Drug Delivery Systems

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Introduction

- Method or process of administering an active pharmaceutical ingredient (API) to achieve therapeutic effect in humans or animals.

- Modify drug release profile and pharmacokinetic parameters for the benefit of improving product efficacy as well as patient convenience and compliance.

- Aims to deliver the drug at a rate directed by the needs of the body during the period of treatment, and target the active entity to the site of action

Disadvantages in current therapy

- Inactivation by gastric juice
- Metabolism before reaching target cell – First pass metabolism in lung / liver / Intestine
- Too many adverse reactions

How to overcome this???

- By improving rate of drug delivery
- Decreasing biodegradation
- Time release medications
- Site-specific targeting
- Administer injectable only medications in oral form
- Costly, multiple-dose, long-term therapies → Inexpensive, potent, time-releasing or self-triggering formulations.

Oral Drug Delivery Systems

- **Ideal –** steadily deliver measurable and reproducible amount of drug to the target site over a prolonged period.

1. Oral Controlled Release Systems

- Mostly solids
- Based on dissolution, diffusion or a combination of both mechanisms in the control of release rate of drug.

A. Continuous release systems

B. Delayed transit and Continuous release systems

C. Delayed release systems

A. Continuous release systems

- Release drug for prolonged period of time along entire length of GIT with normal transit of the dosage form.

a) Dissolution Controlled Release Systems

- Obtained by slowing dissolution rate of drug in GI medium by incorporating drug in an insoluble polymer and coating drug particles or granules with polymeric materials of varying thickness.
- Matrix Dissolution Systems- waxes
- Reservoir Dissolution Systems- cellulose and PEG
- Griseofulvin and digoxin

b) Diffusion Controlled Release Systems

- Diffusion of drug molecule occurs through a polymeric membrane
- Manufactured either by encapsulating drug particle in a polymeric membrane or dispersing in a polymeric matrix.
- Metoclopramide, ibuprofen

c) Dissolution and Diffusion Controlled Release Systems

- Drug core is encased in a partially soluble membrane
- Pores are created due to dissolution of parts of the membrane → entry of aqueous medium into core → diffusion of dissolved drug out of the system

d) Ion exchange resin-drug complexes

- Encouraged because of their physio-chemical stability, inert nature, uniform size, spherical shape
- Amphetamine, codeine

e) Osmotic Pressure Controlled Systems

- Principle of osmosis→ movement of solvent from lower concentration of solute towards higher concentration of solute across a semi-permeable membrane
- Drug release independent of pH
- Indomethacin, levodopa, zafirlukast, nifedipine

B. Delayed transit and Continuous release systems

- Designed to prolong their residence in the GIT along with their release and known as gastroretentive delivery system

a) High density (sinking) system or non-floating drug delivery system

- Dosage form density is higher than normal stomach content
- Prepared by coating drug on heavy core or mixed with inert materials

b) Floating drug delivery system

- Stomach or upper small intestine
- Low density → entrapment of air or by incorporating low density materials such as oil/ foam powder
- **Non-effervescent systems-** prepared from gel-forming or highly swellable cellulose type hydrocolloids, polysaccharides or matrix forming polymers like polyacrylate, polycarbonate.
  - Air trapped by swollen polymers confers buoyancy.
- **Effervescent (gas generating) systems-**
  - Swellable polymers like polysaccharides and effervescent component eg $NaHCO_3$, citric acid
- Acetylsalicylic acid, atenolol, ampicillin

c) Bioadhesive or mucoadhesive drug delivery system

- Enhance absorption in site specific manner
- Bioadhesive polymer adhere to epithelial surface in stomach
- Polyacrylic acid, chitosan, PEG
- Eg. Metoprolol, captopril

d) Expandable, Unfoldable and Swellable Systems

- Rigid to withstand peristalsis and mechanical contractility of stomach
- Swell→ osmotic absorption of water
- Eg. Acyclovir, metformin

e) Superporous hydrogel systems

- Swell to large size (100 times or more) due to rapid water uptake by capillary wetting through numerous interconnected open pores→ withstand sufficient mechanical pressure

- Eg. Octreotide, desmopressin

C. Delayed release systems

- Designed to release drug only at specific site in the GIT
- **Colon specific drug delivery systems**
  - Local treatment of variety of bowel diseases such as ulcerative colitis, Crohn's disease, amoebiasis, colonic cancer
  - Eg. Hydrocortisone, budesonide, olsalazine, mesalazine

2. Chewable Dosage forms

- Gum base contains an active substance either in its core or coating
- Eg. Nicotine, caffeine

3. Genetically Modified Microorganisms/ Biodrug

- Recombinant microorganisms used orally to prevent or treat diseases.
- Aim is to increase body's protection against environmental xenobiotics by ingesting microorganisms expressing phase I (CYP450) or phase II (glutathione S- transferase) xenobiotic metabolizing enzymes.
- Enzyme deficiency (eg lipase)
- Organ failure (eg by removing urea in kidney failure)

Ophthalmic Drug Delivery Systems

1. **Aqueous gel (hydrogels)**

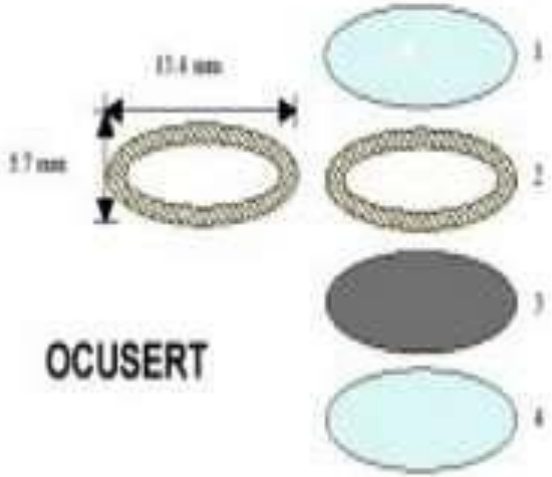
- Consist of high molecular weight, hydrophilic, cross-linked polymers forming a three dimensional network in water.
- Longer residence time
- Eg. Timolol, pilocarpine

2. Solid matrices and devices

- Solid polymeric inserts allow accurate dosing, reduced systemic absorption and better patient compliance.

a) **Ocuserts:** Thin elliptical micro units containing drug in reservoir

- Eg : Pilocarpine ocusert used in Glaucoma
  - Site : Under lower eyelid delivers the drug for a period of 7 days
  - Adv. – Pilocarpine is a short acting drug given 6 hrly is avoided.



b) Bioadhesive ophthalmic drug inserts

- Adhesive rods based on mixtures of hydroxypropyl cellulose, ethyl cellulose, polyacrylic acid cellulose

c) Lacrisert

- Rod shaped device made of hydroxypropyl cellulose
- Dry eye syndrome

3. Cyclodextrin

- Cylindrical oligosaccharides with a lipophilic central cavity and hydrophilic outer surface
- Act as carrier by keeping hydrophobic drug molecules in solution and delivering them to the surface of biological membrane.
- Eg. Steroids, pilocarpine

4. Soft contact lenses

- Poly-2-hydroxyethylmethacrylate
- Correct eyesight and hold and deliver drugs (biodegradable covalent linkages)
- Eg. Gentamicin, ciprofolxacin

5. Liposomes

- Eg. Acetazolamide, tropicamide

6. Niosomes

- Microscopic lammelar structures of size between 10 to 1000 nm
- Constituted from non-ionic surfactant and cholesterol.
- Ampiphillic in nature
  - Hydrophilic drugs entrapped in core cavity
  - Hydrophobic drugs entrapped in non-polar region present within the bilayer.
- Eg. Dorzolamide, timolol

7. Pharmacosomes

- Pure drug vesicle formed by ampiphillic drugs
- Greater shelf stability, facilitated transport across the cornea and controlled release profile

8. Collagen shield

- Cross linked collagen, fabricated with foetal calf skin tissue and developed as a corneal bandage to promote wound healing.
- Corneal ulcers

Transdermal Drug Delivery Systems

- Passive and Active transdermal delivery system
- **Passive**- gradient diffusion
- **Active**- penetration enhanced electric current, Iontophoresis, electrophoration, microporation, laser ablation, mechanical arrays, heat and ultrasound
- Classified : single layer, multilayer, matrix, reservoir, vapour patch
- Eg. Nitroglycerine, estradiol, testosterone,nicotine, clonidine, fentanyl, PTH

1. **Single layer drug in adhesive**

- Adhesive layer contains the drug

2. **Multi-layer drug in adhesive**

- Contains an immediate drug release layer
- Other layer will be controlled release along with adhesive layer.

3. **Vapour Patch**

- Adhesive layer releases vapour
- Eg. Releasing essential oils in decongestion

4. **Reservoir system**

- Drug reservoir is embedded between an impervious backing layer and a rate controlling membrane.

5. **Matrix system**

A. **Drug in adhesive system**

- Drug reservoir is formed by dispersing drug in an adhesive polymer and then spreading this polymer by solvent melting on an impervious backing layer

B. **Matrix-dispersion system**

- Drug is dispersed homogenously in a hydrophilic or lipophilic polymer matrix

6. **Microreservoir system**

- Combination of reservoir and matrix-dispersion system
- Drug reservoir is formed by first suspending the drug in an aqueous solution of water soluble polymer and then solution is dispersed homogenously in a lipophilic polymer matrix forming spheres of drug reservoirs

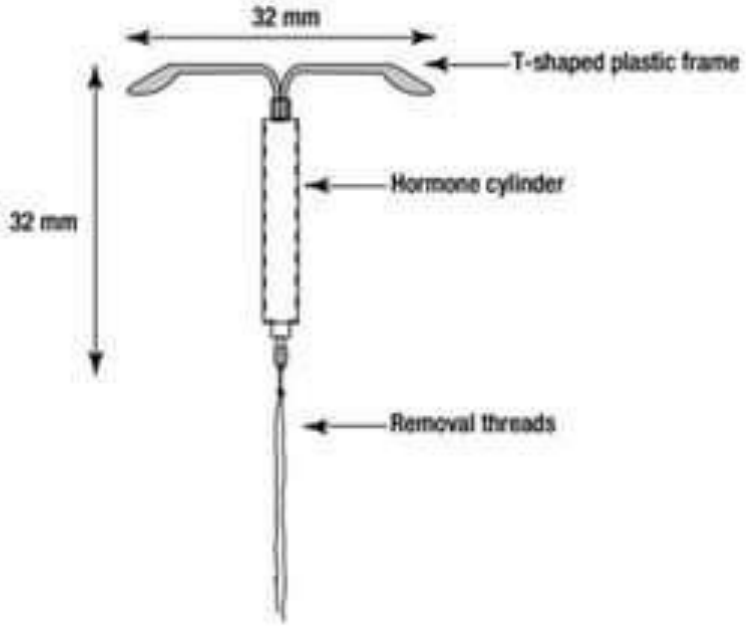
Nasal Drug Delivery Systems

- **Nebulizer** : medication in the form of mist inhaled into the lungs
- **Dry powder inhalers** : delivers medication to the lungs in dry powder form
- **Metered dose inhalers:** delivers a specific amount of medication to the lungs, in the form of a short burst of aerosolized medicine.
  - E.g. salbutamol
  - Desmopressin in Diabetes insipidus
  - Insulin can be given as inhalers instead of SC inj. which have better patient compliance (approved in June 2014 by FDA)

Intravaginal Drug Delivery System

1. Progestasert

- It is an IUCD inserted into uterus delivers progesterone at a constantly specified rate (60 mg/day) for 1yr.
- Advantage : No missing of dose
- Disadvantage :
  - Ectopic pregnancy
  - Chances of PID



2. Dinoprost vaginal insert

- Polymeric slab contains dinoprostone
- Encased in a pouch of a knitted polyster delivery and retrieval systems

3. Mucoadhesive vaginal drug delivery system

- Drugs are formulated as vaginal suppository, bioadhesive tablets, cream, gel→ incorporated into a vaginal device with a carrier
- Miconazole, clotrimazole, fluconazole

Intravesical Drug Delivery Systems

- Direct administration of drug into urinary bladder through a catheter
- Eg.
- Intravesical treatment for bladder cancer by immunomodulators like BCG and INF-α and agents such as doxorubicin, gemcitabine, mitomycin and thiotepa

Urethral Administration

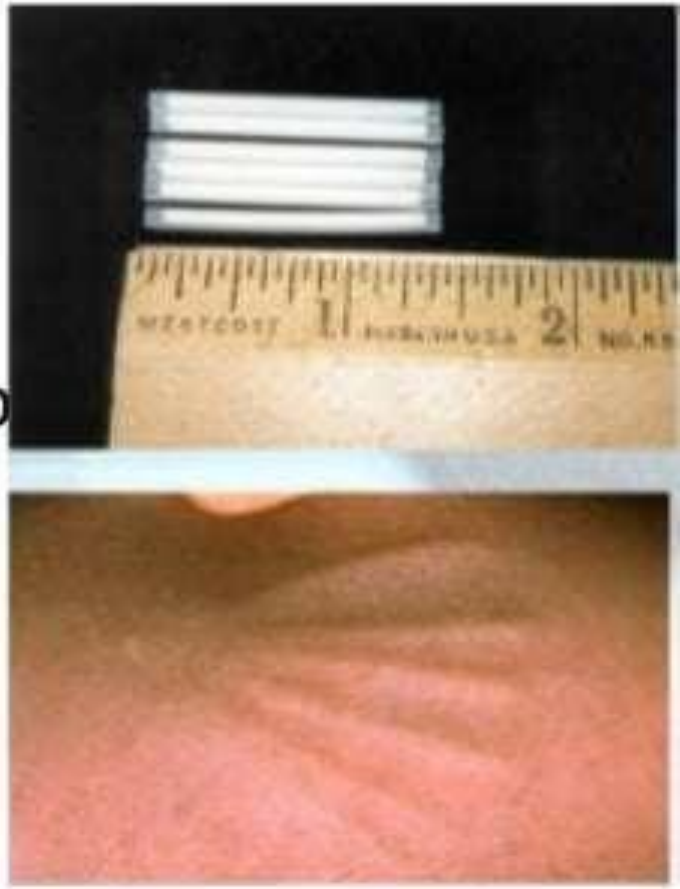
- **Self-microemulsifying drug delivery system**

- Liquid intraurethral PGE1 → erectile dysfunction

Implants

1. Norplant

- Contains levonorgestrel
- 6 capsules of silastic materials is subdermally implanted into inner portion of upper arm in a fan shap within one week of onset of mentruation.
- Contraception for 5 yrs.



2. Gliadel wafer implant

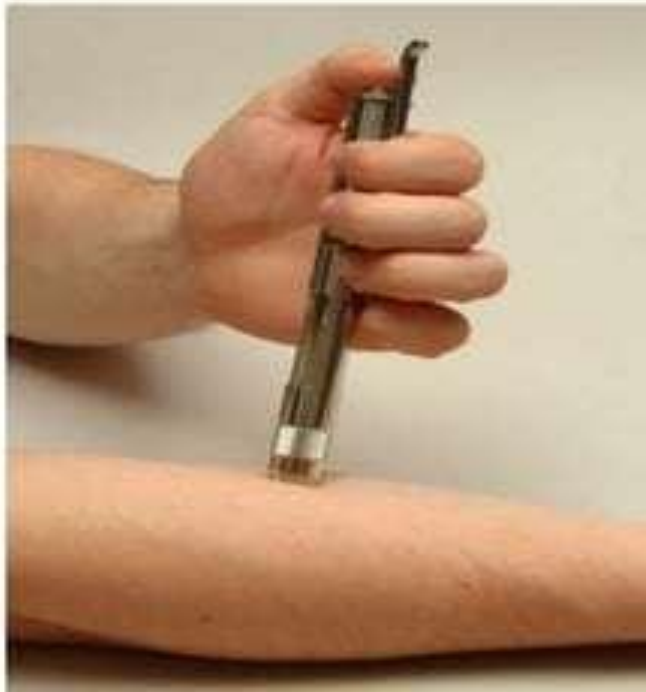
- Contains carmustine
- Delivered directly into surgical cavity created when a brain tumor is resected

3. Zoladex implant

- Goserelin acetate
- 28 days
- Used: Prostate cancer, endometriosis and breast cancer.

Special delivery forms in Subcutaneous route

- **Dermojet :** Needle is not used.
  - A high velocity jet of drug solution injected using gun like implement and solution gets deposited in subcutaneous tissue.
  - Painless and suited for mass inoculations.
  - Eg. Insulin



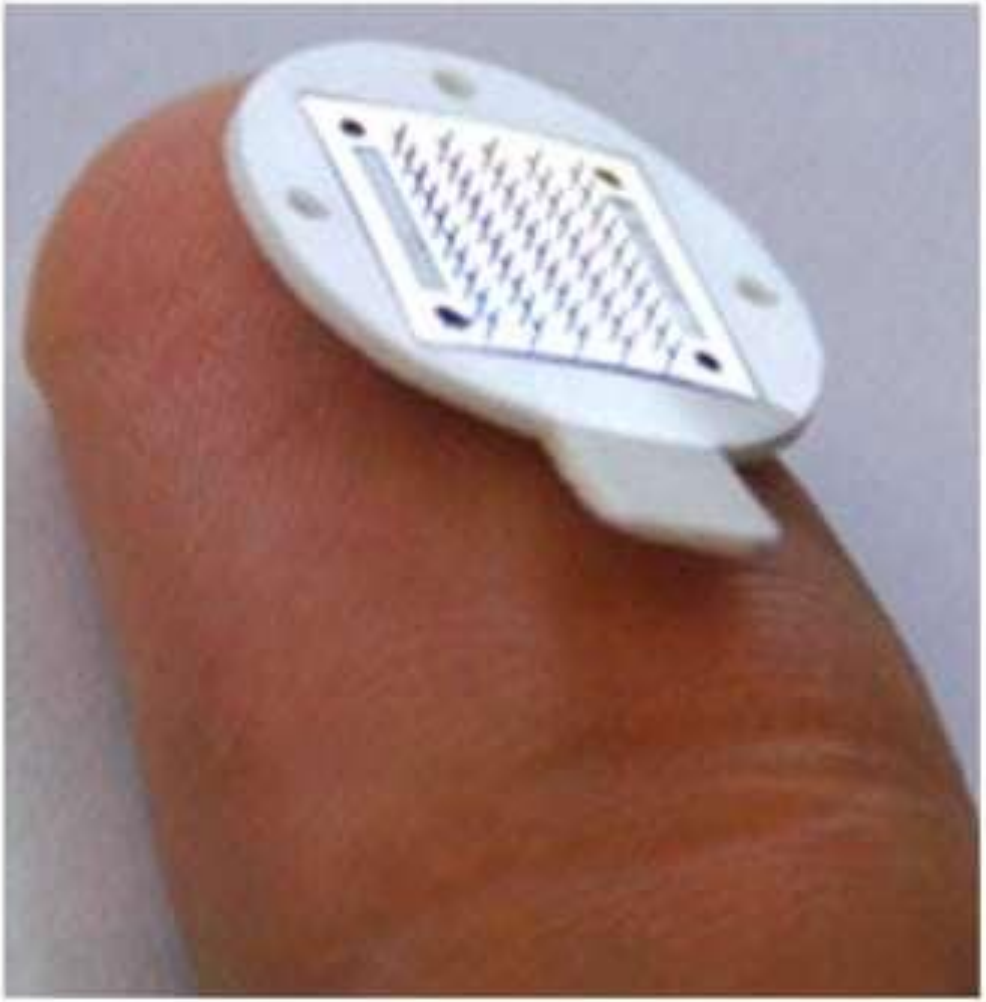
Special delivery forms in Subcutaneous route

- **Pellet implantation :**
- Drug in solid pellet form introduced with a trochar and canula.
  - Provides sustained release of drug over weeks and months. Eg. Testosterone

Micro Electro Mechanical System (MEMS)

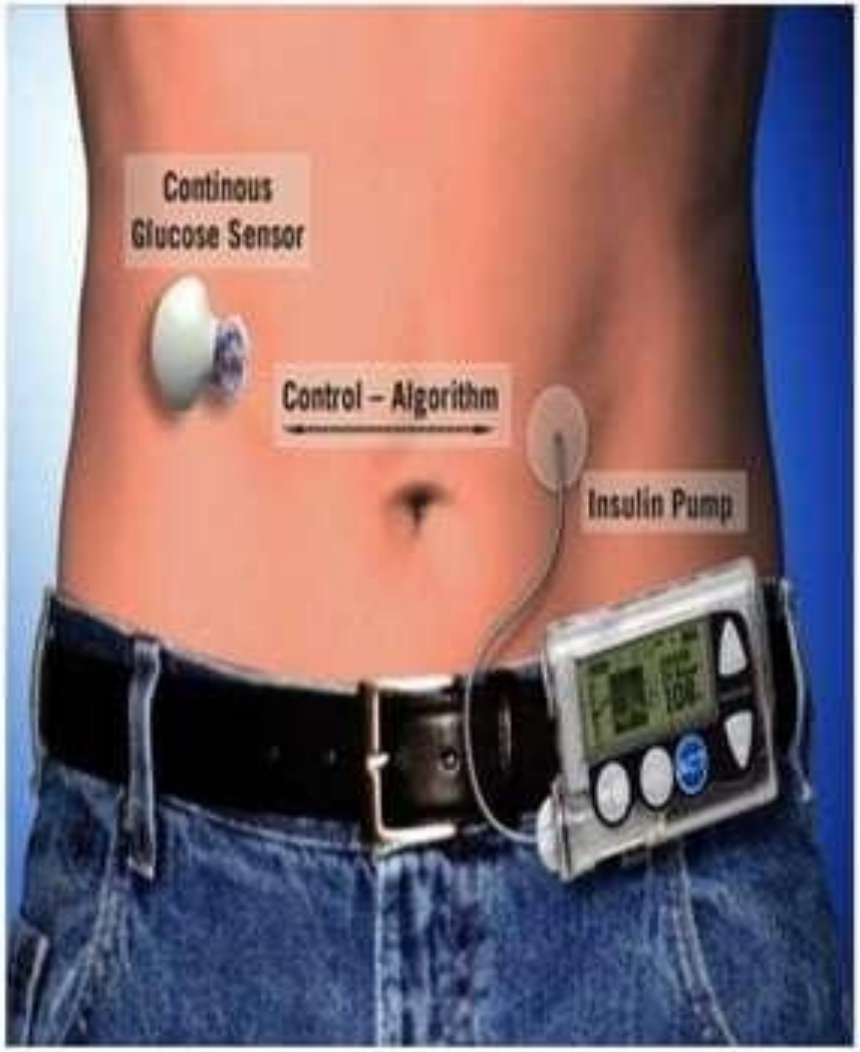
- Dorian Liepmann and Boris Stoeber developed MEMS syringe, the size of a fingernail.
- Pre-loaded with a lyophilized or freeze-dried drug stored in its silicone rubber reservoir.
- The "shot/drug" is delivered by pressing the device against the skin for a few seconds.
- The dry drug is pushed through the microneedles into the skin where the body's interstitial fluids assist in rapidly absorbing the drug directly into the bloodstream.

Micro Electro Mechanical System (MEMS)



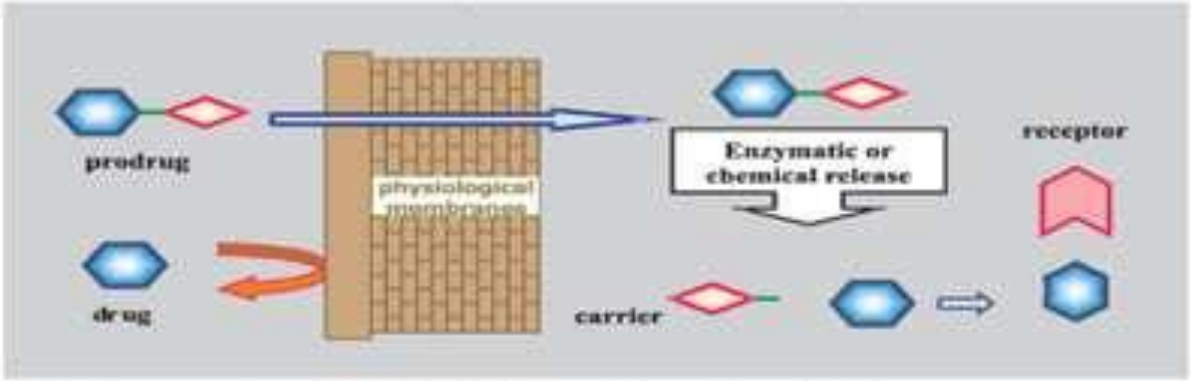
Computerized Miniature Pumps

- These are programmed to release drugs at a definite rate either continuously or intermittently in pulses.
  - Insulin pump
  - GnRH pump



Prodrug

- Inactive form of drug which gets metabolized in the body to an active drug
- Used to overcome the barriers limiting the usefulness of a drug E.g. : levodopa
- To provide longer duration of action. e.g. Procaine penicillin, Benzathine pencillin
- To provide site specific drug delivery e.g. methenamine prodrug for formaldehyde→ urinary tract antiseptic



RE 2 - Representation of a prodrug design to enhance bioavailability.

Targeted Drug Delivery System

- Delivers medication in a manner that increases the concentration of the medication in some parts of the body relative to others.

- Advantage: increased efficacy, reduction in dose and side effect of drug.

- Target: specific organ or group of cells
- Carrier : transport drug to target

Carrier Systems

A. Particulate carrier system

1. Nanoparticles

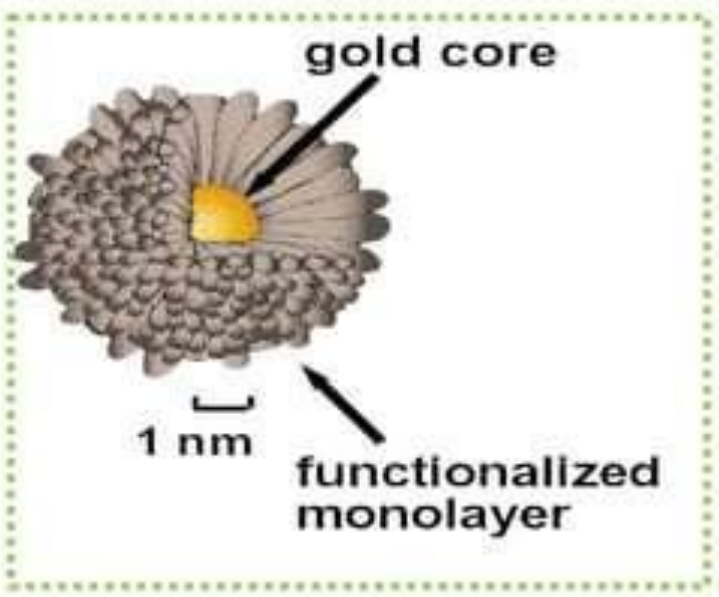
- Solid particles of size 10 to 1000 nm
- Nanocapsules : These are vesicular systems in which the drug is confined to a cavity surrounded by polymer membrane

- Nanospheres : These are matrix systems in which the drug is uniformly dispersed.

- **Nanotubes**
- Hollow cylinders made of carbon filled with drug
- Eg cellular scale needle for attaching drug molecule to cancer cells

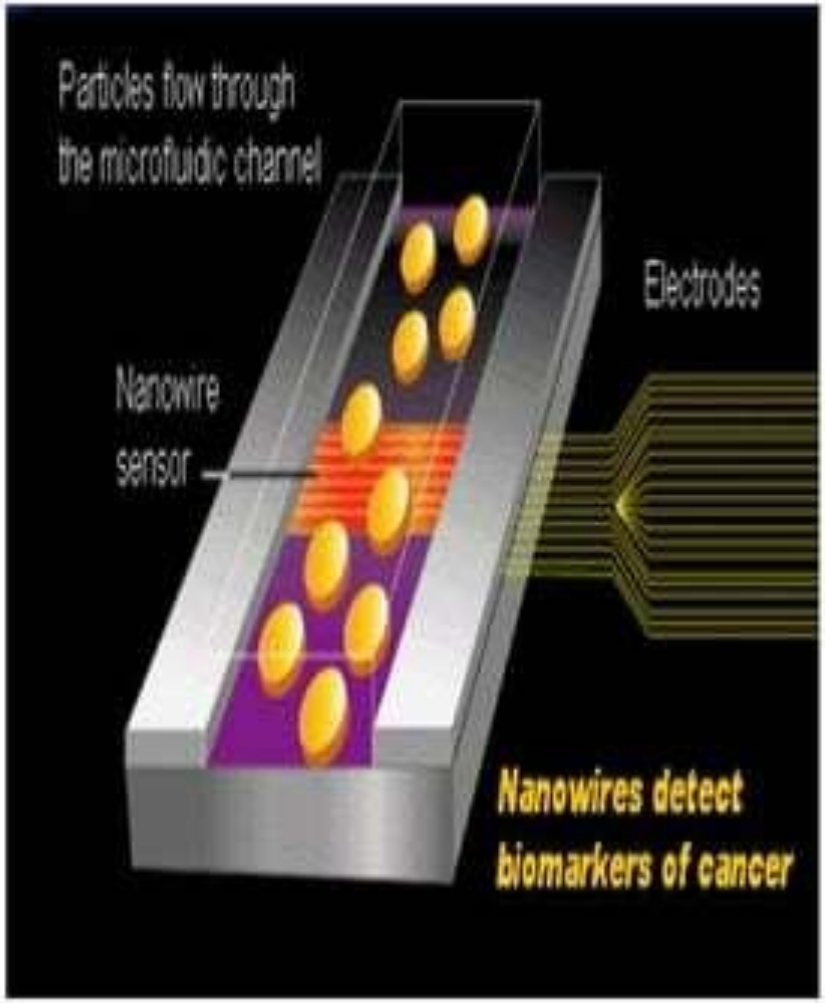
- **Hydrogel nanoparticle**
- Hydrogels are hydrophilic, polymeric networks capable of imbibing large amounts of water or biological fluids.

- Nanoparticles have many applications, including anti-tumour therapy, gene therapy, AIDS therapy, radiotherapy, in the delivery of proteins, antibiotics, vaccines and as vesicles to pass the blood-brain barrier.

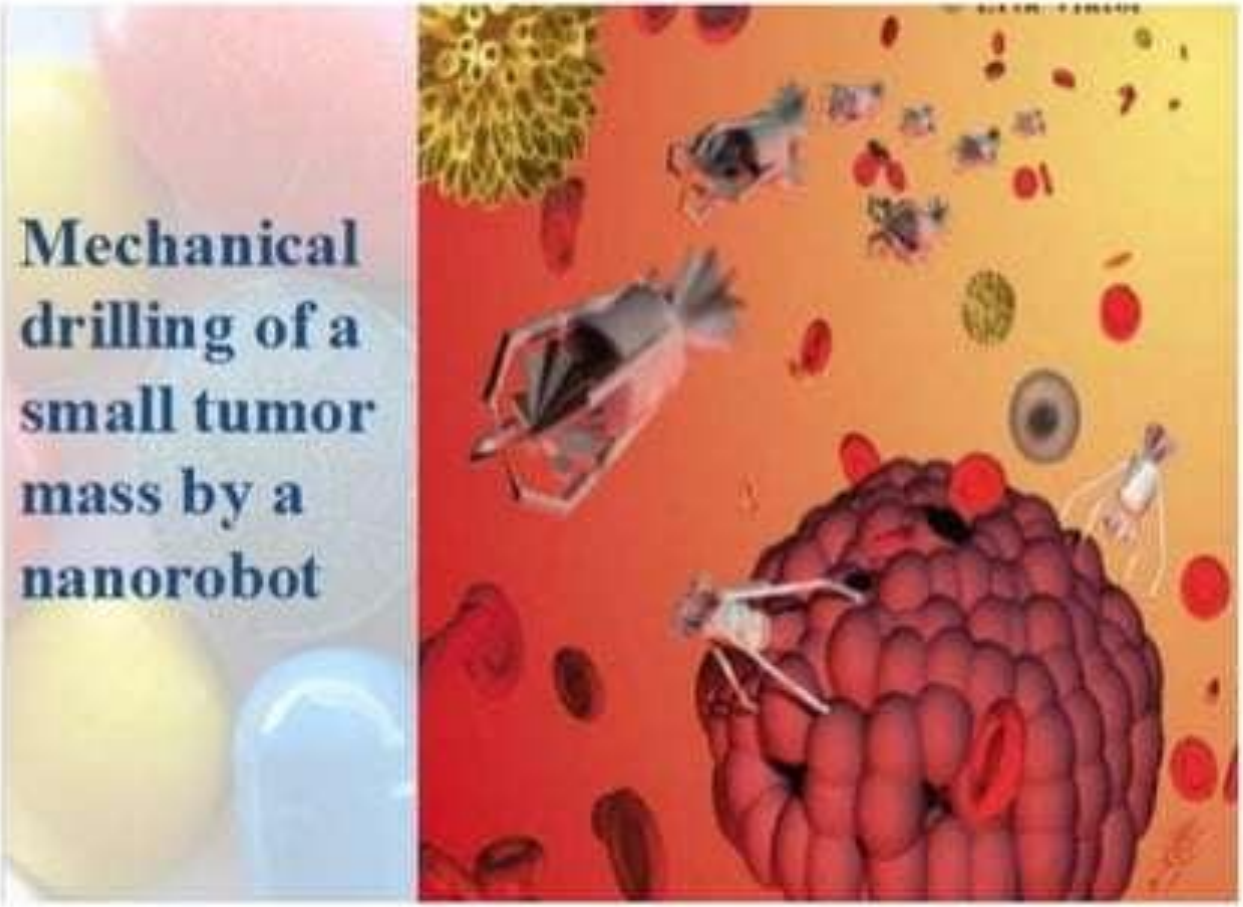


- Nanotechnology offers tools and techniques for more effective detection, diagnosis and Rx of diseases

- Nanowire help in early detection of cancer biomarkers



Nano-Robots in treatment of cancer.

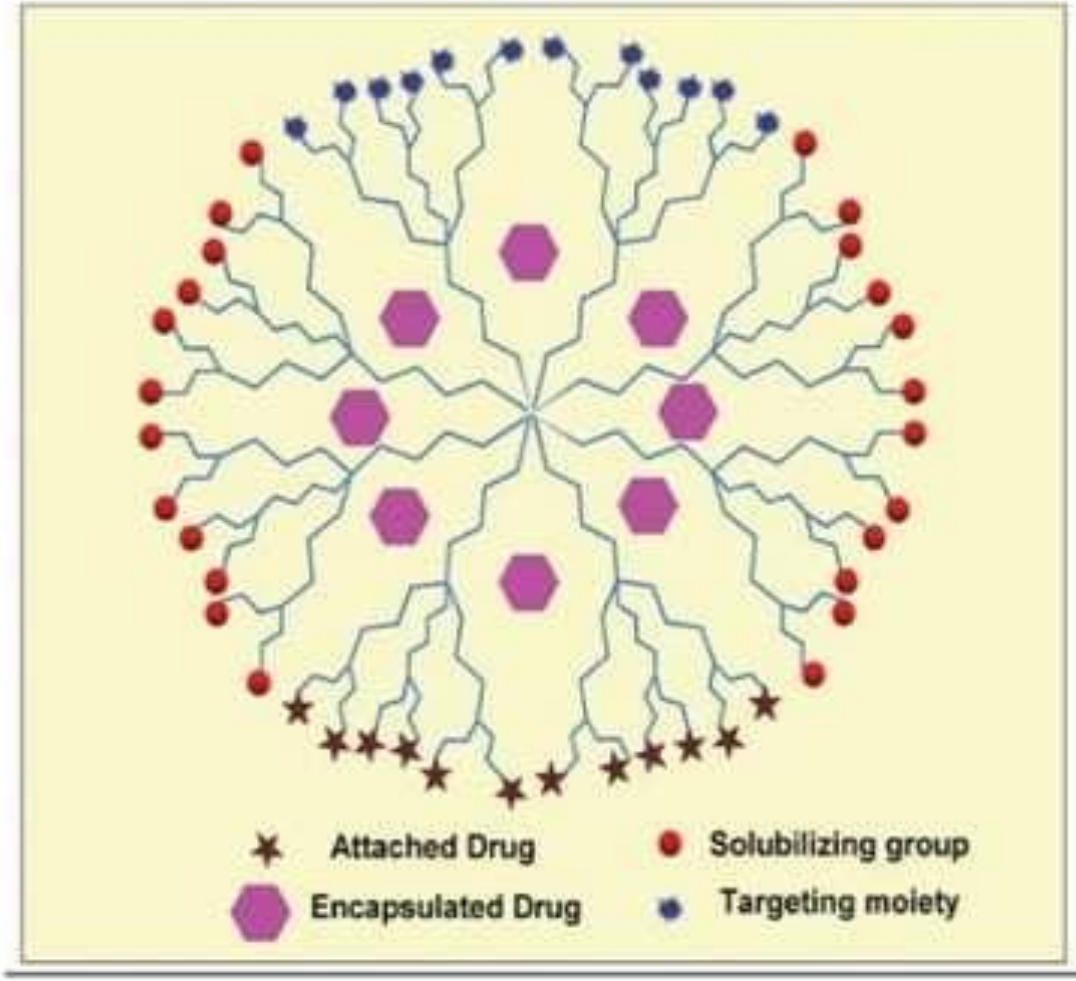


Dendrimers

- Dendritic macromolecules (highly branched, globular)
- Used to encapsulate individual small drug molecules
- Can also serve as "hubs" onto which large numbers of drug molecules can be attached via covalent bonds.

- Eg.
- 5-fluorouracil to polyaminoamine dendrimers
- Methotrexate to hydrazide-terminated dendrimers formed from poly aryl ether.

Dendrimers


Attached Drug
Encapsulated Drug
Solubilizing group
Targeting moiety

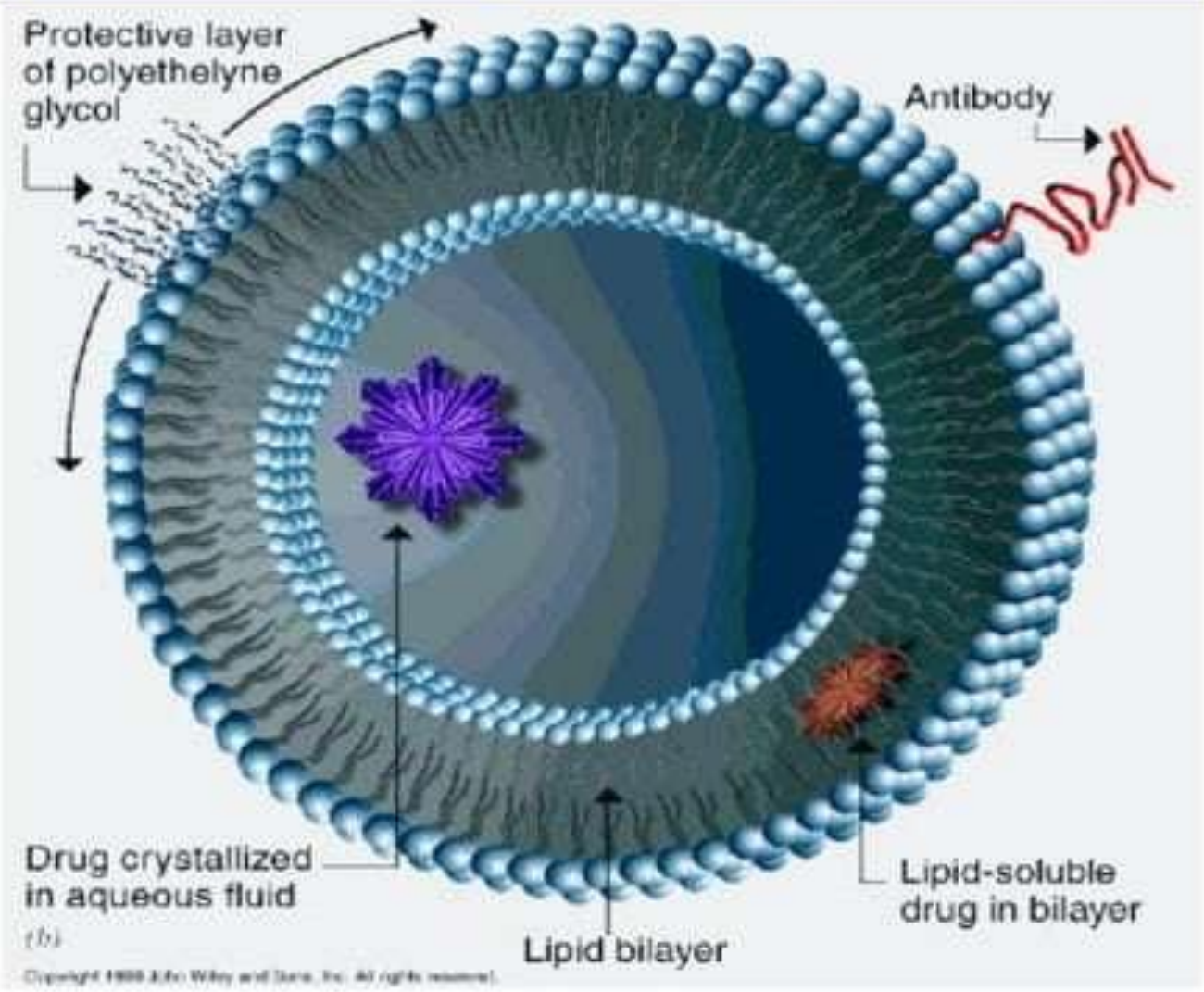
2. Liposomes

- These are minute vesicles and consists one or more phospholipids bilayers.

- Filled with non lipid soluble drugs and retained until liposome is disrupted.

- Eg : Amphotericin, Daunorubicin, Doxorubicin, Azithromycin, Vincristine(approved in 2012)

Liposomes


Protective layer of polyethelyne glycol
Antibody
Drug crystallized in aqueous fluid
Lipid bilayer
Lipid-soluble drug in bilayer
(b)

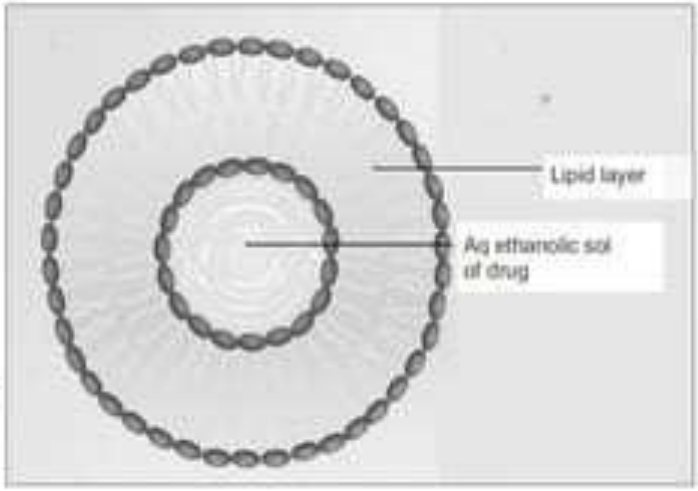
Advantages of liposomes

- Increased stability and decreased toxicity of encapsulated drug.
- Better pharmacokinetic, good therapeutic index.
- Both hydrophilic and hydrophobic drugs can be carried.
- Biologically inert, biodegradable, non-toxic, non-antigenic, non- pyrogenic.

- Disadvantage: Highly expensive

3. Ethosomes

- Non-invasive delivery carriers that enable drugs to reach the deep skin layers
- Phospholipids, alcohol and water



4. Aquasomes

- Core is composed of noncrystalline calcium phosphate or ceramic diamond and is covered by a polyhydroxyl oligomeric film

B. Natural Carrier Systems

1. **Neutrophils**

- Transport agents to areas of acute inflammation

2. **Lymphocytes**

- Transfer macromolecules like DNA

3. Nanoerythrosomes

- Drug loaded in body's own erythrocytes.
- Also called GOLDEN EGGS.

- ADVANTAGES:
  - Biocompatible
  - Nontoxic with minimum ADR.
  - Non-nucleated so large space available for drug incorporation.

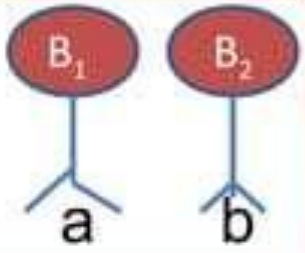
C. Monoclonal antibodies

- These are Antibodies produced by a single clone and are directed against a single antigenic determinant (epitope)

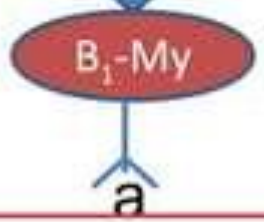
- Mabs are produced on large scale using Hybridoma technique.

Mouse inj. with Ag having epitopes a & b

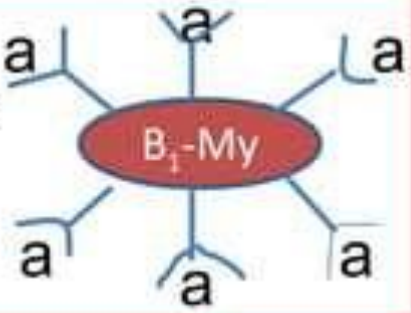
It produces B-lymphocytes to each epitope



The desired activated Bi fused with Myeloma cell in Polyethylene glycol



Expansion & elusion of MAb



Growth of hybridoma in HAT medium & cloning

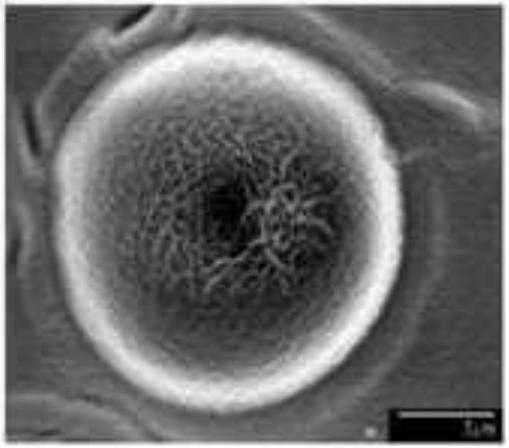
- Murine MAbs not preferred now a days due to shorter half life and ability to induce allergic reactions
- Chimeric MAbs : partly human and partly mouse antibody
- Humanised MAbs –least Antigenic

- In the name of Mabs the letter before mab indicates source of antibody i.e., "O" for murine (Muromonab)
  - "Xi" – chimeric (Rituximab, Abciximab)
  - "Zu" - human (Omalizumab, Pavlizumab)

Thank you

5. Colloidosome

- Colloidosomes are microcapsules whose shells consist of coagulated or fused colloid particles.



6. Proniosomes

- Dry formulation of water soluble carrier particles that are coated with surfactant.
- They are rehydrated to form niosomal dispersion immediately before use on agitation in hot aqueous media within minutes.