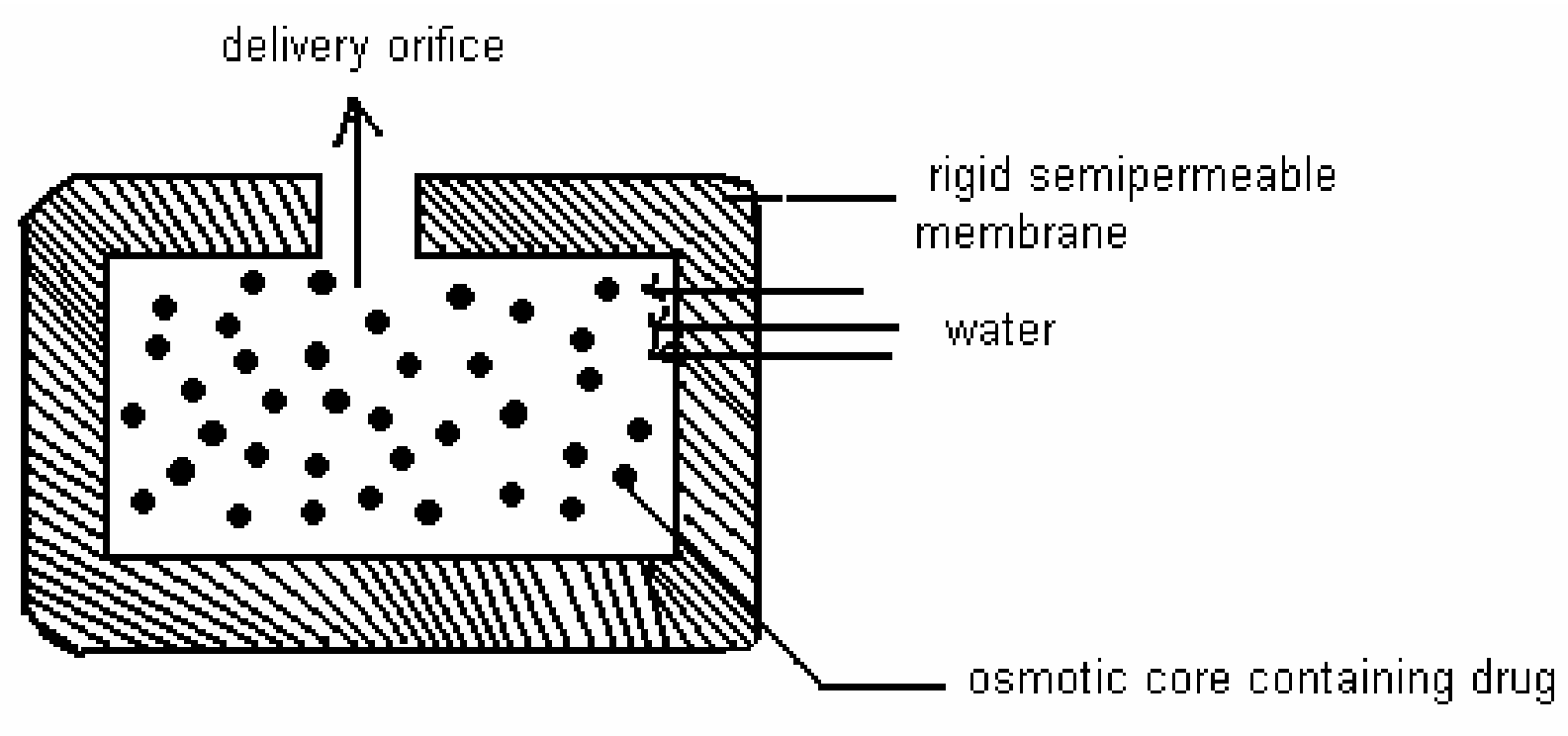
h = membrane thickness

$\Delta\pi$ = osmotic pressure difference

ΔP = hydrostatic pressure difference

Rate Controlling Factors:

Orifice diameter
Membrane area
Membrane thickness
Membrane permeability
Osmotic properties of the core
Drug solubility



Oral Osmotic Pump (oros)

Advantages of osmotically controlled devices:

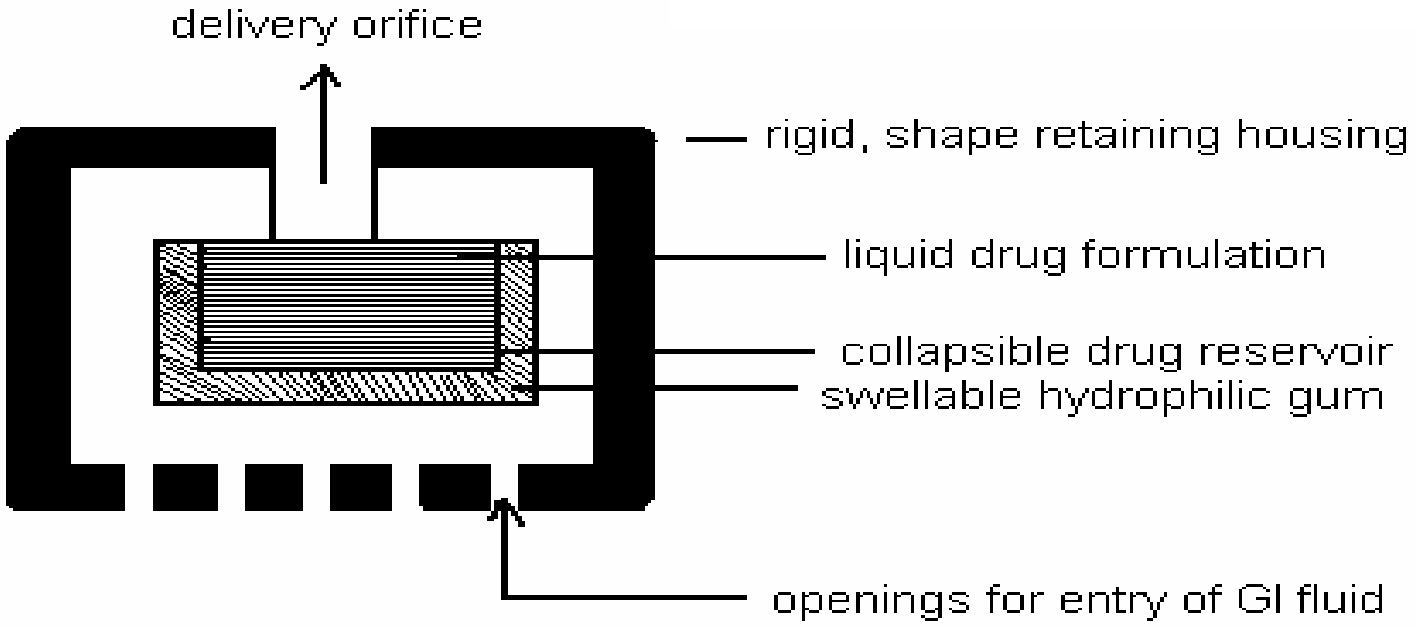
- Zero-order release obtainable.
- Preformulation not required for different drugs.
- Release of drug independent of the environment of the system.

Disadvantages of osmotically controlled devices:

- Systems can be much more than expensive than conventional counterparts.
- Quality control more extensive than most conventional tablets.

Hydrodynamic Pressure Controlled Systems

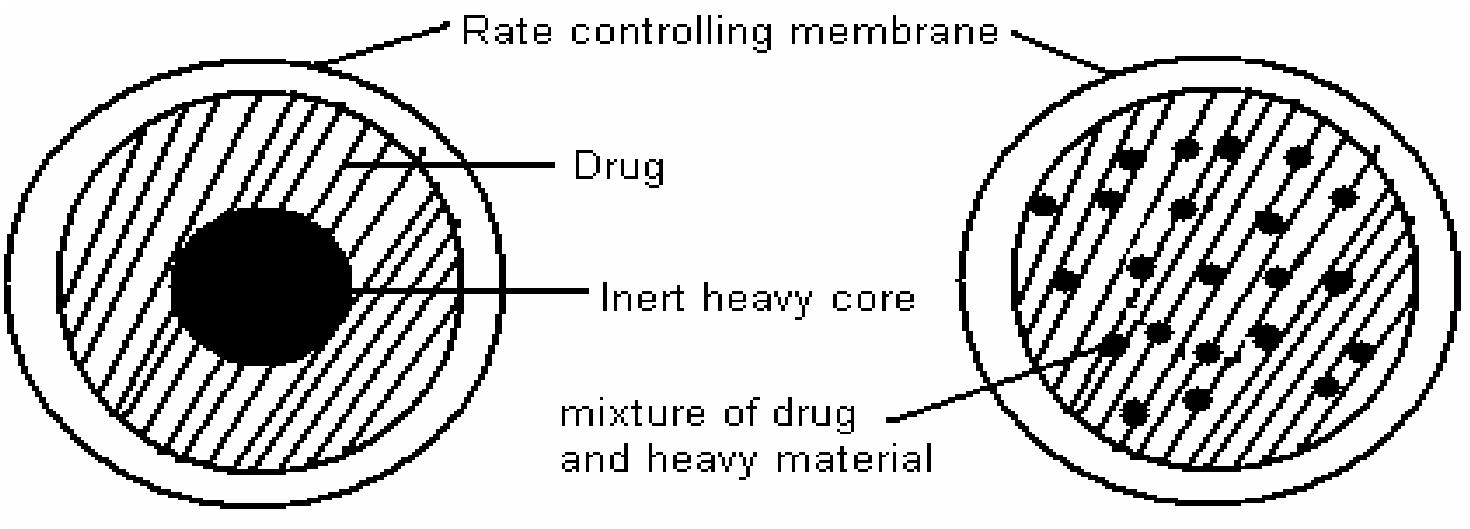
Rate Controlling Factors:
Fluid Permeability
Surface area of wall with openings
Hydrodynamic pressure gradient



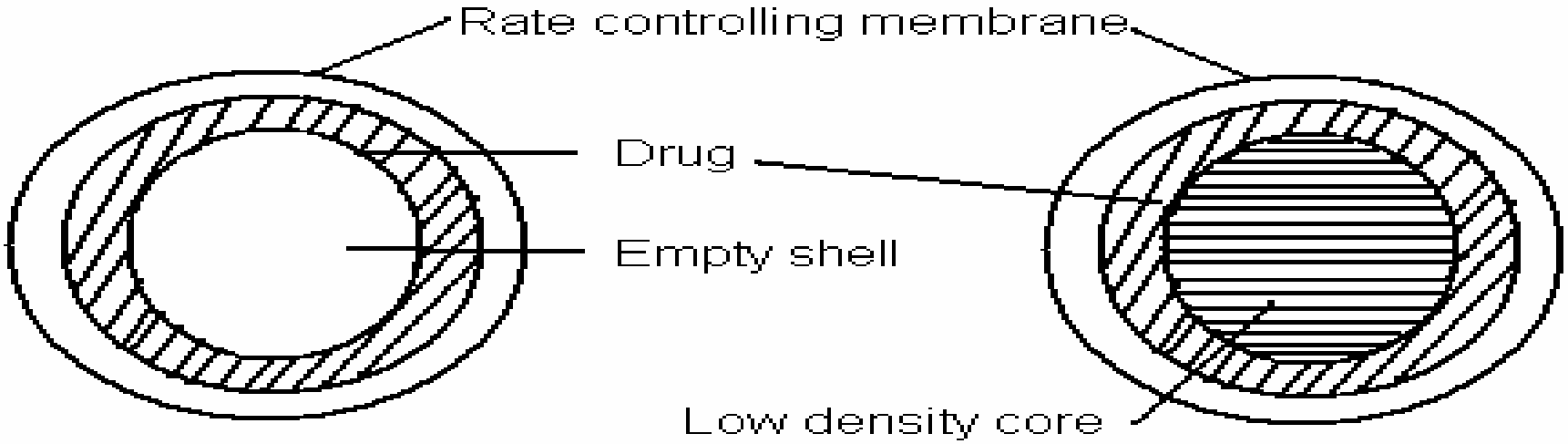
Hydrodynamic Pressure Controlled Systems

(Push-pull Osmotic Pump)

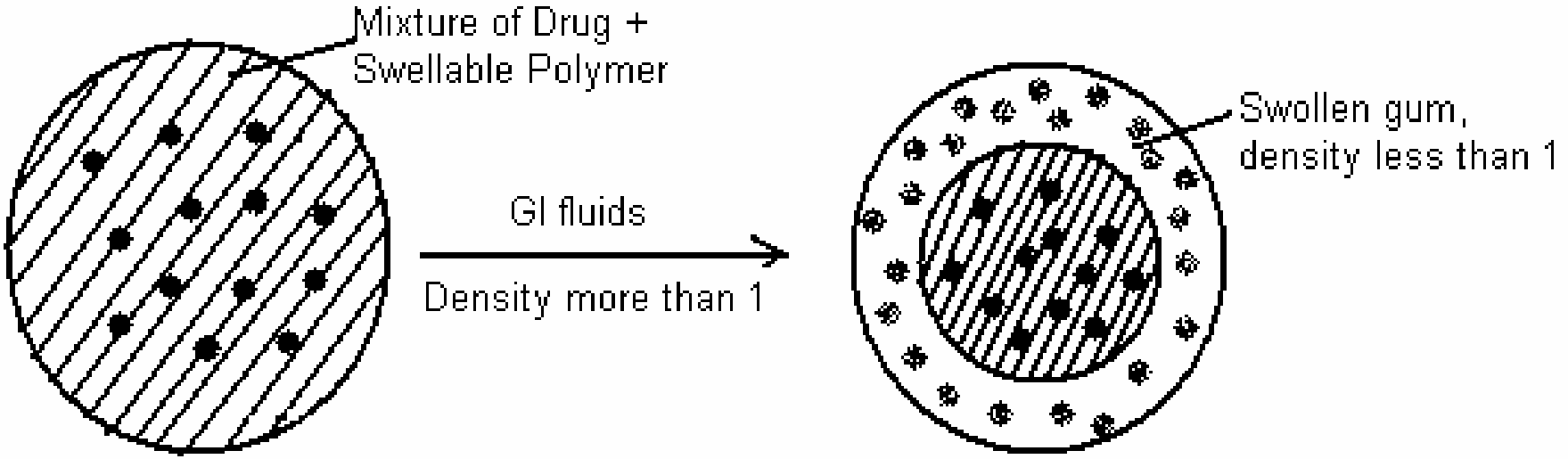
- Altered Density Systems:



High Density Pellets



Low Density Pellets with Hollow Core



Low Density Pellets with Hydrogels

Others

- Slow Dissolving Salts and Complexes
- pH-Independent Formulations
- Floating or Buoyant Tablets/Capsules

Thank you