UNIT 1
CONTROLLED DRUG DELIVERY SYSTEMS-2

Dr. Meenakshi Gupta
Senior Assistant Professor
University Institute of Pharmacy
C. S. J. M. University Kanpur U.P

Contents

- Activation Modulated Drug Delivery System**Selection of drug candidates.**
- **Approaches to design controlled release formulations based on**
- **diffusion, dissolution and ion exchange principles.**
- **Physicochemical and biological properties of drugs relevant to controlled release formulations**

Classification Of Controlled Release System

1.Rate pre-programmed drug delivery system

- The release of drug molecule is preprogrammed at specific rate profile

2.Activated modulated drug delivery system

- The release of drug molecules from the delivery system is activated by some physical, chemical, or biochemical process and/or by energy supplied externally

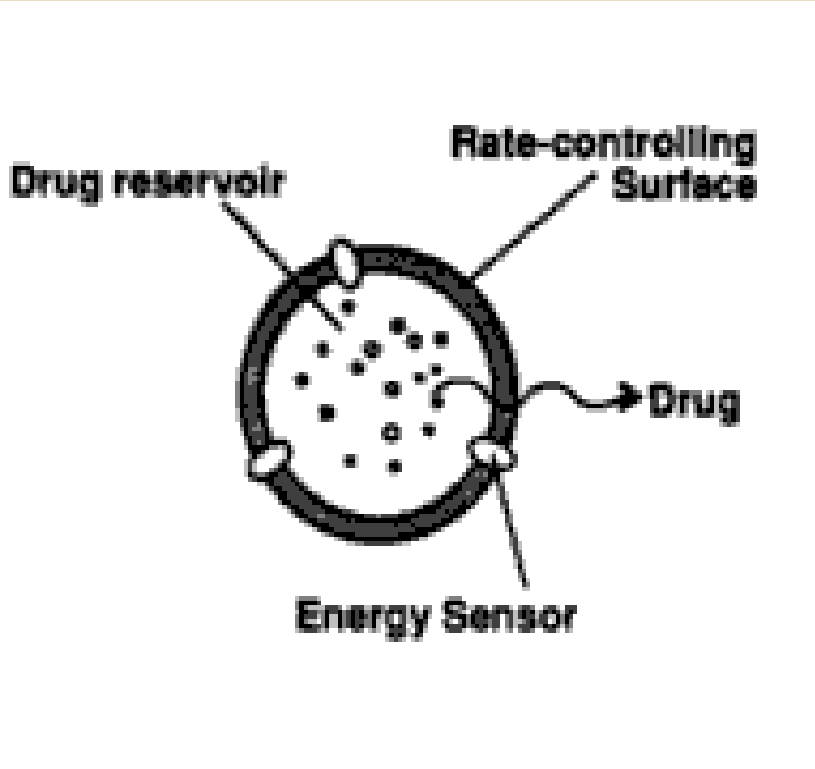
3. Feedback regulated drug delivery system

- physiological response activates the release of drugs from the carrier
- rate of drug release is synchronized by the concentration of a triggering agent

4. Site targeting drug delivery system

- (1)First order targeting: - drugs carrier release the drugs at the targeted site such as organ, tissue, cavity, etc.
- (2) Second order targeting: - drugs carrier release the drugs in the specific cell such as tumors cells not to the normal cells.
- (3) Third order targeting: - drugs carrier release the drugs to the intracellular site of targeted cells.

Activation Modulated Drug Delivery System



- The release of drug molecules from the delivery system is **activated** by some physical, chemical, or biochemical process and/or by energy supplied externally.

Based on nature of type of activation energy used they can be classified into

A. Physical means

1. Osmotic pressure-activated DDS
2. Hydrodynamic pressure-activated DDS
3. Vapor pressure-activated DDS
4. Mechanically activated DDS
5. Magnetically activated DDS
6. Sonophoresis activated DDS
7. Iontophoresis activated DDS
8. Hydration-activated DDS

B. Chemical means

1. pH- activated DDS
2. Ion- activated DDS
3. Hydrolysis- activated DDS

C. Biochemical means

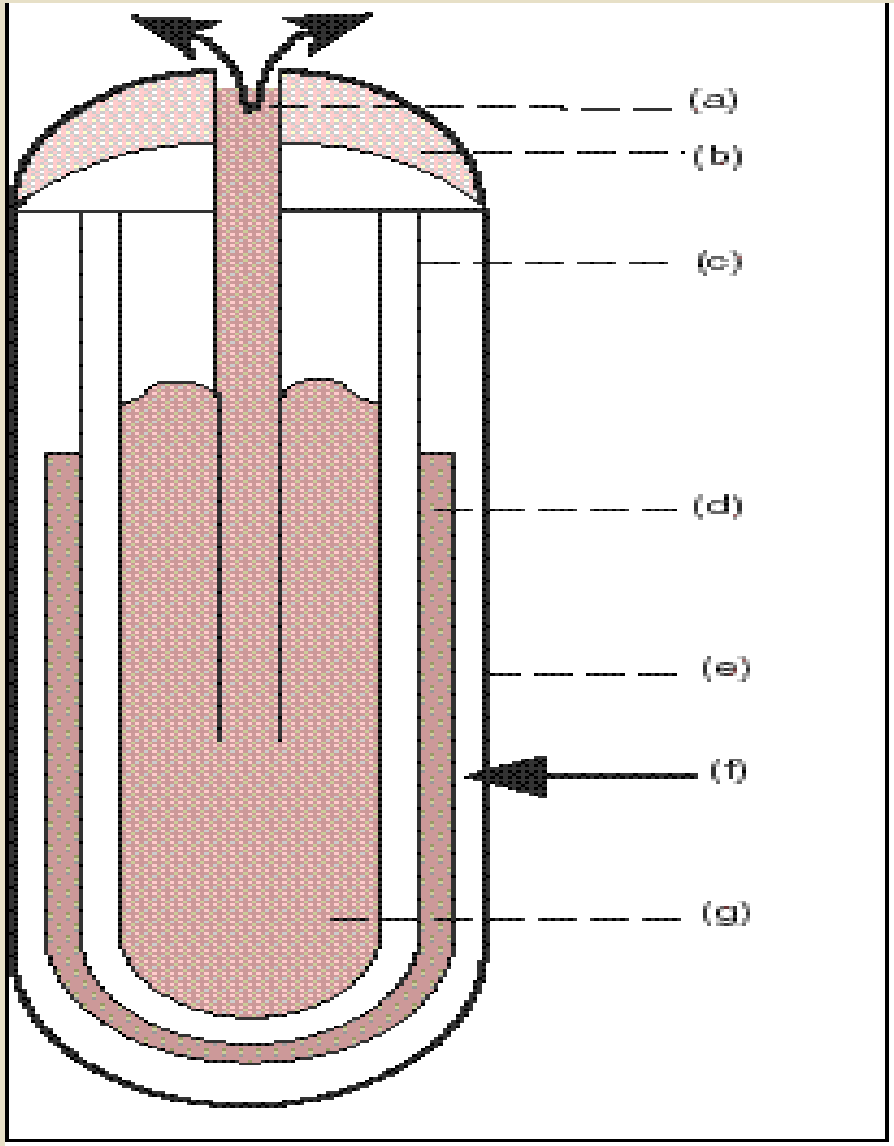
1. Enzyme- activated DDS
2. Biochemical- activated DDS

Physical energy Activated Drug Delivery System

1. Osmotic Pressure Controlled Activated Drug Delivery System

Drug reservoir is either solution or solid formulation contained within semi permeable housing with controlled water permeability.

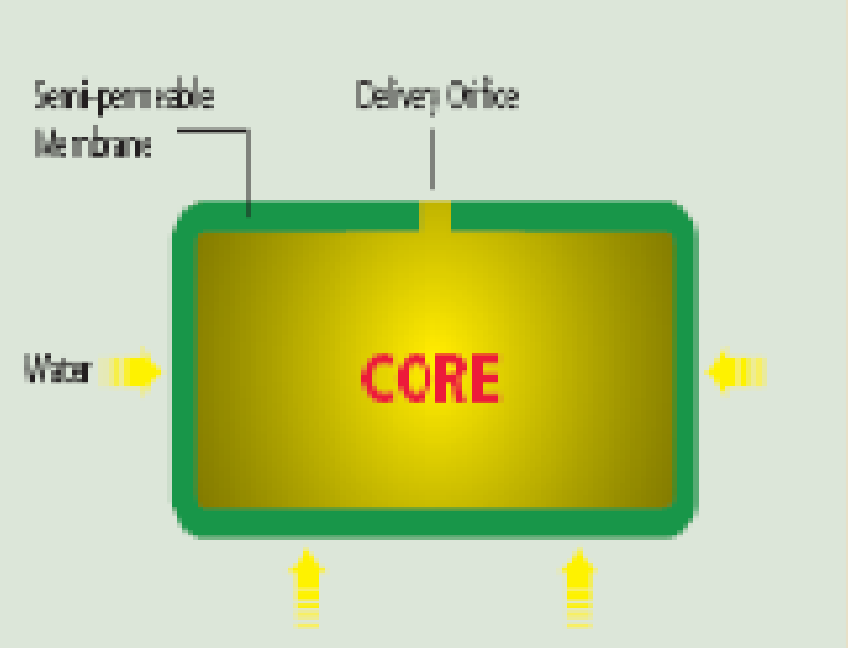
The **gradient of osmotic pressure** activate the release of drug(solution form) at a constant rate through a special delivery orifice.

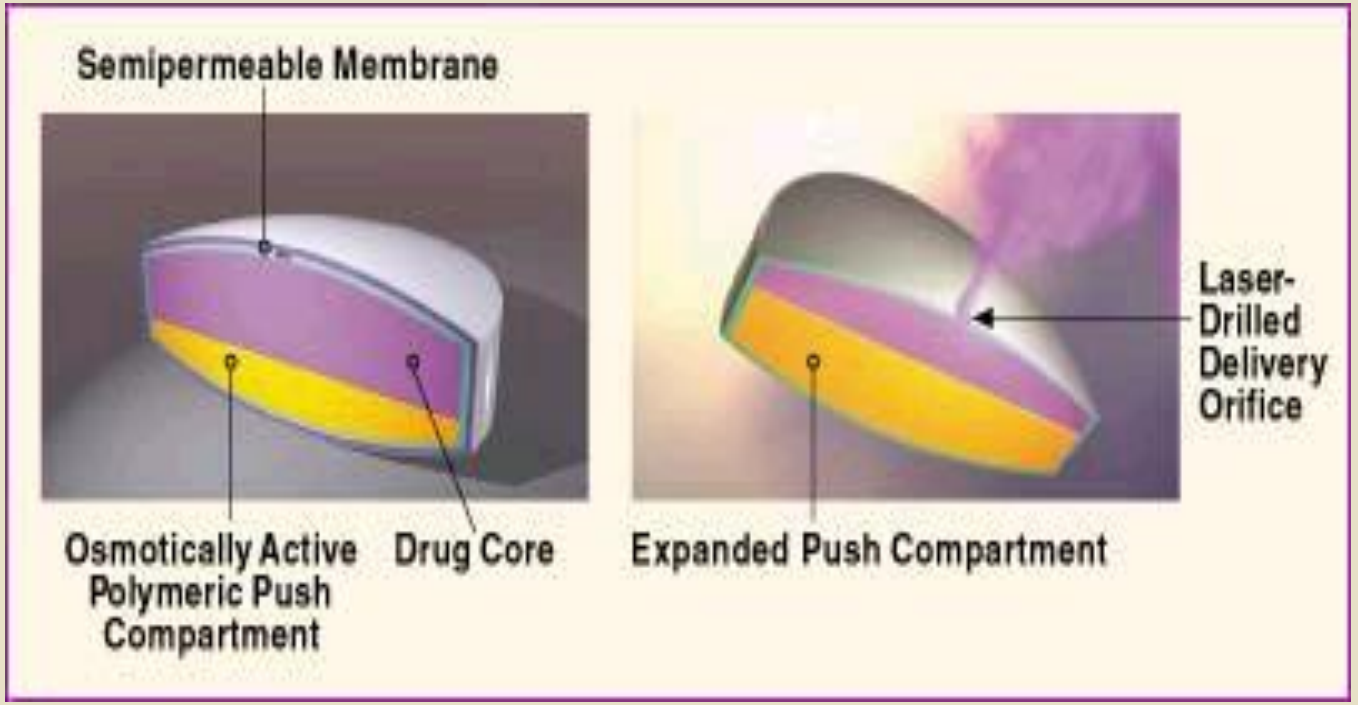


The elements of an osmotic pump:
(a) drug solution leaving through delivery portal;
(b) removable cap;
(c) impermeable reservoir wall;
(d) osmotic agent;
(e) semipermeable membrane;
(f) water entering through semipermeable membrane; and
(g) reservoir.

Ex. Alzet Osmotic pump

ELEMENTARY OSMOTIC PUMP





For the drug delivery system containing a solution formulation, the intrinsic rate of drug release is defined by,

$$\frac{Q}{t} = \frac{P_w A_m}{h_m} (\pi_s - \pi_e)$$

For the drug delivery system containing a solid formulation, the intrinsic rate of drug release is defined by,

$$\frac{Q}{t} = \frac{P_w A_m}{h_m} (\pi_s - \pi_e) S_d$$

Where,

Q/t - rate of drug release

P_w - permeability of semipermeable housing

A_m -effective S.A. of semipermeable housing

h_m - thickness of semipermeable housing

$(p_s - p_e)$ – differential osmotic pressure between the drug delivery system with osmotic pressure p_s & the environment with osmotic presure p_e.

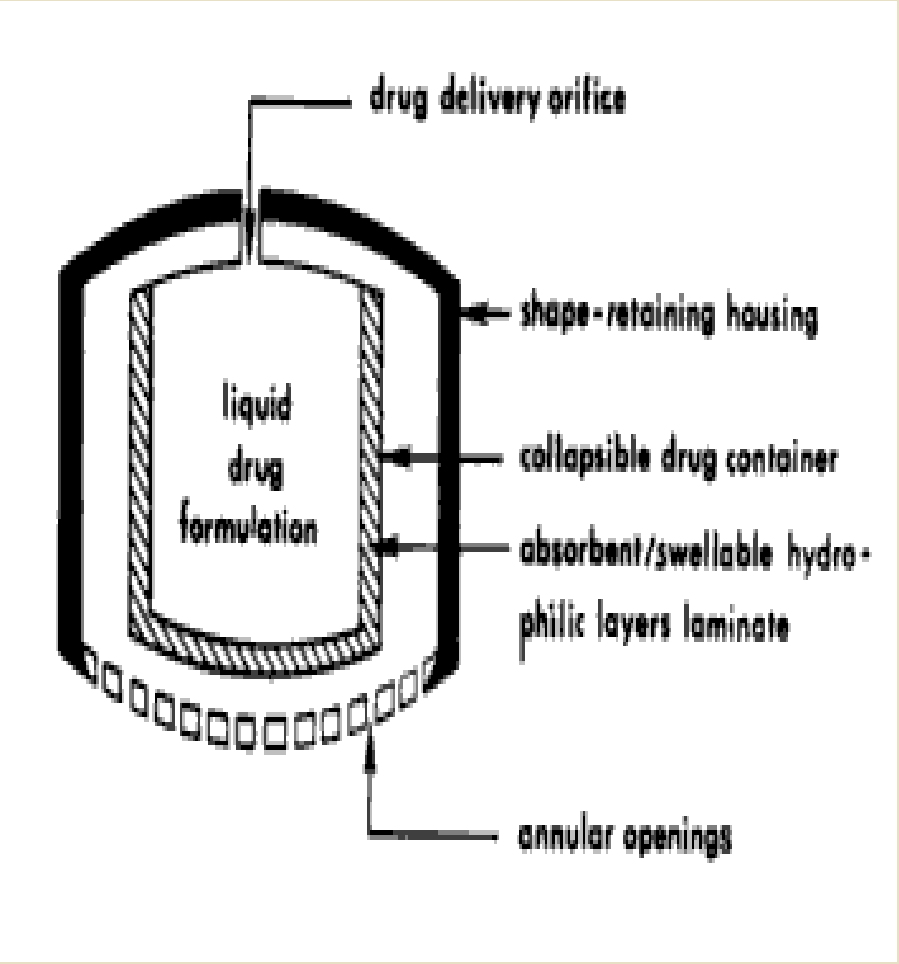
S_d – aqueous solubility of the drug contained in the solid formulation.

Rate controlling factors :

- Water permeability of the semi permeable membrane.
- Effective surface area of the semi permeable membrane.
- Osmotic pressure difference across the semi permeable membrane.

2. Hydrodynamic Pressure-Activated Drug Delivery System

- This system is fabricated by enclosing a **collapsible, impermeable container,** which contains liquid drug formulation to form a drug reservoir compartment inside rigid shape-retaining housing.
- The induced hydration stimulate the release the drug.
- The release of the drug is controlled by the rate of swelling of polymer matrix



- In the GIT, the laminate absorb the GI fluid through the annular openings at the lower end of the housing & becomes increasingly swollen, which generates hydrodynamic pressure in the system.
- Rate of drug release is defined by,

$$\frac{Q}{t} = \frac{P_f A_m}{h_m} (q_s - q_e)$$

Where,

P_f = fluid permeability

A_m = effective Surface area

h_m = thickness of wall with anular opening

$(q_s - q_e)$ = differential hydrodynamic pressure between the drug delivery system & the environment.

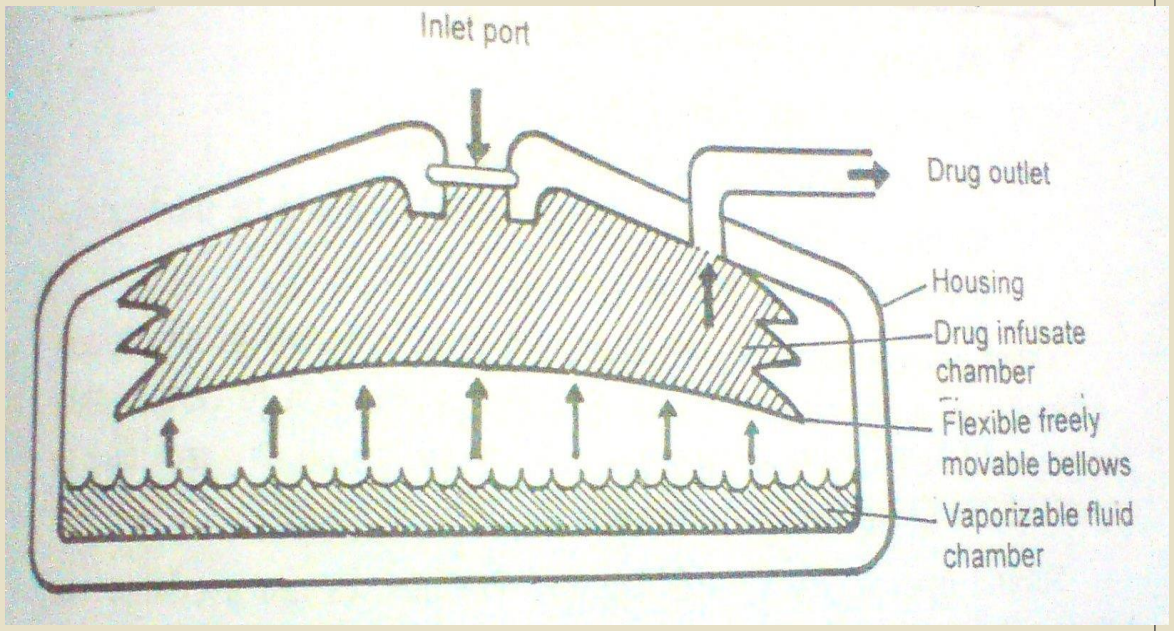
Hydrodynamic Pressure-Activated Drug Delivery System

Rate controlling factors :

- Fluid permeability
- Effective surface area of the wall with the annular opening.
- Hydrodynamic pressure gradient.

3. Vapor Pressure-Activated Drug Delivery System

- the drug reservoir in a solution formulation contained inside an **infusate chamber**
- It is physically separated from the vapor pressure chamber by a freely movable bellows.
- The vapor chamber contains a vaporizable fluid, which vaporizes at body temp. & creates a vapor pressure.
- Under the vapor pressure, the bellows moves upward & forces the drug solution in the infusate chamber to release at a constant flow rate.



Vapor Pressure-Activated Drug Delivery System

The rate of drug release is defined by,

$$\frac{Q}{t} = \frac{d^4 (P_s - P_e)}{40.74\ ml}$$

Where-

Q/t - rate of drug release

d – inner diameter of cannula

l – length of cannula

$(P_s - P_e)$- the difference between the vapor pressure in the vapor chamber & pressure at the implantation site.

m - viscosity of the drug solution.

Vapor Pressure-Activated Drug Delivery System

Rate controlling factors :

- Differential vapor pressure
- Formulation viscosity
- Size of the delivery cannula

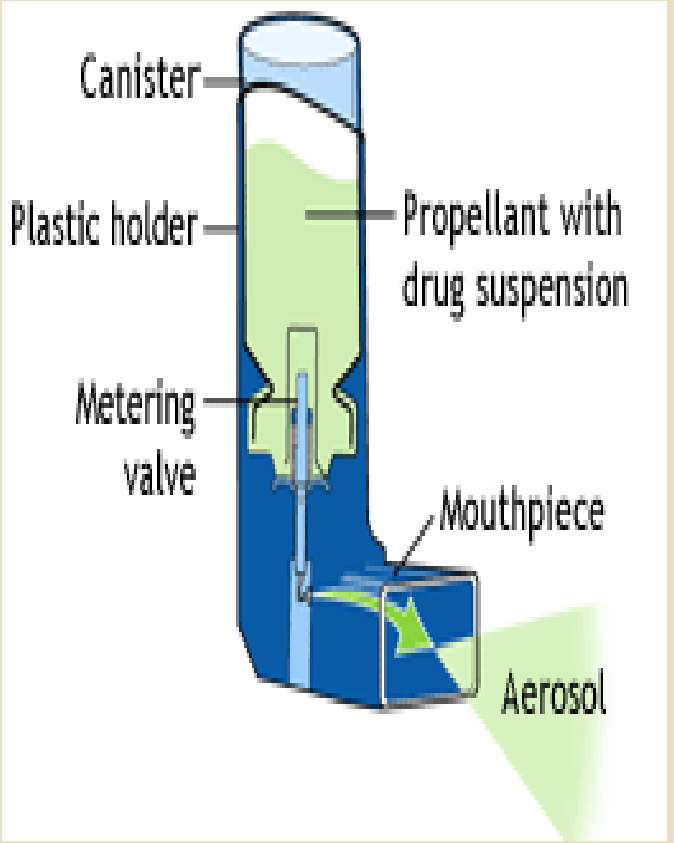
Ex. An implantable infusion pump for the constant infusion of heparin for anti-coagulant therapy, insulin in diabetic treatment & morphine for patient suffering from the intensive pain of terminal cancer.

Mechanically Activated drug delivery system

- In this type, drug reservoir is in solution form retained in a container equipped with mechanically activated pumping system.
- A measured dose of the drug formulation is reproducible delivered in to a body cavity

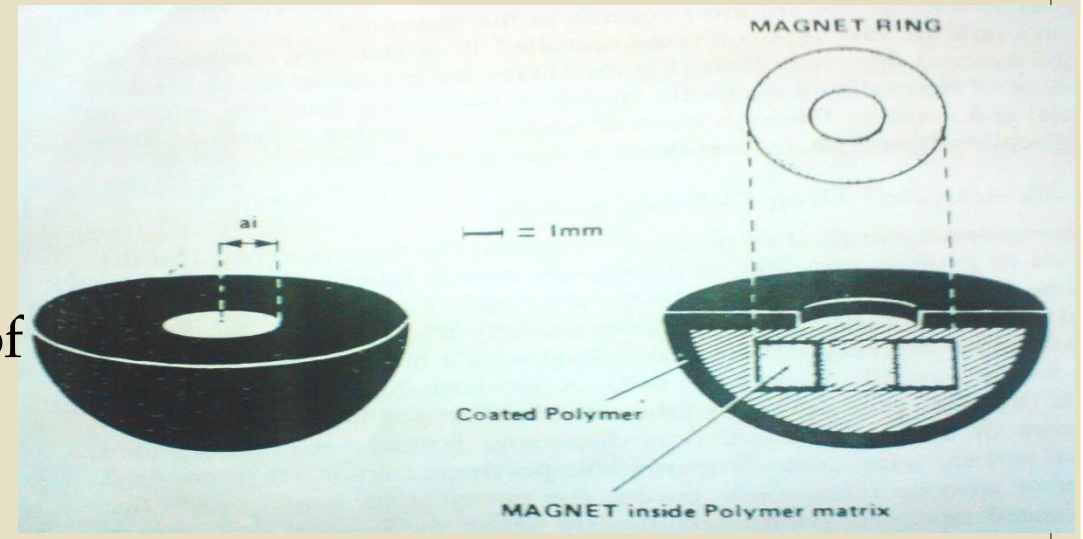
Ex. Metered-dose inhaler

- the volume of solution delivered is controllable, as small as 10-100 ml & is independent of the force & duration of the activation applied as well as the solution volume in the container.

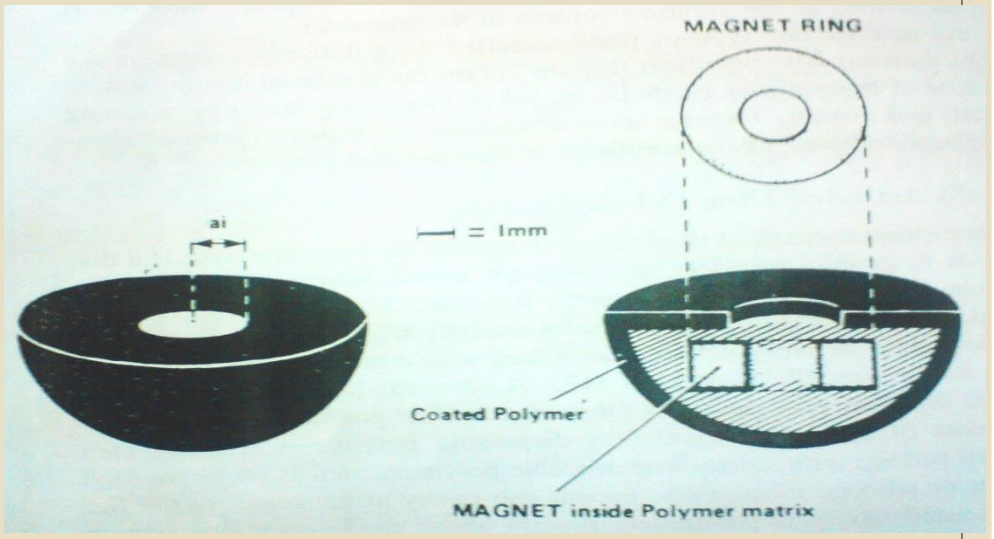


Magnetically Activated Drug Delivery System

- drug reservoir is a **dispersion of peptide or protein powders in polymer matrix in hemispherical design** from which macromolecular drug can be delivered only at a relatively slow rate.
- Device is fabricated by positioning a tiny magnet ring in core of hemispherical drug dispersing polymer matrix.
- The external surface is coated with drug impermeable polymer (ethylene vinyl acetate or silicon elastomer) except one cavity at the centre of the flat surface.

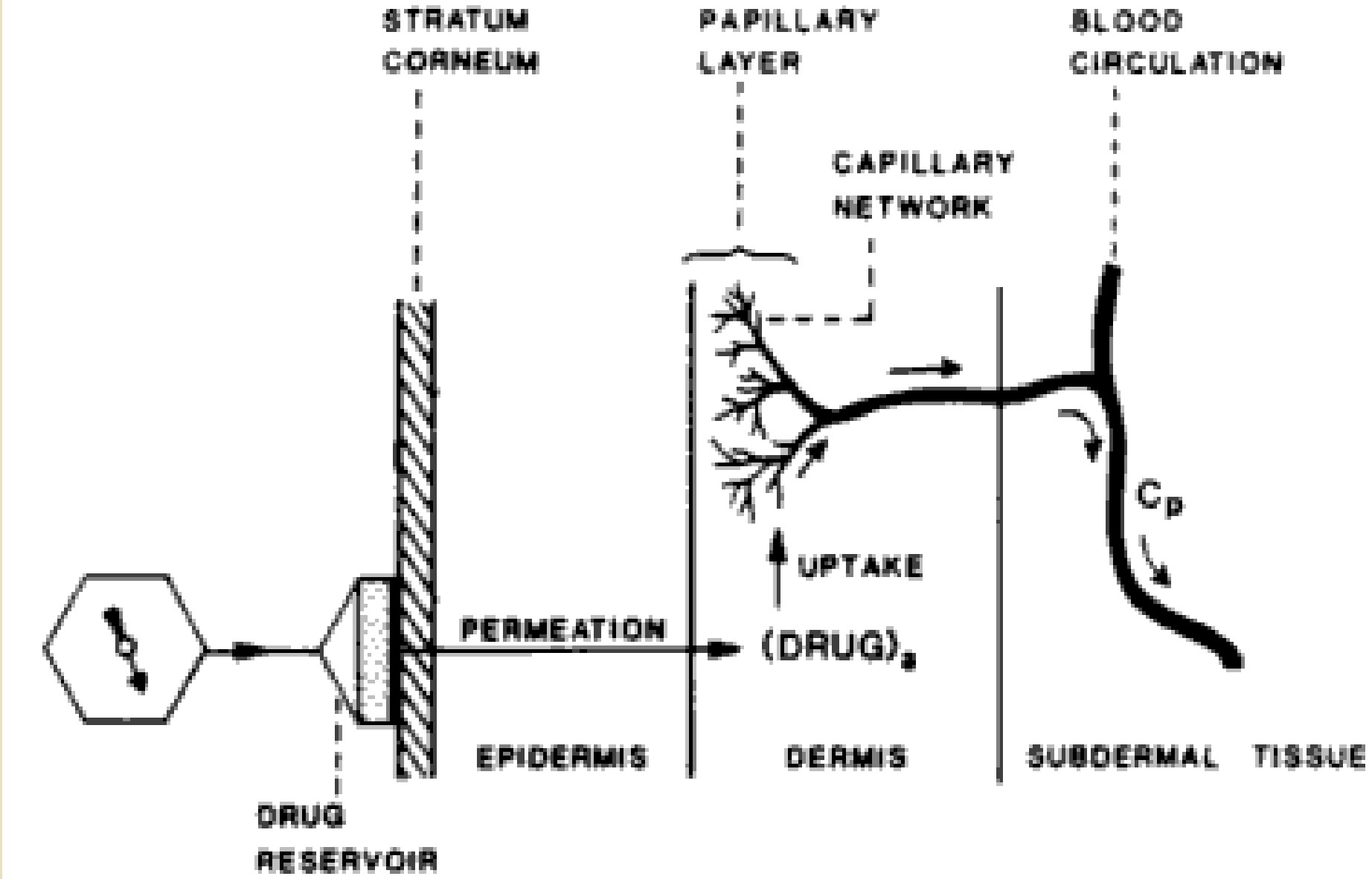


- This low rate of delivery can be improved by incorporating **electromagnetically triggered vibration** mechanism into polymeric device
- This delivery device used to deliver protein drugs such as bovine serum albumin, at a low basal rate, by a simple diffusion process under non triggering condition.
- As the magnet is activated to vibrate by external electromagnetic field, drug molecules are delivered at much higher rate.



Sonophoresis - Activated Drug Delivery System

- Also called as Phonophoresis.
- This type of system utilizes **ultrasonic energy to activate or trigger the delivery of drug** from polymeric drug delivery device.
- System can be fabricated from nondegradable polymer (ethylene vinyl acetate) or bioerodiable polymer (poly[bis(p-carboxyphenoxy) alkane anhydride]


STRATUM
CORNEUM
PAPILLARY
LAYER
BLOOD
CIRCULATION
CAPILLARY
NETWORK
C_p
UPTAKE
PERMEATION
$(DRUG)_s$
EPIDERMIS
DERMIS
SUBDERMAL TISSUE
DRUG
RESERVOIR

Iontophoresis activated drug delivery system

- This type of system uses **electrical current** to activate & to modulate the diffusion of charged drug across biological membrane.
- Iontophoresis – facilitated skin permeation rate of charged molecule (i) consist of 3 components & is expressed by,

$$J_i^{isp} = J^p + J^e + J^c$$

Where,

J^p – passive skin permeation flux.

$$= K_s D_s \frac{dC}{h_s}$$

K_s = partition coefficient for interfacial partitioning from donor solution to stratum corneum

D_s = diffusivity across the skin

$\frac{dC}{h_s}$ = concentration gradient across the skin

J^e – electrical current driven permeation flux

$$= \frac{Z_i D_i F}{RT} C_i \frac{dE}{h_s}$$

Z_i = electric valency of the ionic species i

D_i = diffusivity of ionic species i in the skin

F = faraday constant

T = absolute temperature

C_i = donor conc. of ionic species i in the skin

$\frac{dE}{skin}$ = electrical potential gradient across the

h_s

J^c = convective flow driven skin permeation flux

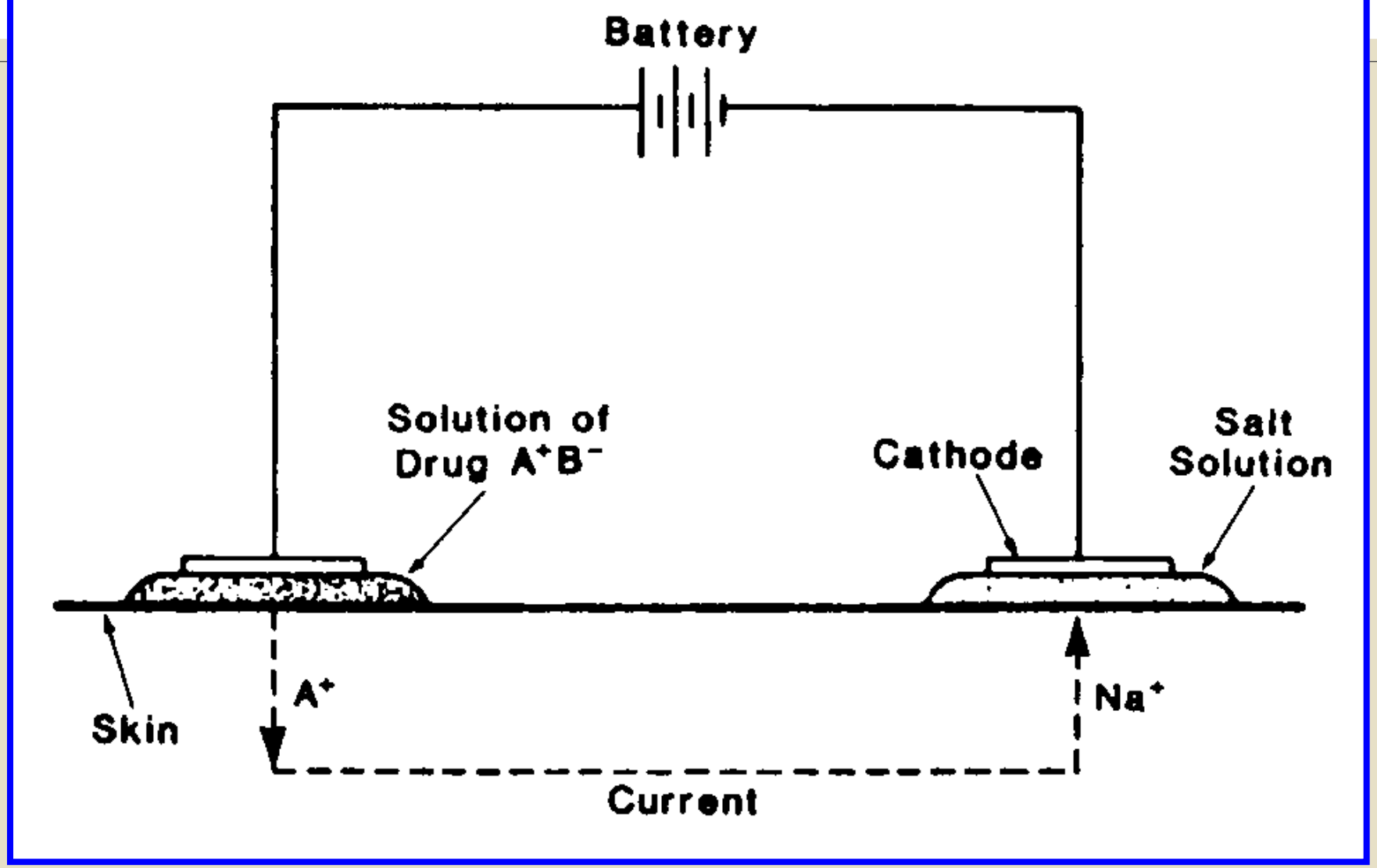
$= k C_s I_d$

Where,

K = propertionality constant

C_s = conc. In the skin tissue

I_d = current density applied

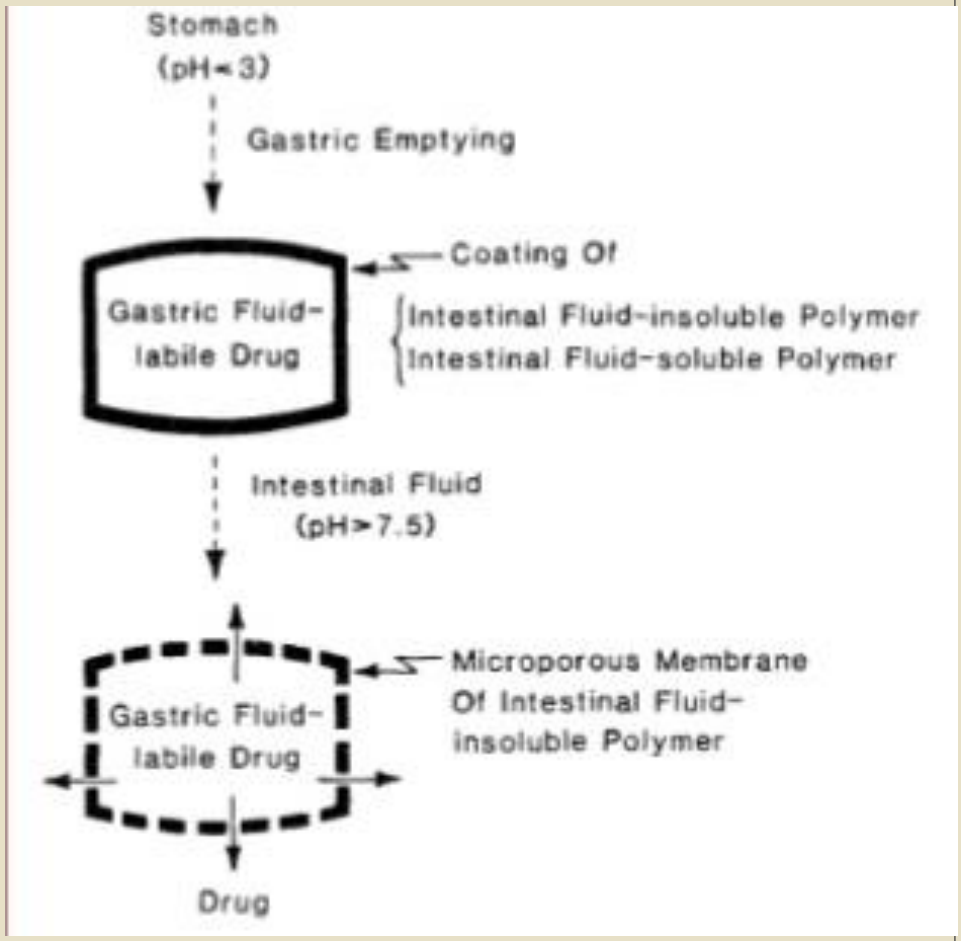


Schematic diagram illustrating the principles of iontophoresis

Chemically Activated Drug Delivery System

pH- Activated Drug Delivery System

- This type of system permits the delivery of drug only in the particular region with selected pH range.
- It is fabricated by coating the drug-containing core with a **pH – sensitive polymer**.
- gastric fluid labile drug is protected by encapsulating it inside a polymer membrane

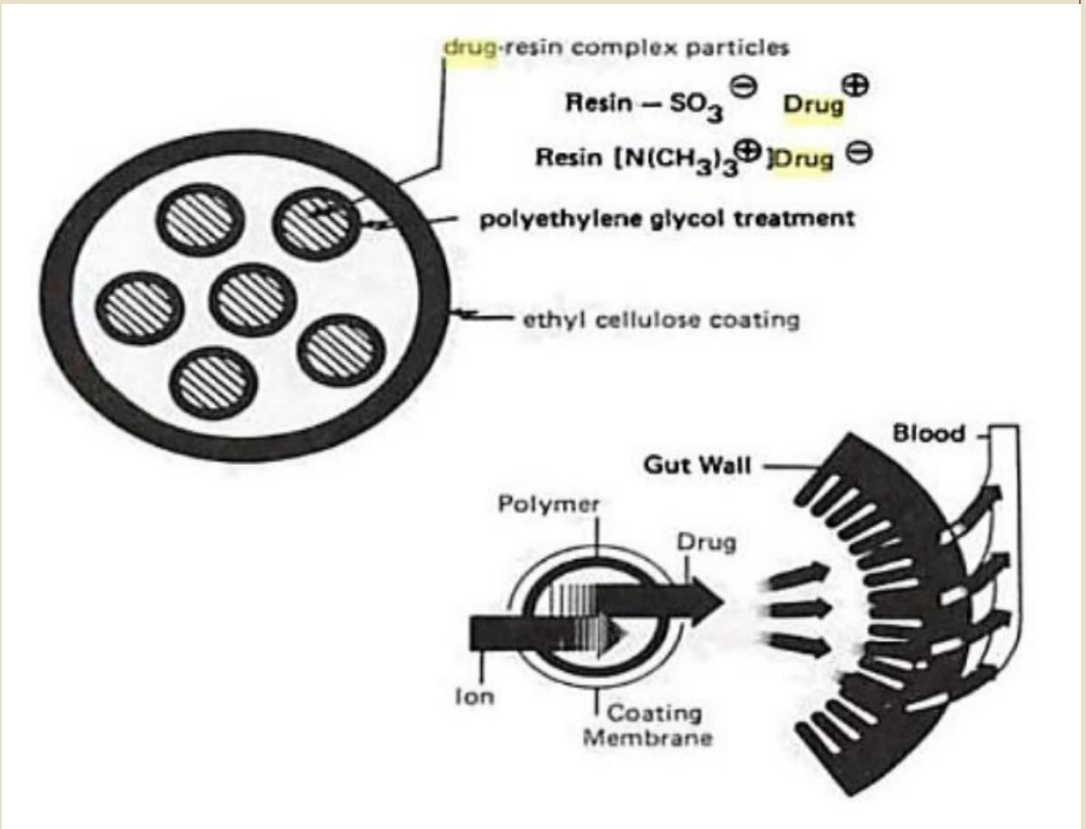


pH- Activated Drug Delivery System

- In the stomach, polymeric coating remain intact and the drug molecule thus protected from acid degradation.
- After gastric emptying the DDS reaches to the small intestine. pH of intestinal fluid (pH>7.5) activates the erosion of polymeric coating.
- This leaves a micro porous membrane which controls the release of drug from the core tablet.
- The drug solute is thus delivered at a controlled manner in the intestine by a combination of drug dissolution & pore-channel diffusion.

Ion- activated DDS

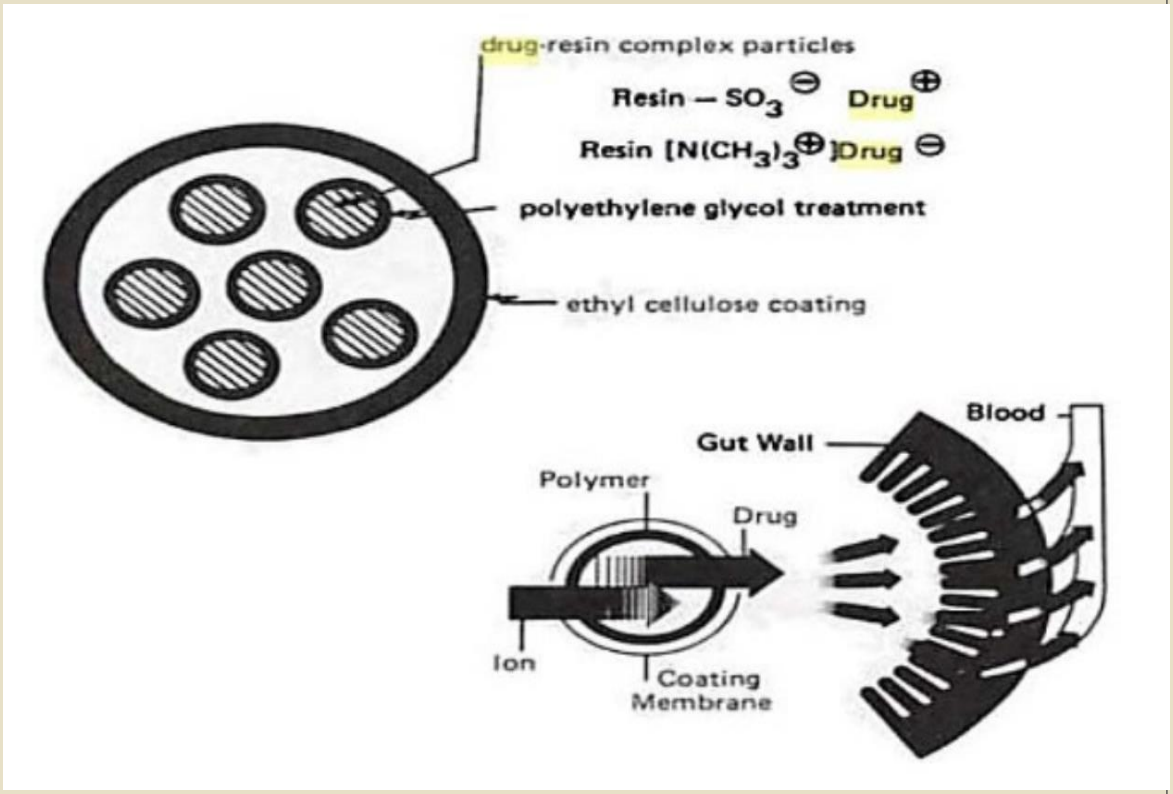
- An **ionic or a charged drug** can be delivered by this method
- ionic drug is formed complex with an **ion-exchange resin** containing a suitable counter ion.
- The granules of drug-resin complex are first treated with an impregnating agent & then coated with a water-insoluble but water-permeable polymeric membrane.
- membrane serves as a **rate-controlling membrane** that control the influx of ions release of drug from the system.



In an ionic medium, such as gastric fluid ions diffuse into the system and reacts with drug resin complex & trigger the release of ionic drug

Ex.

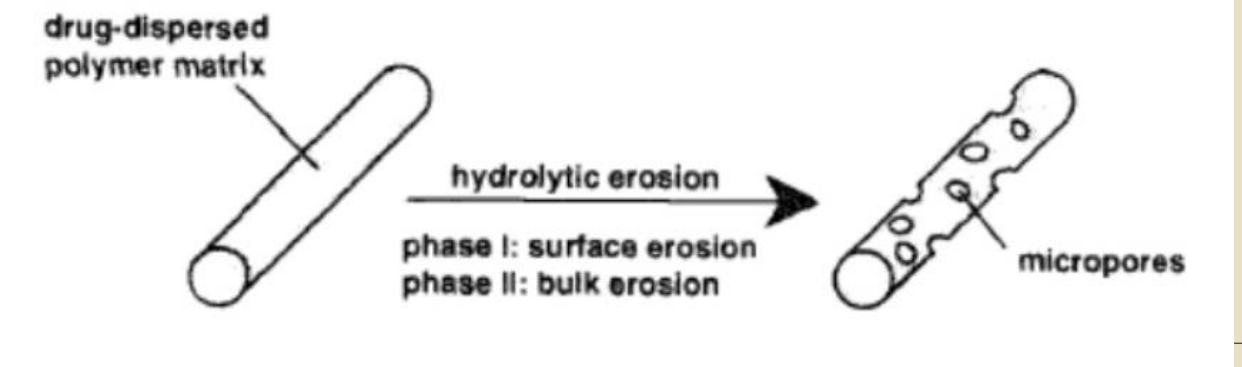
- cationic drug form complex with a resin having a So_3^- group or
- an anionic drug with a resin having a $N(CH_3)_3$ group



Hydrolysis- activated DDS

- This type of system depends on the **hydrolysis process** to activate the release of drug.
- It can be fabricated as drug reservoir (encapsulated in microcapsules or microspheres or nano particles) for injection or as an implantable device.
- systems prepared from **bioerodible or biodegradable** polymers (polyanhydride, polyorthoesters).
- Drug release is controlled by rate of hydrolysis-induced polymer degradation.

Ex. LHRH – releasing biodegradable subdermal implant for once a month treatment of prostate carcinoma.



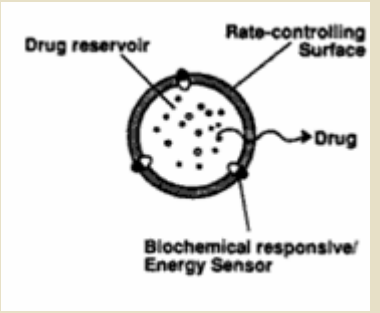
Biochemically Activated Drug Delivery System

Enzyme- activated DDS

- The release of drug is activated by **enzymatic hydrolysis** of biopolymers (albumins or polypeptides) by specific enzyme in target tissue
- Drug reservoir is either physically entrapped in microspheres or chemically bound to polymer chains from biopolymers (**albumins** or polypeptides).
- Albumin microspheres release 5 – fluorouracil in a controlled manner by protease – activated biodegradation

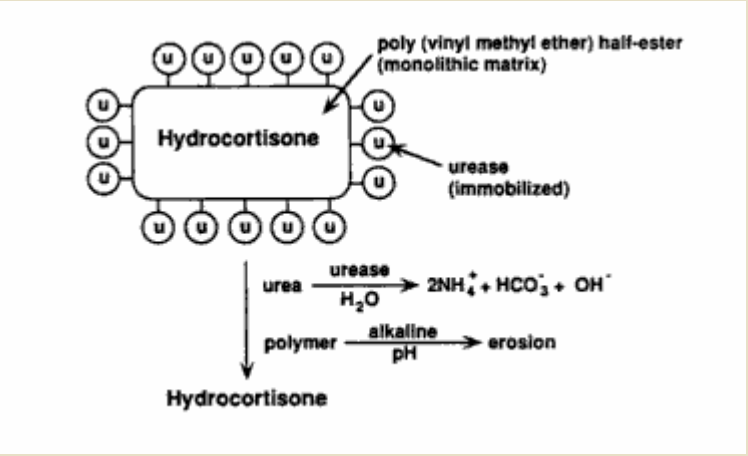
Feedback regulated drug delivery system

- The drug release is activated by a **triggering agent** and rate of drug release depend on the concentration of triggering agent.
  - Bioerosion-regulated drug delivery system
  - Bio responsive drug delivery system
  - Self-regulating drug delivery system



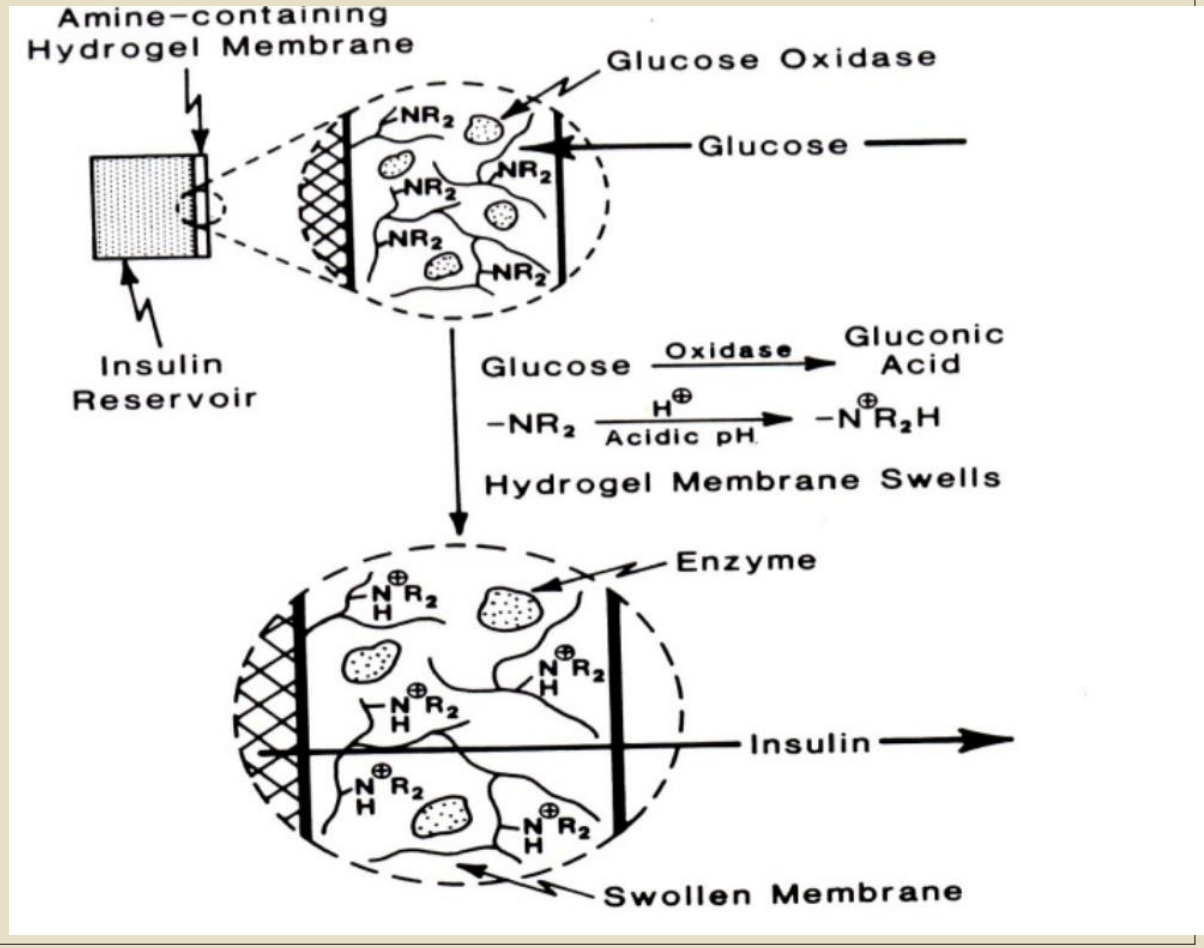
Bioerosion-regulated drug delivery system

- The system consisted of drug-dispersed bioerodible matrix fabricated from poly (vinyl methyl ether) ester which is coated with layer of immobilized urease.
- At neutral pH, the polymer only erodes very slowly
- urease enzyme metabolizes urea to form ammonia.
- This causes increase in pH & rapid degradation of polymer with release of drug molecule.



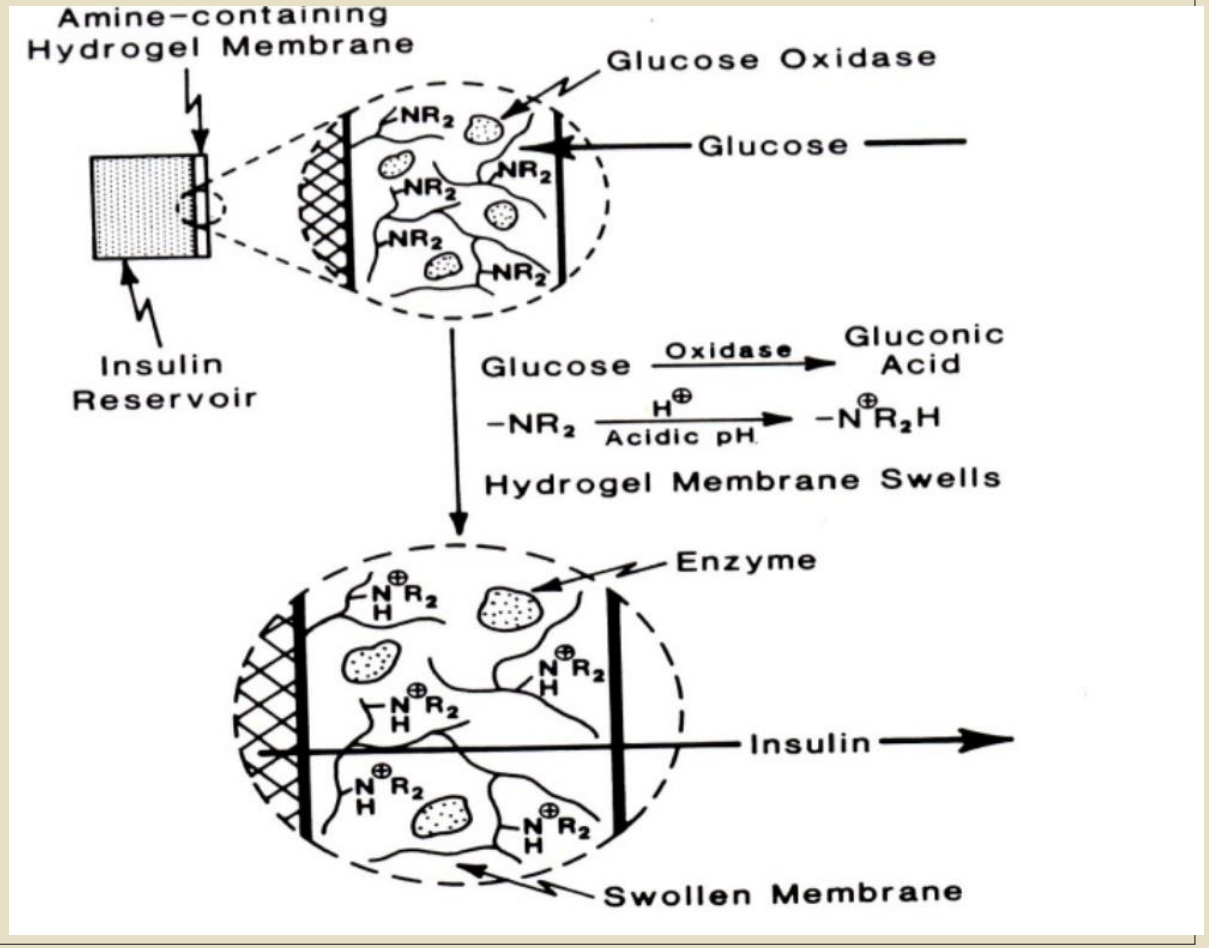
Bioresponsive Drug Delivery System

- Drug is enclosed in **bioresponsive polymeric membrane** whose drug permeability is controlled by concentration of biochemical agent.
- Example-Glucose-triggered Insulin delivery system



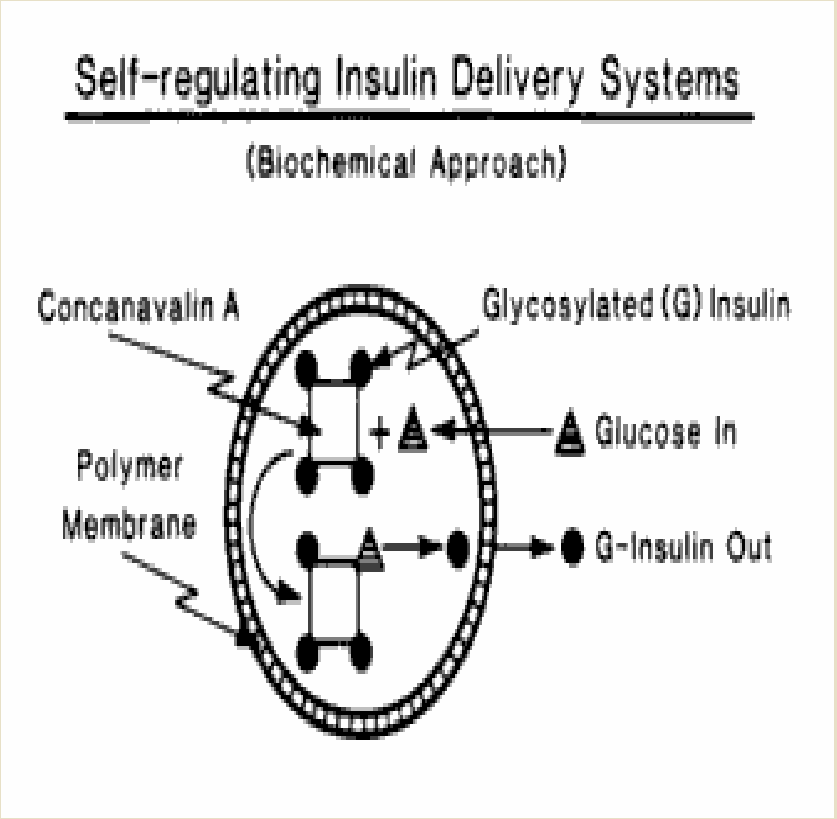
Bioresponsive Drug Delivery System

- the insulin is encapsulated within hydro gel polymeric membrane having $-NR_2$ group.
- at alkaline pH, the $-NR_2$ are neutral & the membrane is unswollen & impermeable to insulin.
- **Glucose oxidase** is entrapped between the polymeric membrane
- Glucose penetrates into the membrane and get oxidizes enzymatically to form gluconic acid.
- The $-NR_2$ group is protonated to form $-NR_2H^+$ & the hydro gel membrane then becomes **swollen & permeable** to insulin molecules.



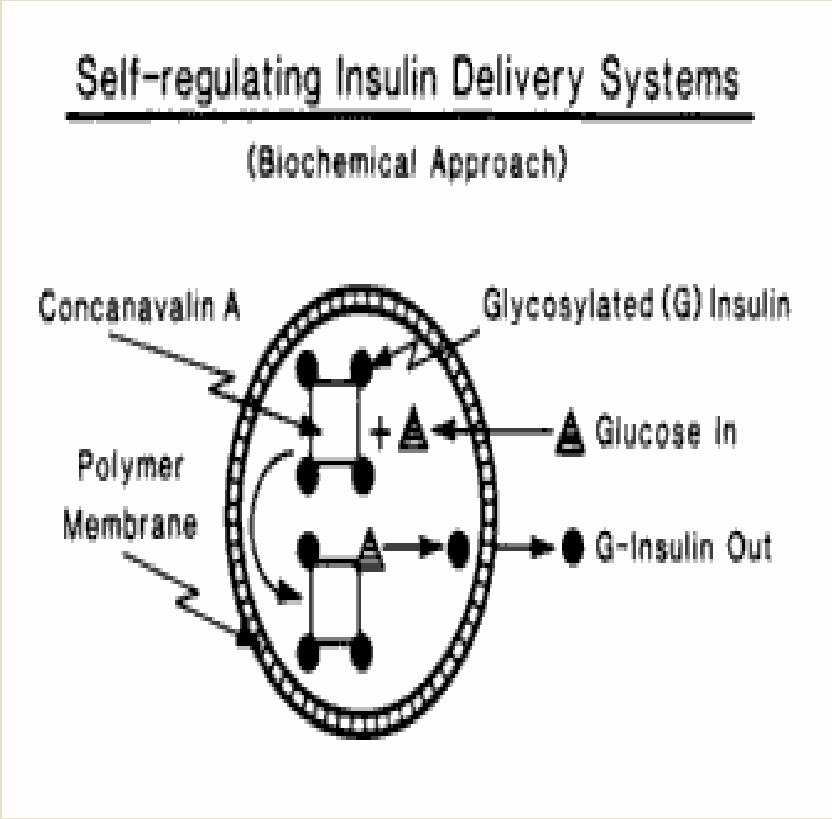
Self-regulating Drug Delivery System

- This type of system based on a **reversible & competitive binding mechanism to activate and regulate the release of drug**.
- Drug complex is encapsulated within a polymeric membrane.
- The release of drug is activated by the membrane permeation of biochemical agent from the tissue in which the system is located.



Self-regulating Drug Delivery System

- complex of **glycosylated insulin & concanavalin A**, is encapsulated inside a polymer membrane.
- Glucose enters into the system & it activates the release of glycosylated insulin from the complex for controlled delivery out of system.



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