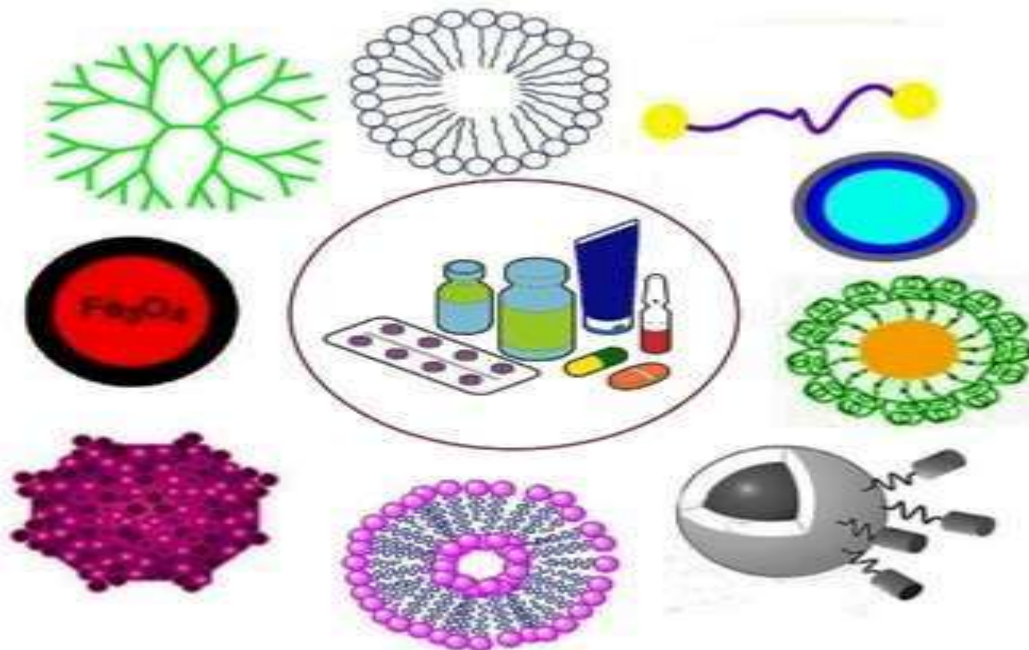




SNS COLLEGE OF PHARMACY AND HEALTH SCIENCES

Sathy Main Road, SNS Kalvi Nagar,
Saravanampatti Post, Coimbatore - 641 035,
Tamil Nadu.



New Drug Delivery System

Contents

- ▶ Introduction
- ▶ Disadvantages of current routes of administration
- ▶ Novel drug delivery system
- ▶ Types : controlled & Target DDS
 - ▶ Mechanism of CDDS
 - ▶ Drug carriers in target DDS

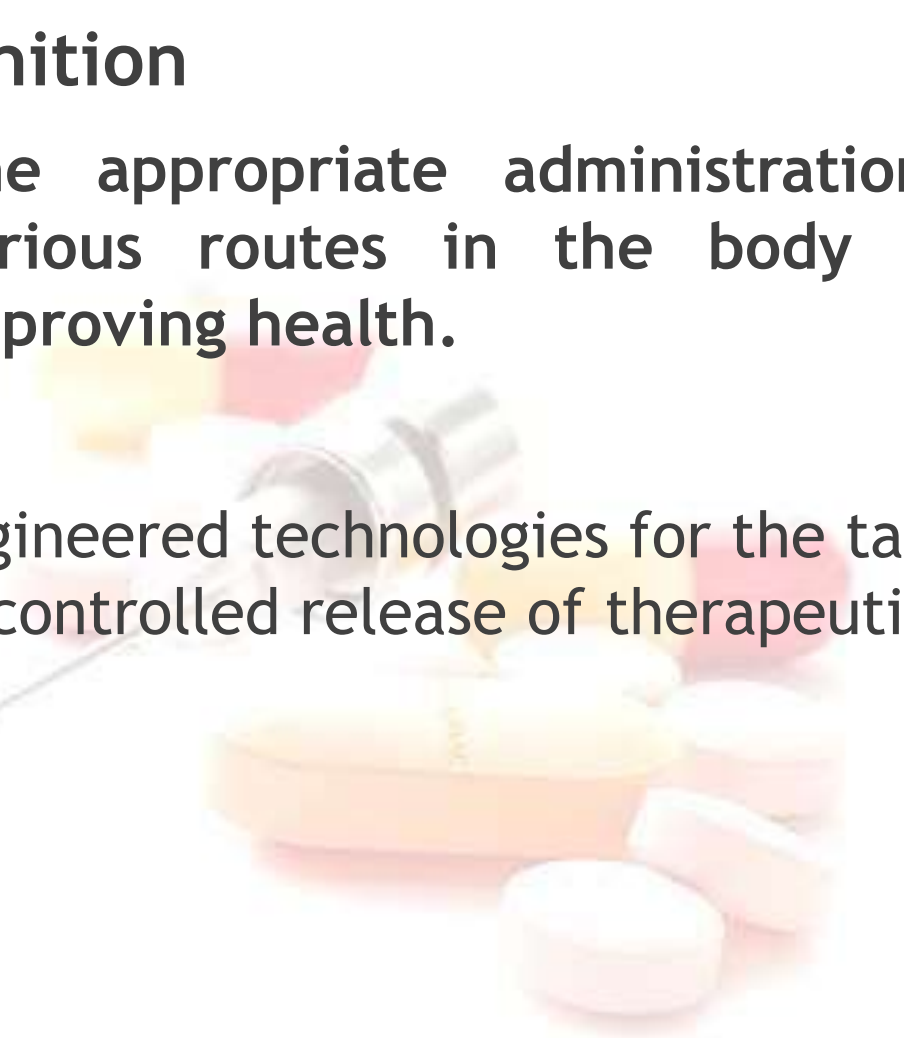
Introduction...

- ▶ The method by which a drug is delivered can have a significant effect on its efficacy.
- ▶ Some drugs have an optimum concentration range within which maximum benefit is derived (Therapeutic Index) and concentrations above or below this range can be toxic or produce no therapeutic benefit at all.

Drug Delivery

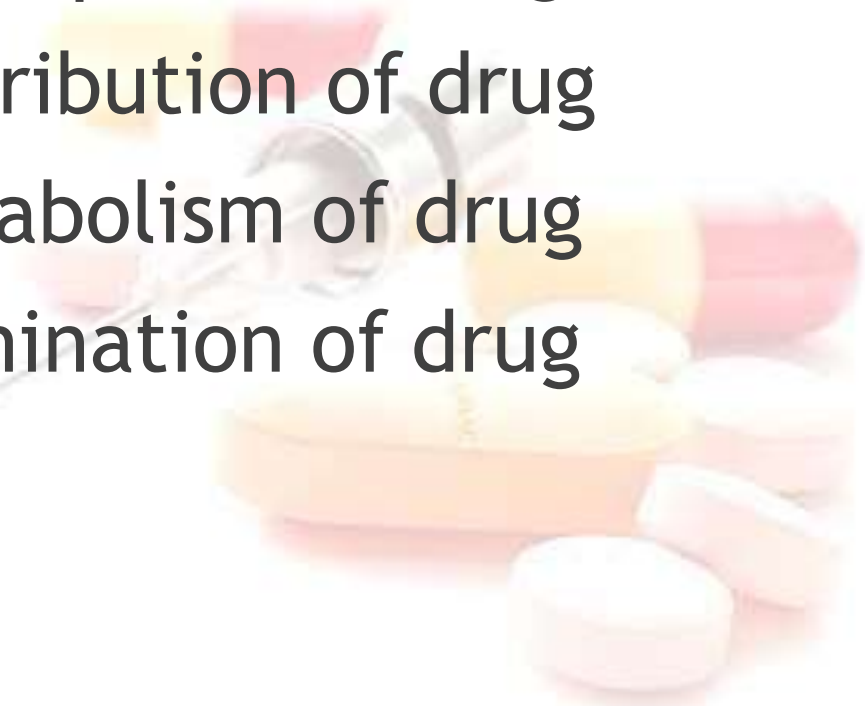


▶ Definition

- ▶ The appropriate administration of drugs through various routes in the body for the purpose of improving health.
 - engineered technologies for the targeted delivery and/or controlled release of therapeutic agents.
- 

► **Goal of new technologies is to alter 4 pharmacokinetic properties:**

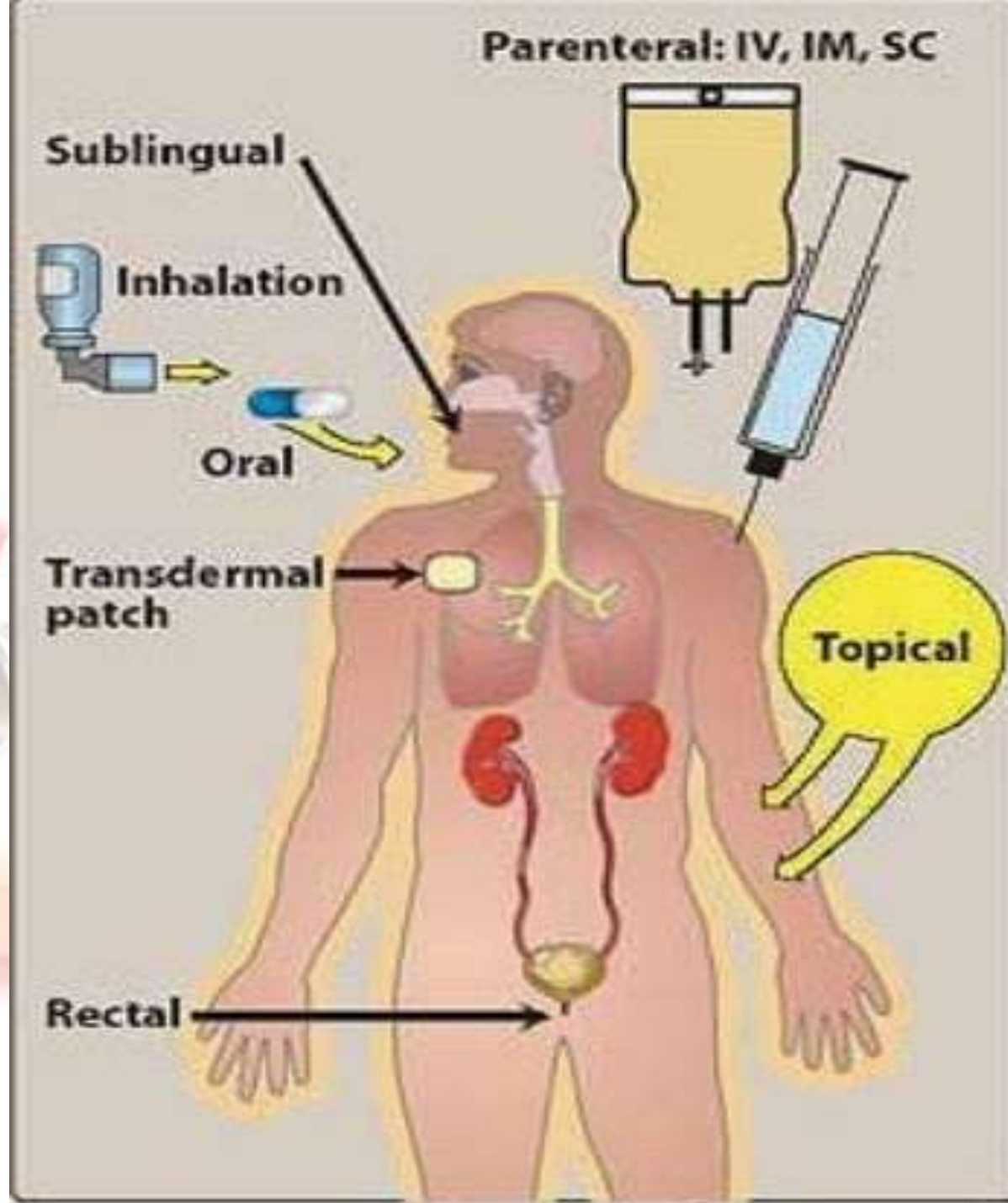
- Absorption of drug
- Distribution of drug
- Metabolism of drug
- Elimination of drug



Need for new drug delivery systems



Routes of Administration

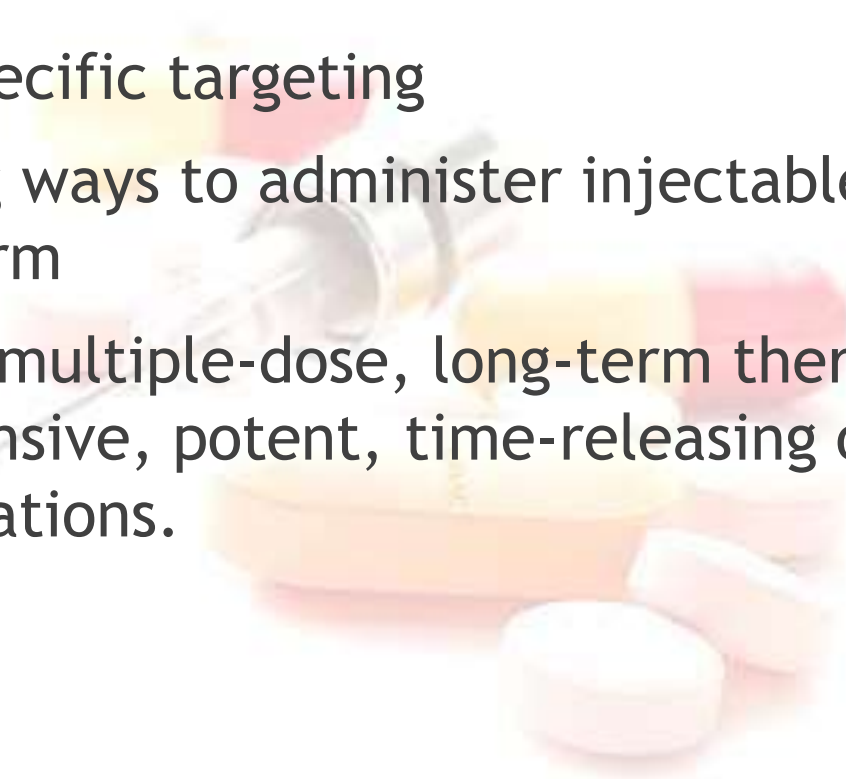


Disadvantages in current therapy

- ▶ 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
- ▶ Finding ways to administer injectable only medications in oral form
- ▶ Costly, multiple-dose, long-term therapies → Inexpensive, potent, time-releasing or self-triggering formulations.



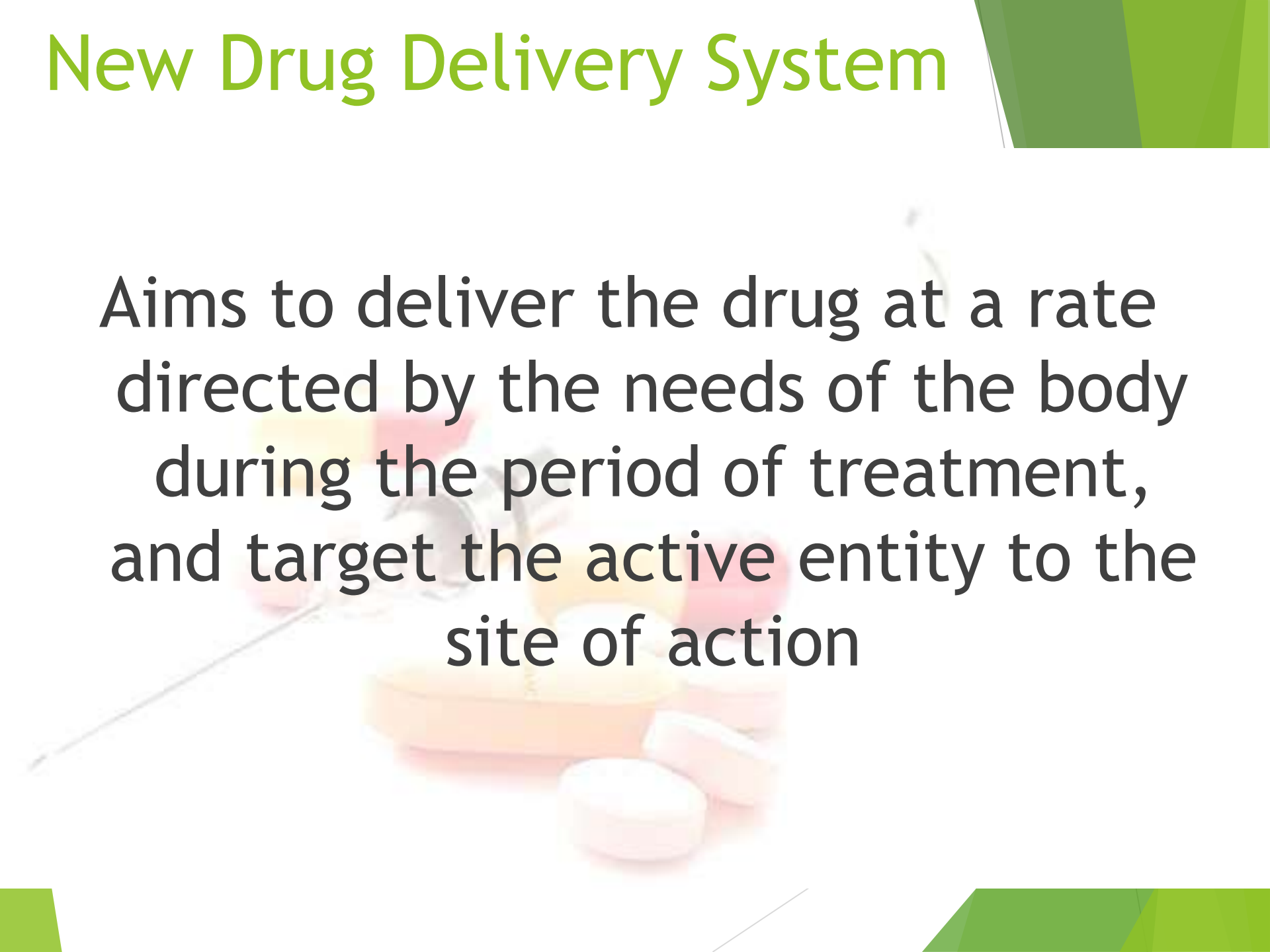
How to overcome this???

To combat this a multidisciplinary approach that combine **Pharmaceutics, Polymer Science, Bioconjugate Chemistry, and Molecular Biology** in controlling the **Pharmacokinetics, Pharmacodynamics, Non-specific Toxicity, Immunogenicity, Bio recognition and efficacy of drugs** was generated to develop novel drug delivery systems (DDS).

New Drug Delivery System



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



Drug Delivery Systems

- ▶ Controlled drug delivery system
- ▶ Target drug delivery system

Controlled Drug Delivery System (CDDS)

- ▶ **Some of the examples for CDDS**
 - ▶ Oral CDDS
 - ▶ Nasal CDDS
 - ▶ Drug eluting stents



CDDS cont...

Advantages of CDDS :

- ▶ Patient compliance is improved due to decreased frequency in dosing
- ▶ Reduced severity and toxicity of side effects.
- ▶ More constant blood level improves therapeutic action.

Disadvantages of CDDS :

- ▶ Cost
- ▶ Uncontrolled poisoning if poor formulation result in fast and high drug release.
- ▶ Not suitable for many drugs that are absorbed from particular region.
- ▶ Irritation at site of application.

Oral CDDS

- ▶ Modified Release DDS
- ▶ Extended Release DDS
- ▶ Delayed Release DDS
- ▶ Repeated Action DDS
- ▶ Prodrug

Modified Release DDS : drug is released based on time course and/or location for therapeutic or convenience. Eg. **Enteric coated-diclofenac EC**

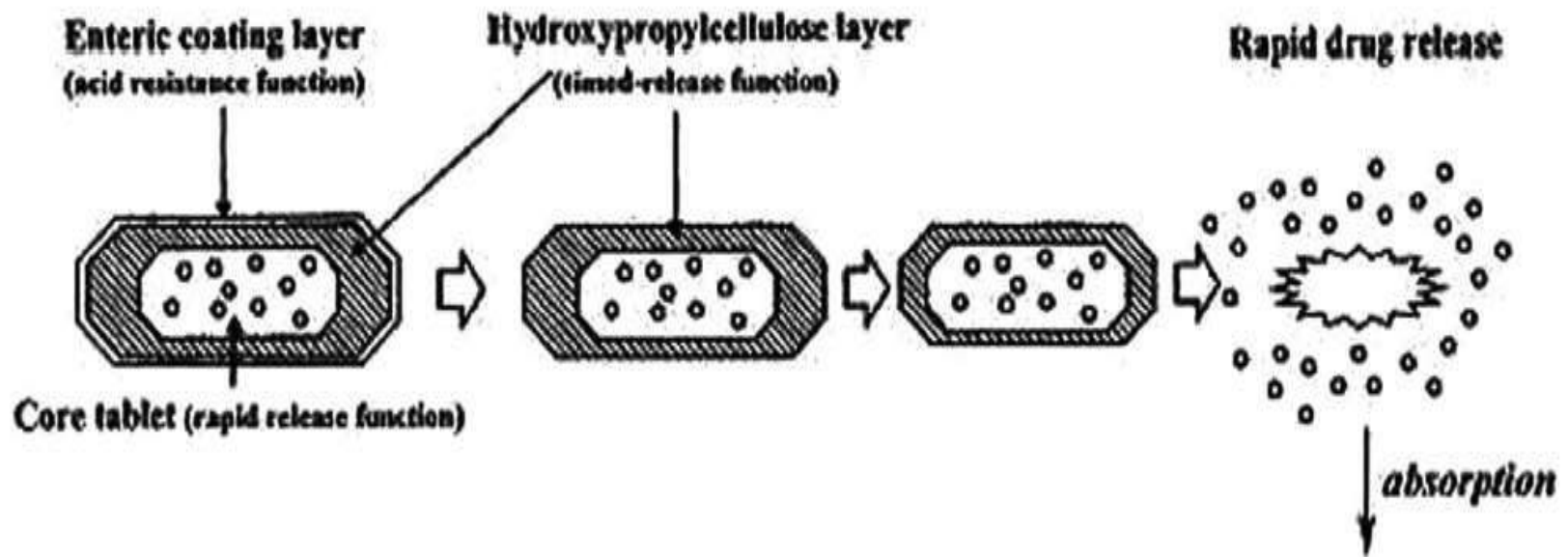
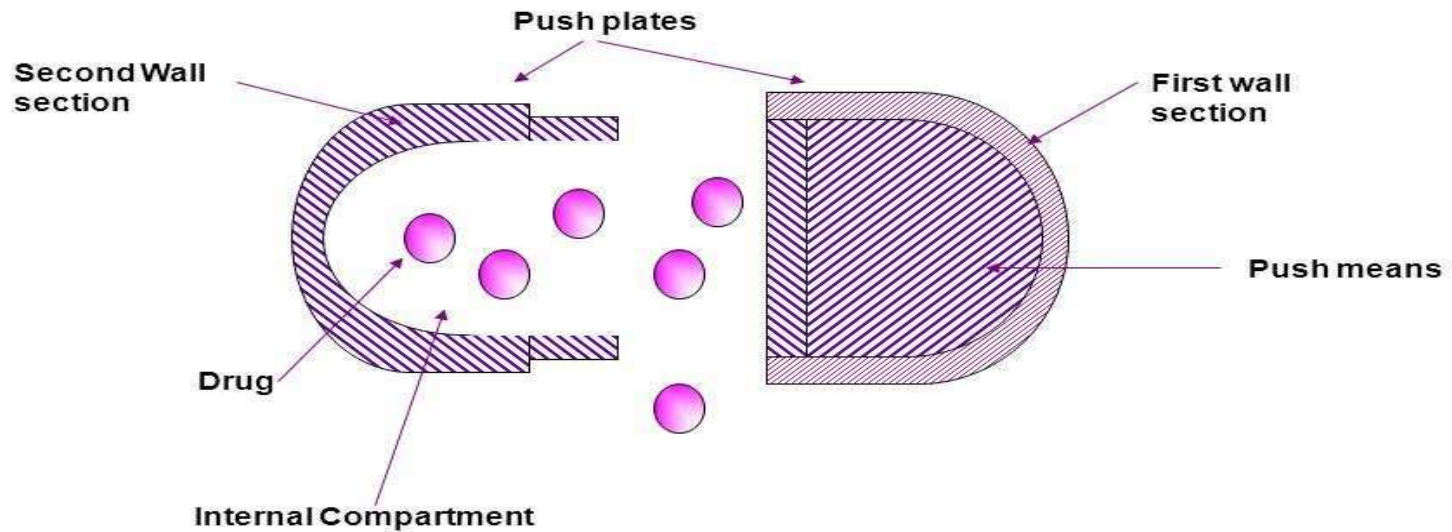


Figure 1: Design of enteric coated timed-release press coated tablet (ETP Tablet)

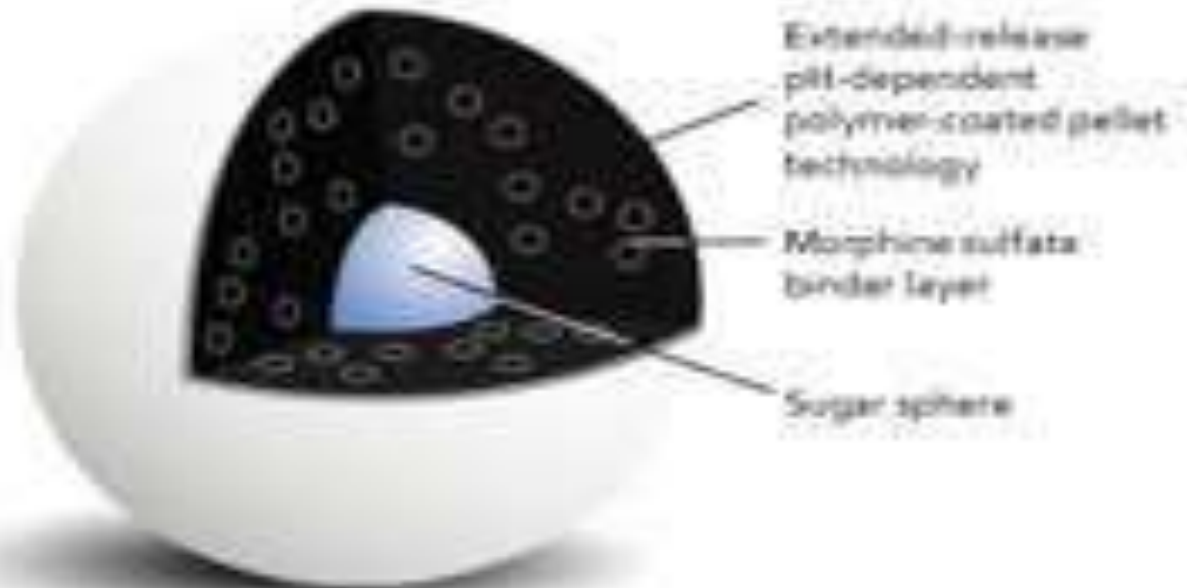
Delayed Release DDS : one or more immediate release unit. The delay may be time-base or based on influence of environmental conditions as GIT pH.



A delayed release telescopic capsule release contents after expansion.

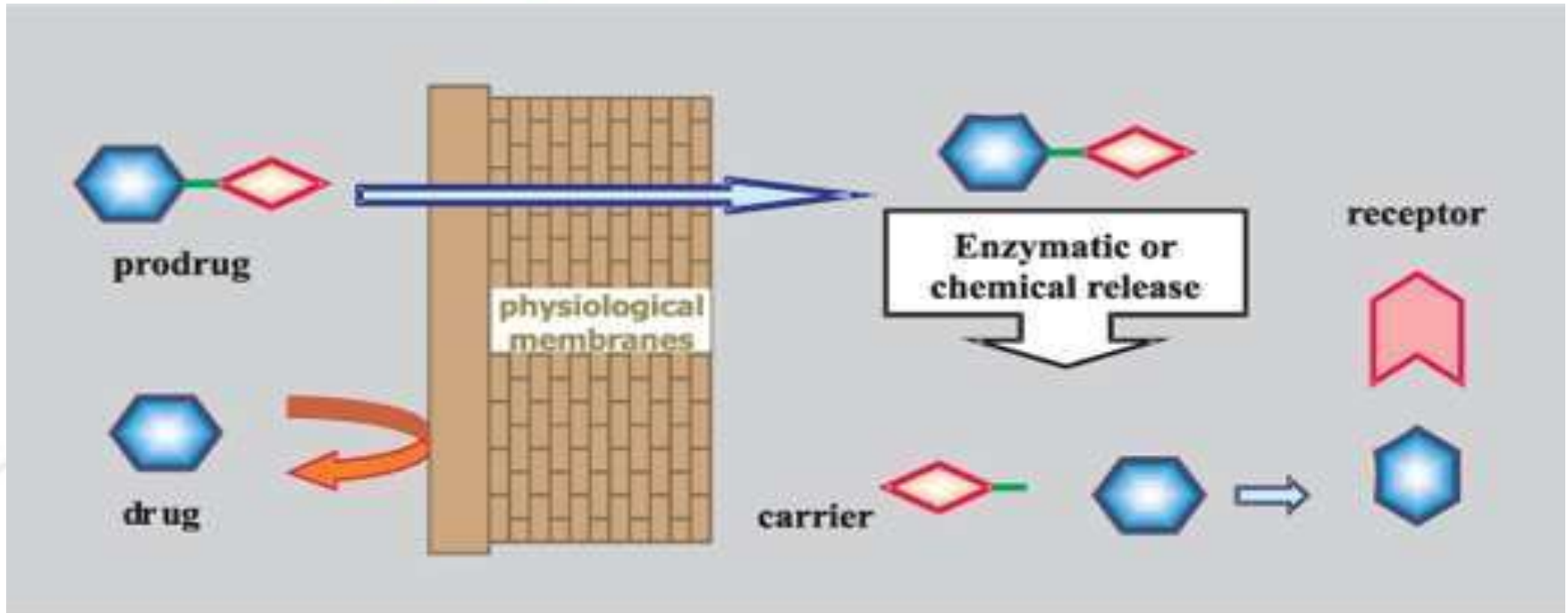
Oral CDDS

- ▶ **Extended Release DDS** : ↓ dosing frequency. Eg. **Diclofenac SR, nifedipine SR**
- ▶ **Repeated Action DDS** : Layer tablet - 2 or 3 compressed together: sustained release + immediate release unit.
- ▶ **Prodrug**



Prodrug

- ▶ Prodrug is an inactive form of drug which gets metabolized in the body to an active drug
- ▶ Used to overcome the pharmacokinetic disadvantage of useful drug E.g. : [levodopa](#)
- ▶ To provide longer duration of action. e.g. - [Procaine Penicillin](#), [Benzathine penicillin](#)



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

Nasal drug delivery

- ▶ As aerosols, metered dose inhalers, dry powder inhalers (rotahalers) and Nebuliser
 - ▶ E.g .: Anti histaminic - Astemizole
 - ▶ Desmopressin in Rx of Diabetes insipidus
 - ▶ Calcitonin
 - ▶ Insulin can be given as inhalers instead of SC inj. Which have better patient compliance (approved in June 2014 by FDA)

Recent advances in pulmonary delivery

► Oxygen concentrator

-An **oxygen concentrator** is a device which concentrates the oxygen from a gas supply (typically ambient air) to supply an oxygen enriched gas mixture.



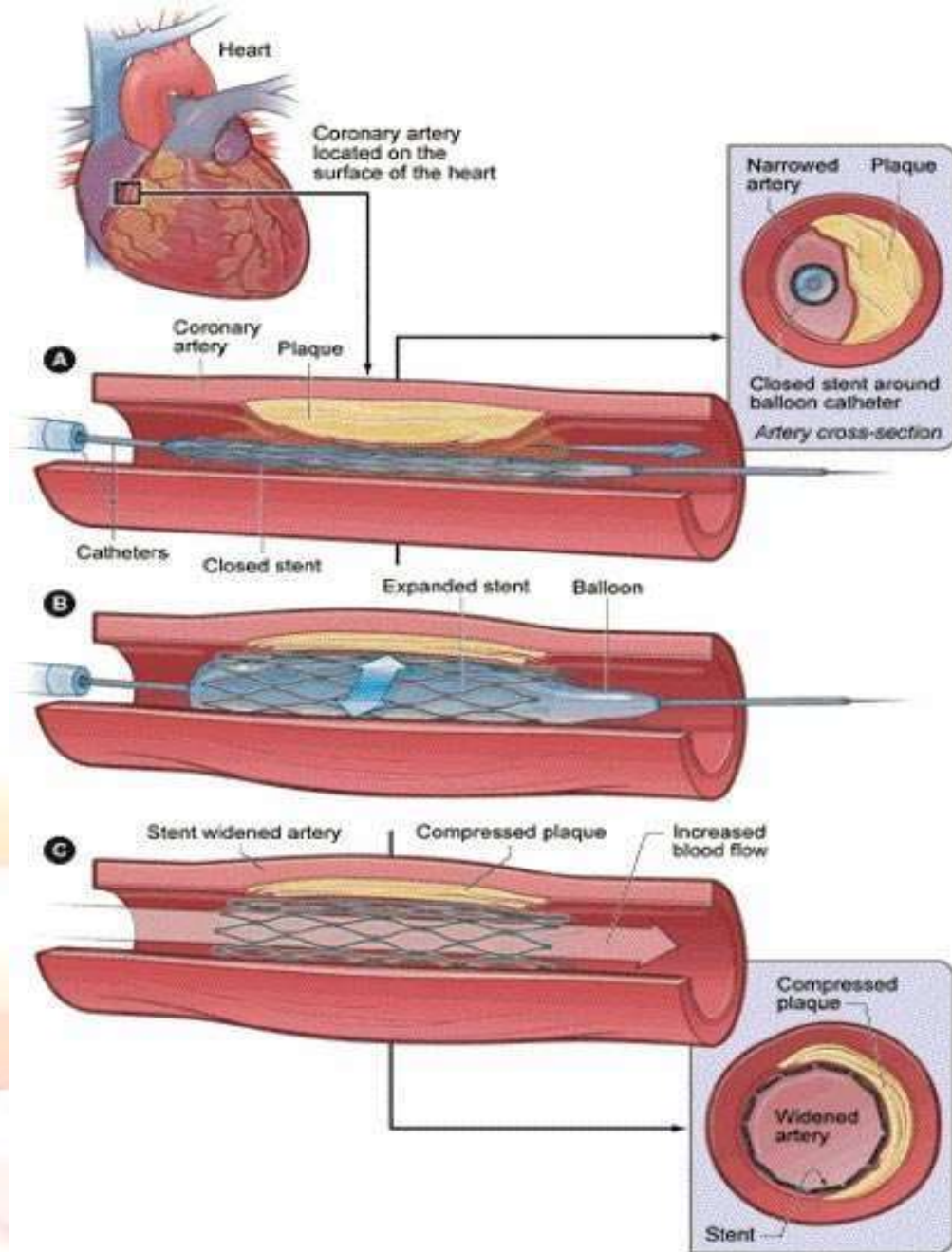
A home oxygen concentrator in an emphysema patient's house.

Pulmonary microspheres

- ▶ A novel process for generating sustained release (SR) particles for pulmonary drug delivery.
- ▶ High purity nanoparticles of a hydrophilic, ionised drug are entrapped within hydrophobic microspheres using a spray-drying approach.
- ▶ Eg- terbutaline sulphate

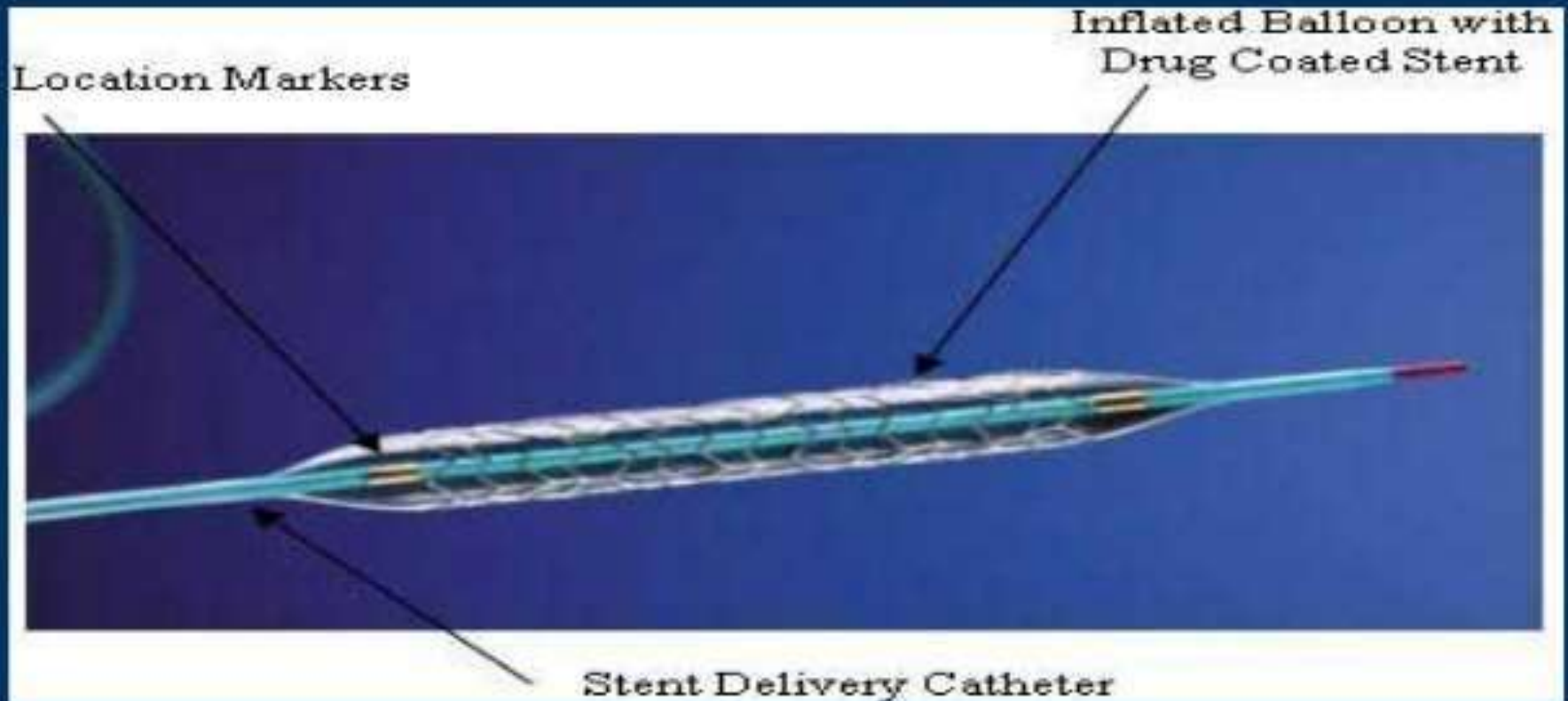
Drug Eluting stents

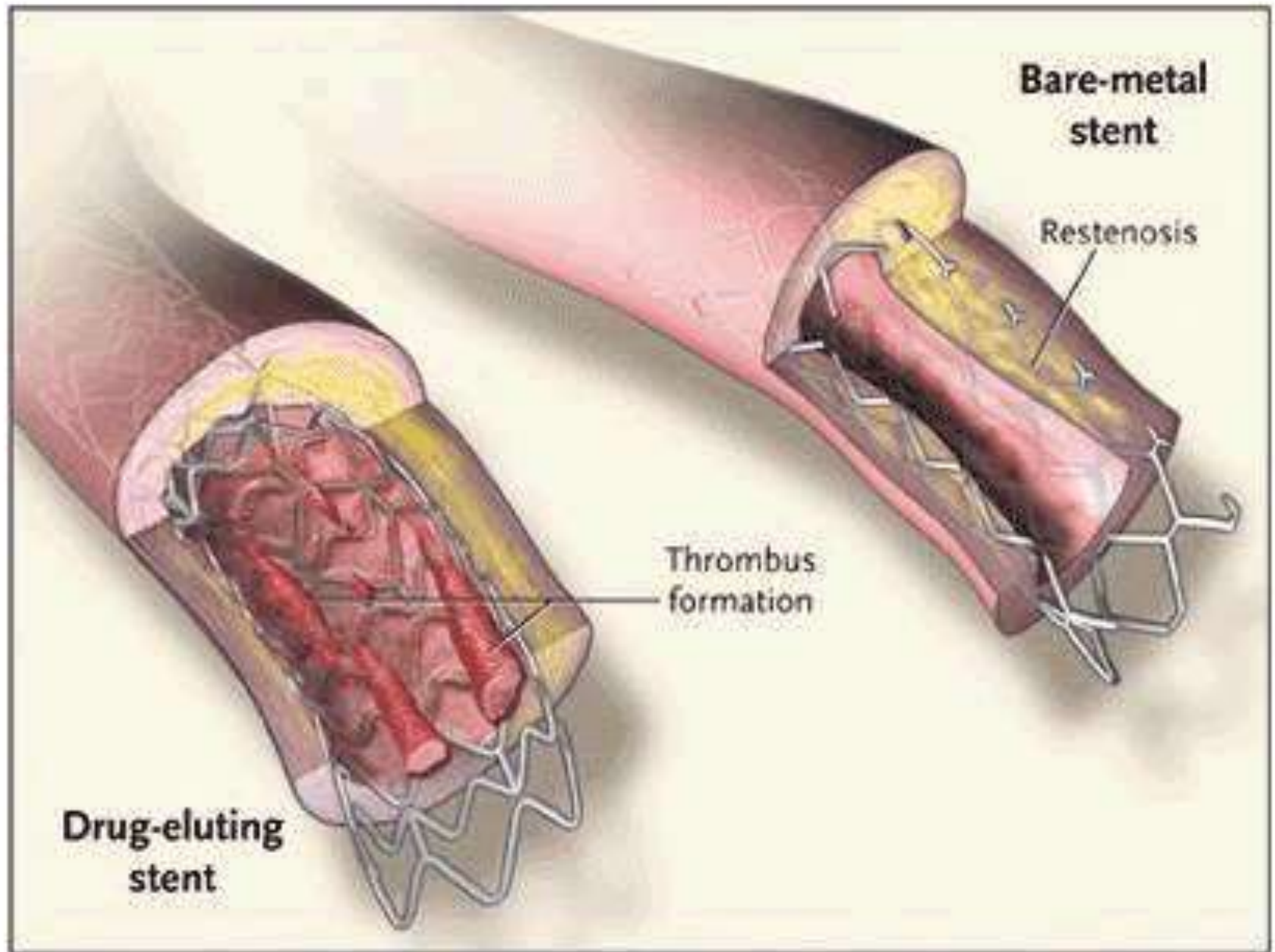
- ▶ A metallic stent contains drug which is gradually released over 14-30 days
- ▶ Drugs used are : Sirolimus, Paclitaxel, everolimus



Drug eluting stents:

Stents can be coated with drugs embedded in a surface polymer





Computerized Miniature Pumps

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

- ▶ Insulin pump

- ▶ GnRH pump



Insulin pump

- ▶ A medical device used for the administration of insulin in the treatment of diabetes mellitus, also known as continuous subcutaneous insulin infusion therapy. The device configuration may vary depending on design.



Insulin pump, showing an infusion set loaded into spring-loaded insertion device. A reservoir is attached to the infusion set (shown here removed from the pump).

Targeted drug delivery

Examples

- ▶ Liposomes
 - ▶ Progestasert
 - ▶ Transdermal drug delivery / subcutaneous delivery
 - ▶ Ocuserts
 - ▶ Monoclonal antibodies
 - ▶ Erythroosomes
 - ▶ Dendrimers
 - ▶ Nanotechnology- nanosomes, nanorobots
- 

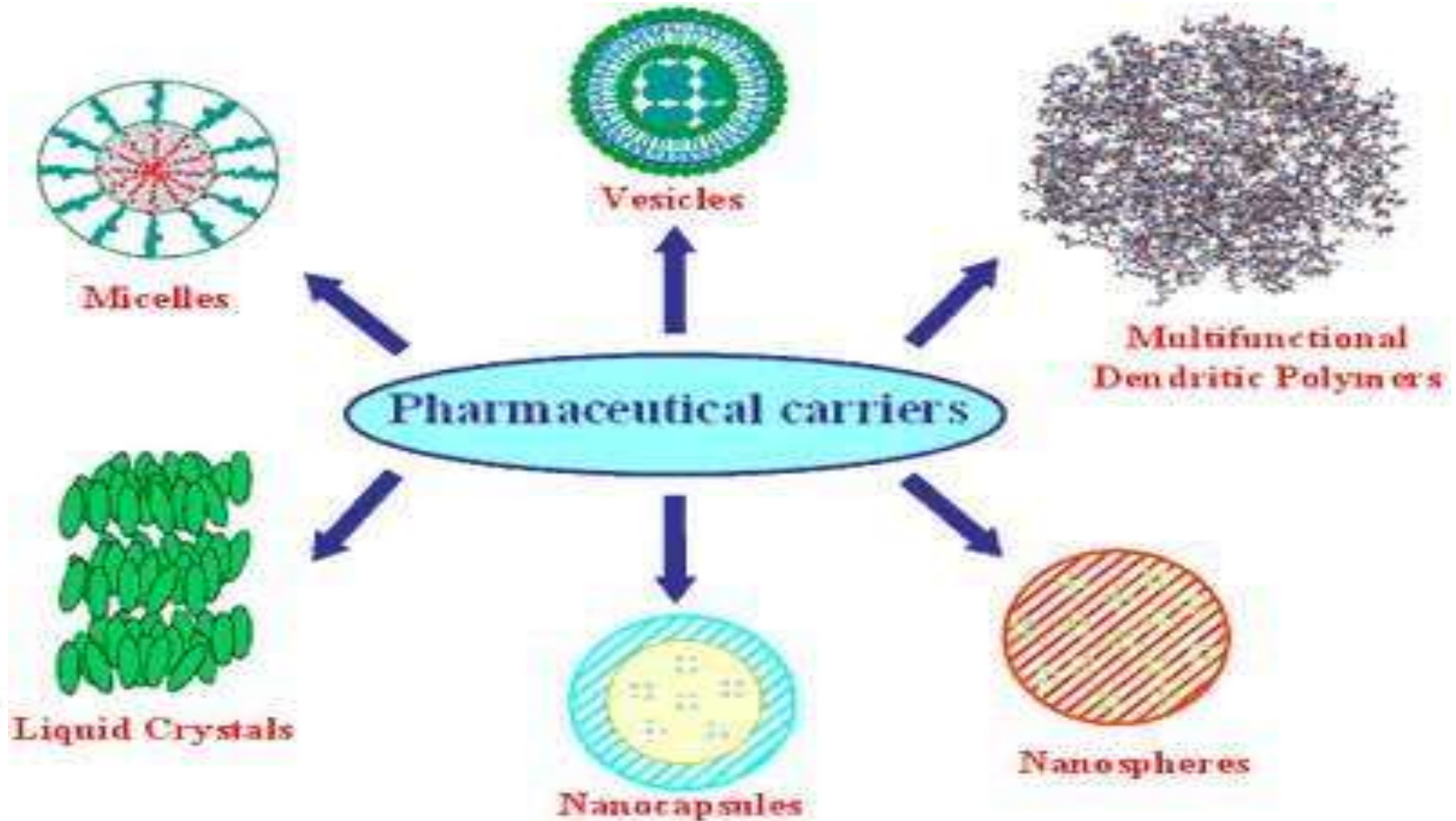
Site Specific / Targeted DDS

- ▶ **Specific medium / carrier** is required that can control the therapy's administration by means of either a physiological or chemical trigger
- ▶ To achieve this vast research going in micro & nano technology.

Drug carriers

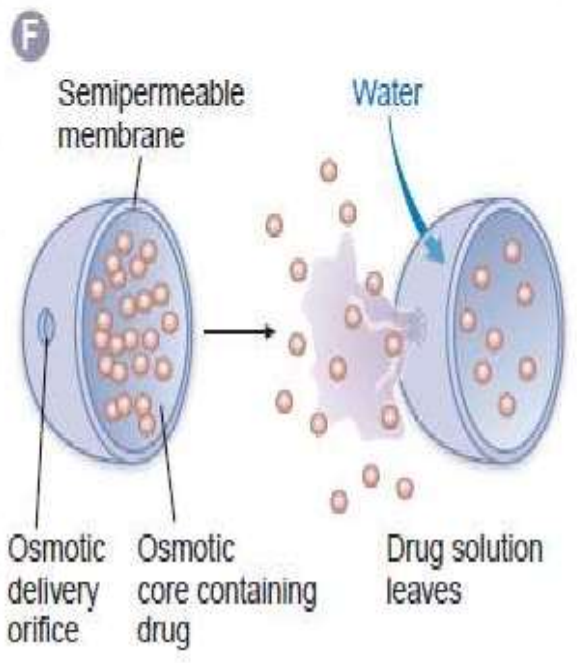
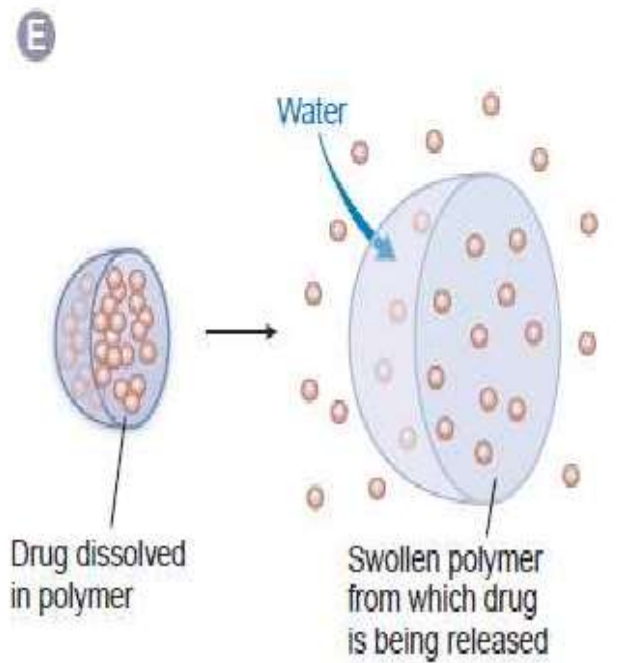
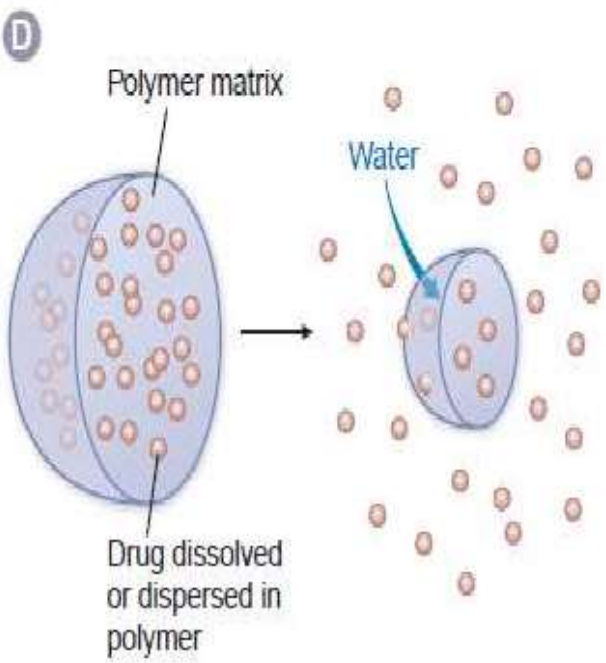
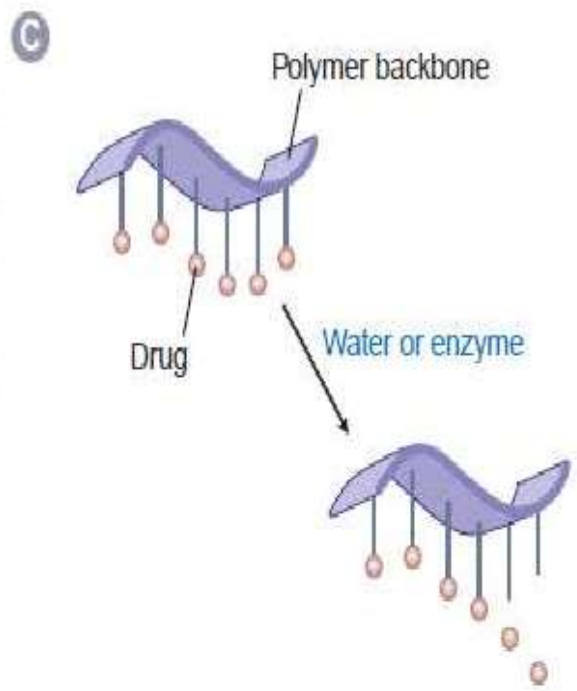
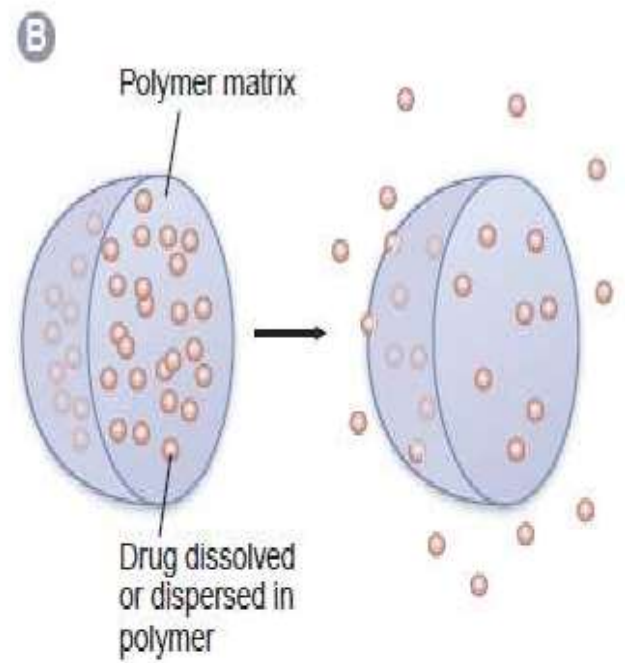
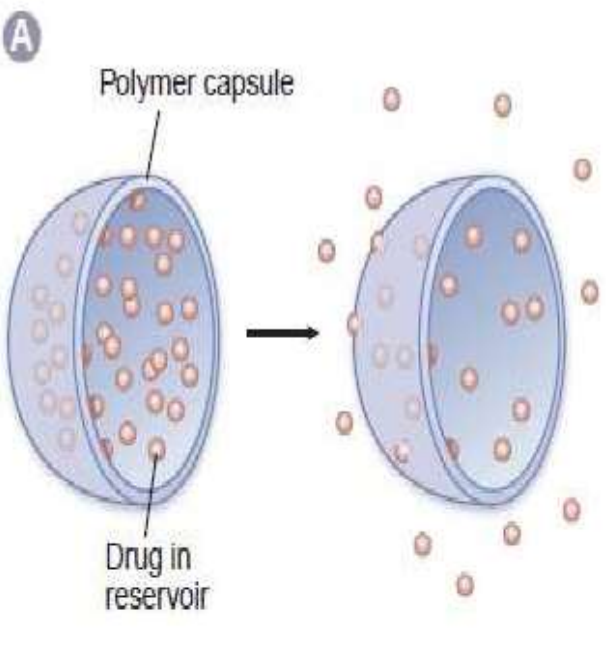
- ▶ **Polymeric microspheres**
- ▶ **Polymer micelles**
- ▶ **Biodegradable polymers** (natural-cellulose or synthetic-polyanhydrides/polyesters/polyacrylic acids/polyurethane)
- ▶ **Dendrimers (star polymers)**
- ▶ **Electro-active polymers**
- ▶ **Magnetic microcarriers**
- ▶ **Hydrogel-type materials**

Some Drug carriers...



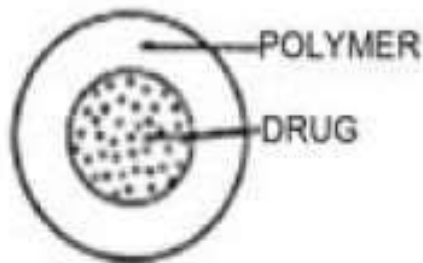
Types of polymers

- ▶ **Polymer Microspheres** : Two types
 - ▶ **Reservoir type** (drug is encapsulated-chocolate wrapper)
 - ▶ **Matrix like** (drug physically entrapped in a polymer network-cookie with chocolate crunch in between)
- ▶ **Polymers micelle** may be **single or polymeric micelle** (hydrophobic and hydrophilic)

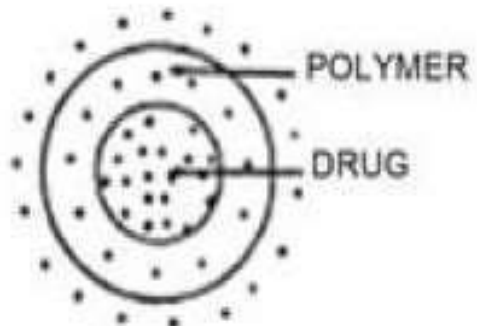


Polymer microspheres

MEMBRANE ENCLOSED RESERVOIR SYSTEM



TIME 0

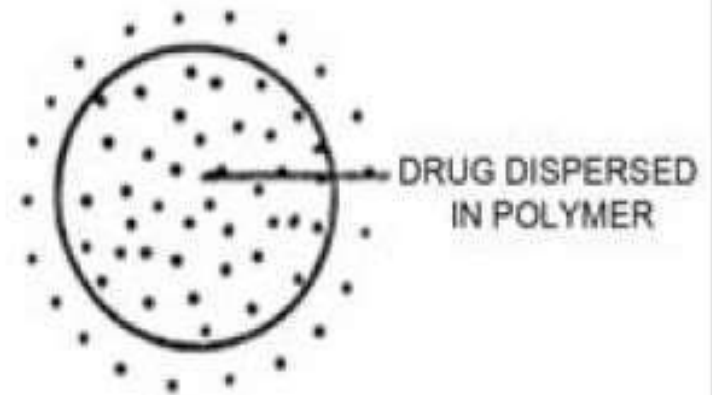


TIME T

NON-ERODIBLE MATRIX SYSTEM



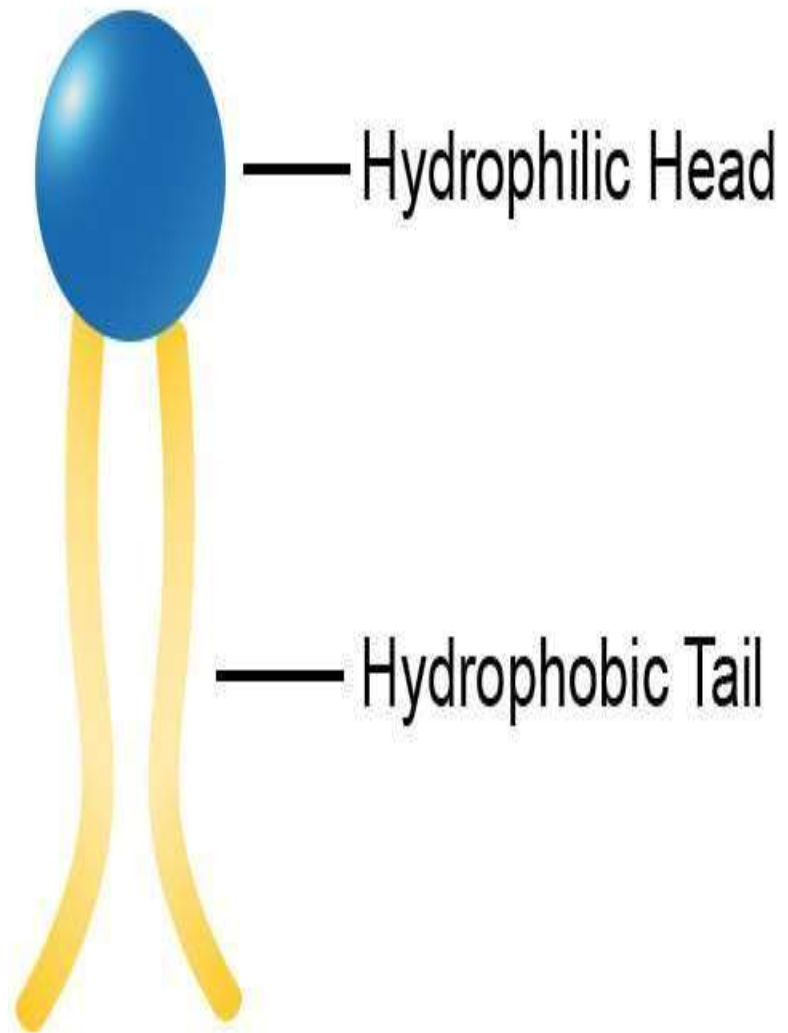
TIME 0



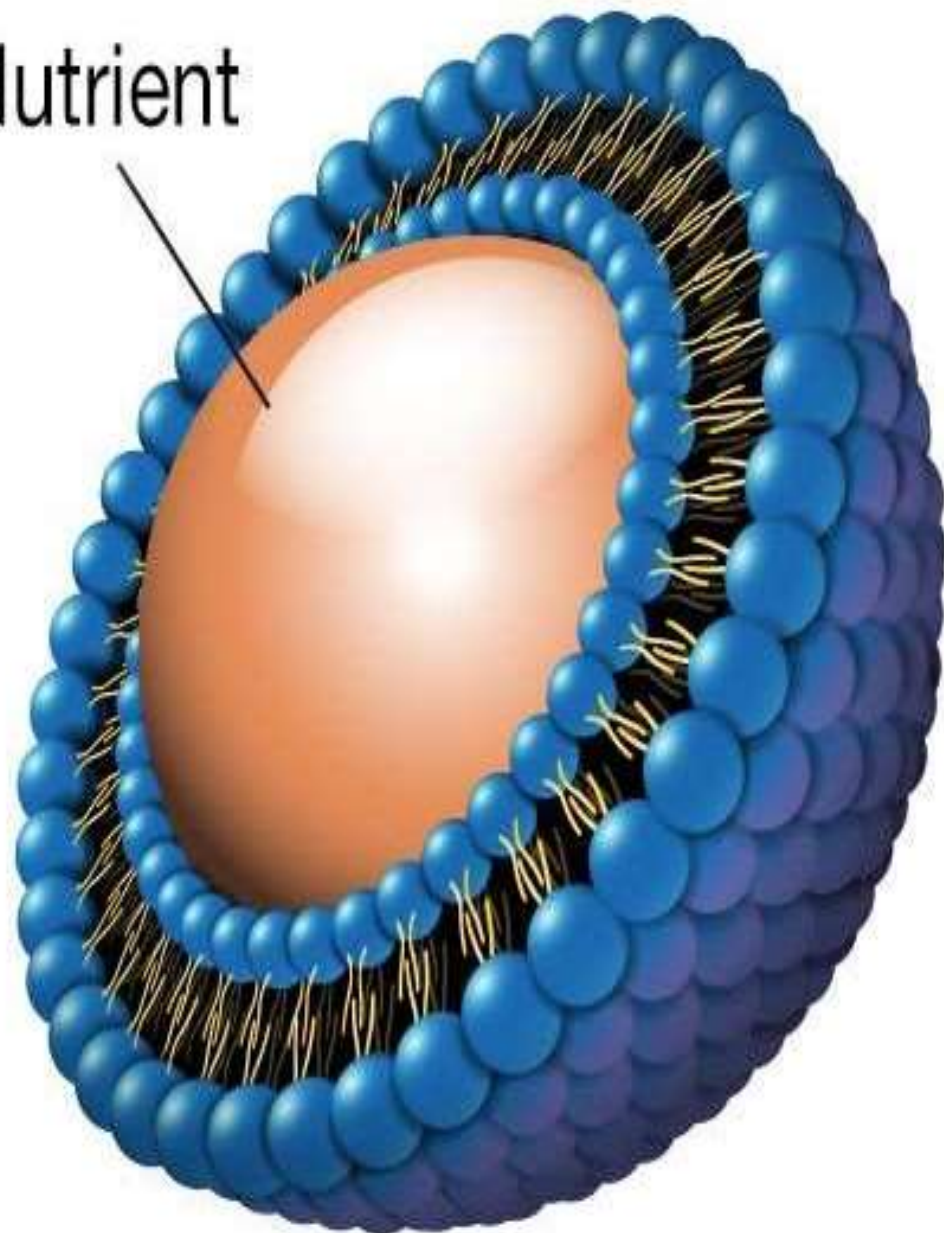
TIME T

Liposomes as Drug carriers

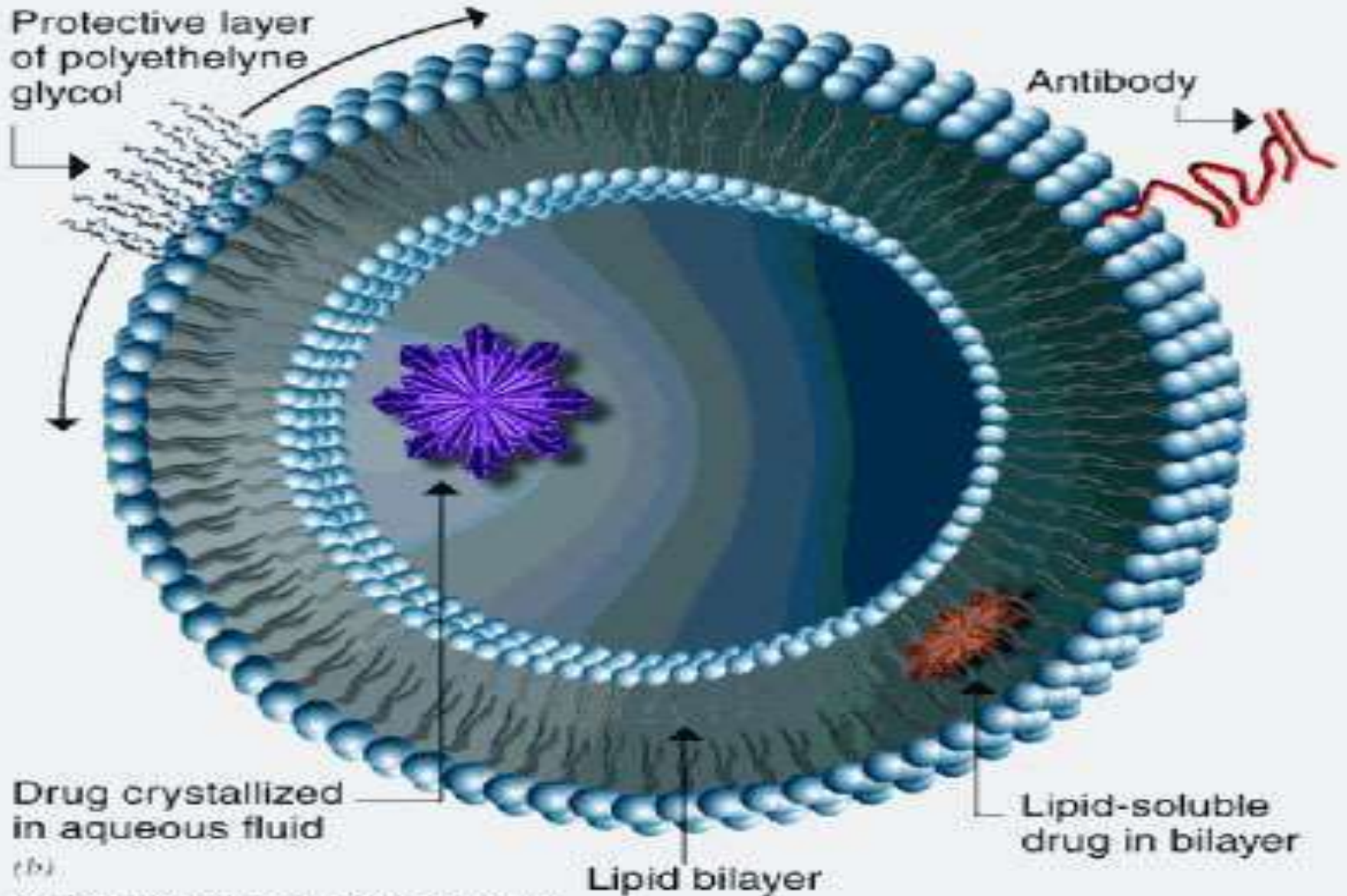
- ▶ These are minute vesicles and consists one or more phospholipids bilayers.
- ▶ May be unilamellar, multilamellar or multivesicular
- ▶ Filled with non lipid soluble drugs and retained until liposome is disrupted.
- ▶ **Niosomes** : similar to Liposomes but has non-ionic surfactants instead of phospholipids in the bilayer formation
- ▶ Eg : Amphotericin, Daunorubicin, Doxorubicin, Azithromycin, Vincristine(approved in 2012)



Nutrient



Liposomes



Advantages of Liposomes in DDS:

- 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

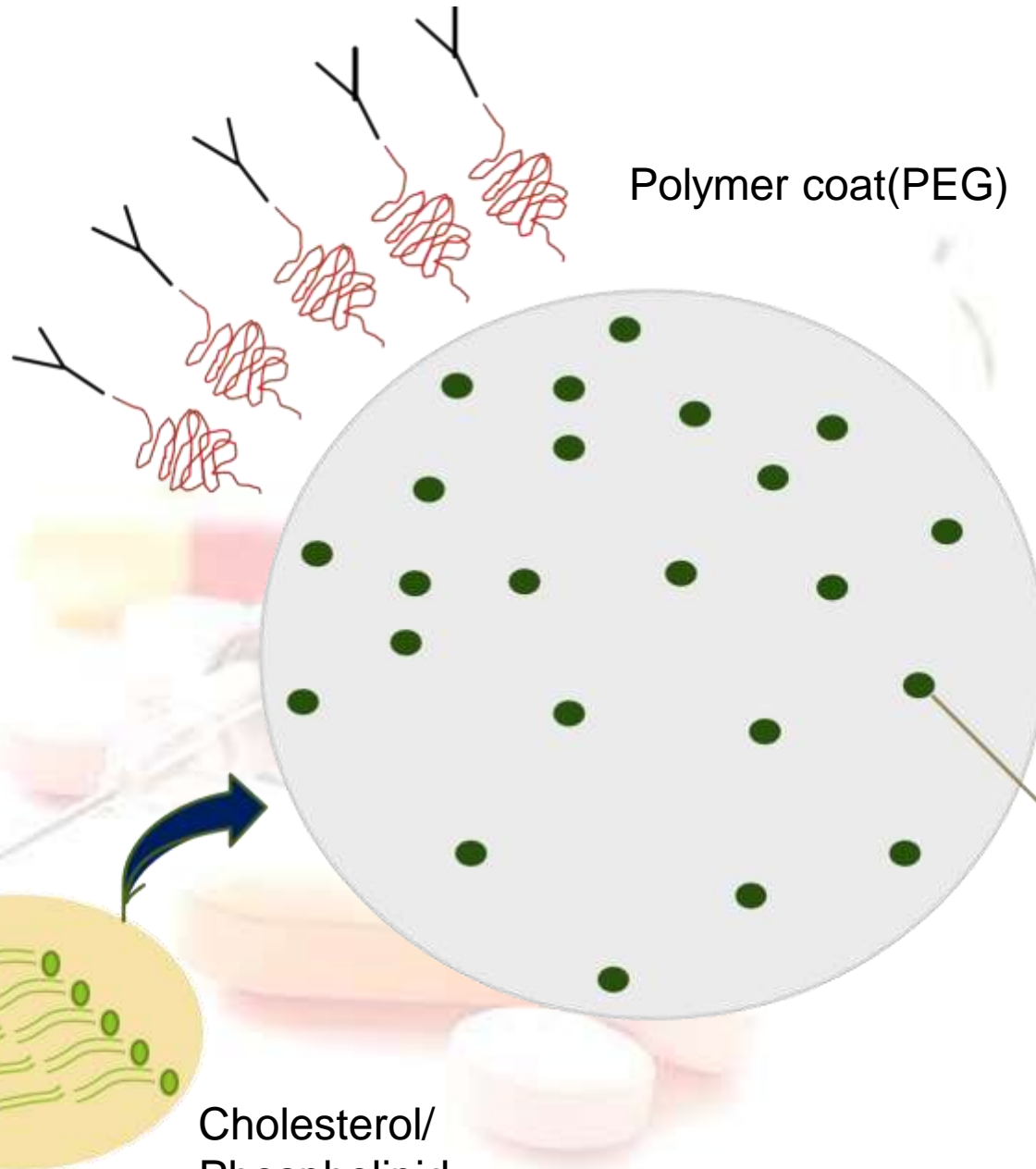
Targetting
Molecules
(Antibody)

Polymer coat(PEG)

Liposome

Drug
substance

Cholesterol/
Phospholipid
bilayer



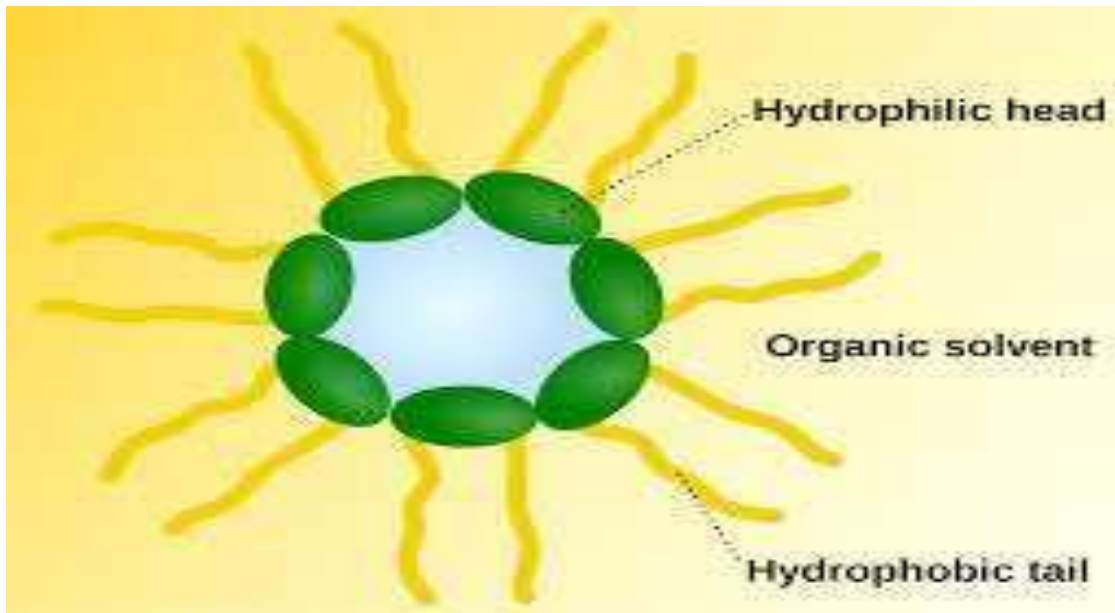
Micelles

Consist of aggregates of a few hundred **amphiphilic** molecules

That contains distinct **Hydrophilic** regions facing the surrounding water

And

Hydrophobic regions forming an inner core.



Types of micelle



spherical micelle



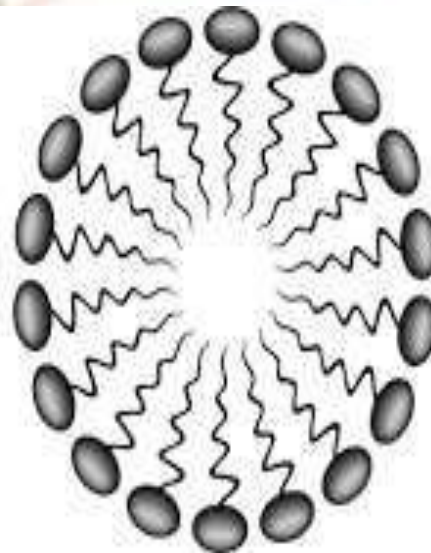
rod-shape micelle



lamellar micelle

hydrophilic group

hydrophobic group



Advantages of Micelles

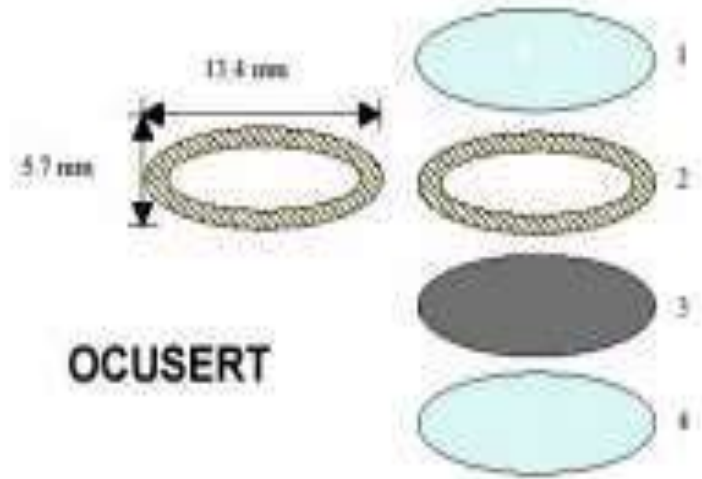
- ❖ Typically have diameter of 10-80 nm, Small enough not to sediment under gravity
- ❖ But large enough -Can't cross tight capillary endothelium (BBB)
- ❖ Malignant tumors and inflamed tissues have large fenestrated capillaries, so transfer into such tissues more rapid than normal tissues
- ❖ Absorption directly to the lymphatic system rather than vascular system to bypass first pass metabolism
- ❖ Protect the drug from metabolic degradation, so half life is prolonged

Eye Targeting Drug Delivery



Ocusert

- ▶ Thin elliptical micro units containing **drug in reservoir**
- ▶ Eg : **Pilocarpine ocusert** used in Glaucoma placed
 - ▶ **Site** : Under lower eyelid delivers the drug for a period of 7 days
 - ▶ **Adv.** - Pilocarpine is a short acting drug given 6th hrly is avoided.

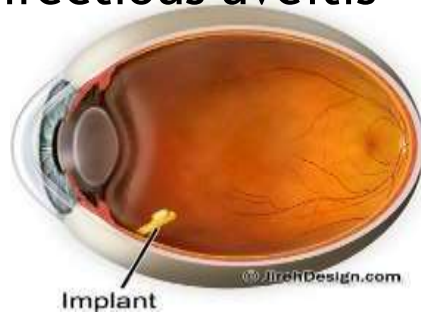




Gancyclovir -
Rx of CMV
retinitis

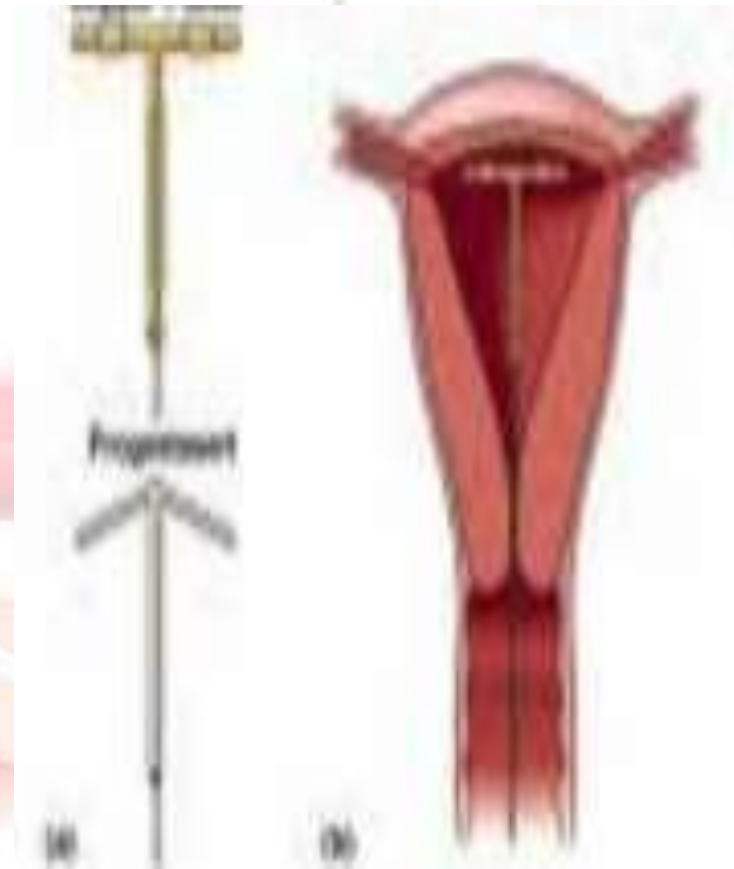
Retiserit -
Fluocinolone
acetonide - Rx non -
infectious uveitis

Latanoprost



Progestasert

- ▶ Drug is entrapped in solid polymer i.e., silicon rubber and implanted or injected in to the body.
- ▶ **Progestasert** : It is an IUCD inserted into uterus delivers progesterone at a constantly specified rate for 1yr.
- ▶ **ADV.** : No missing of dose
- ▶ **DISADV.** : Ectopic pregnancy
 - ▶ Chances of PID



UROGENITAL

- ▶ **Pessary**- medical device inserted into the vagina, either to provide structural support, or as a method of delivering medication.

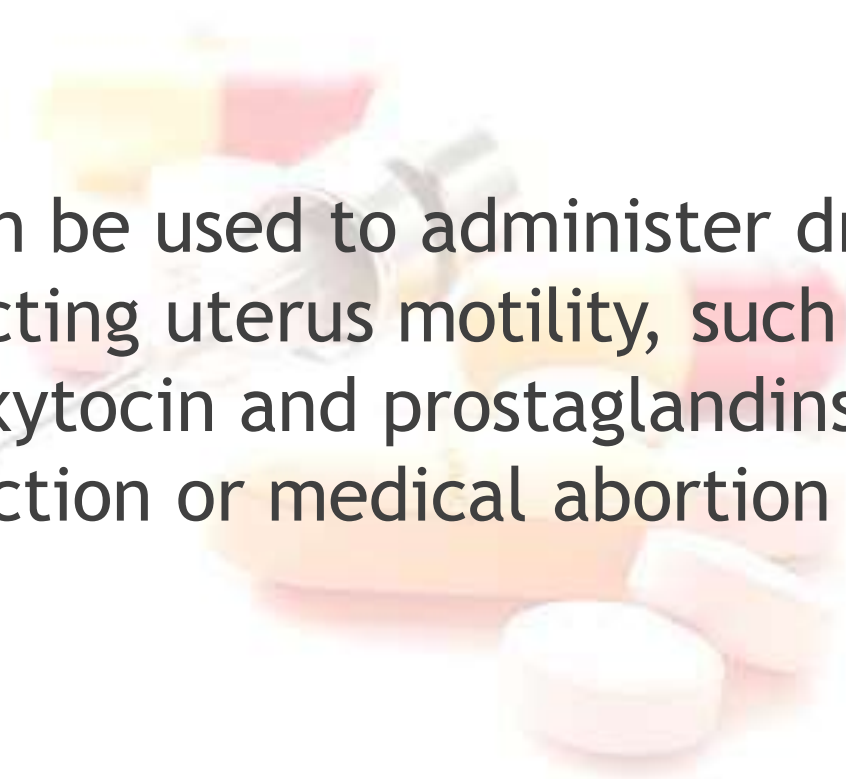


- ▶ **Vaginal ring-** polymeric drug delivery devices designed to provide controlled release of drugs for intravaginal administration over extended periods of time.



- ▶ **Intrauterine device-** small contraceptive device, often 'T'-shaped, often containing either copper or levonorgestrel, which is inserted into the uterus.



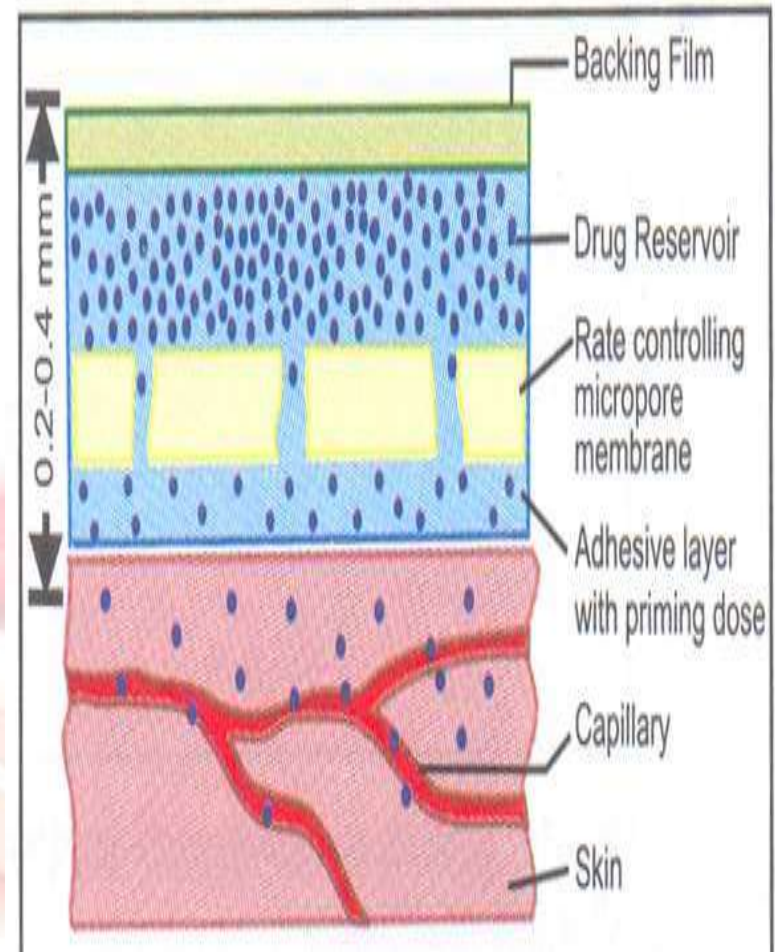


► **Extra-amniotic administration-** a route of administration to the space between the fetal membranes and endometrium inside the uterus of a pregnant woman.

► It can be used to administer drugs affecting uterus motility, such as oxytocin and prostaglandins, e.g. in labor induction or medical abortion

Transdermal Adhesive Patch

- ▶ Drug is incorporated into a **polymer reservoir**
- ▶ Provides steady & smooth plasma conc. for a period of 1-7 days
- ▶ **Site of application** : Chest, Abdomen, Upper Arm, lower Back, Buttock Or Mastoid Region
- ▶ **Size** : 5-20 cms and available in various shapes.
- ▶ **E.g.** : Nitroglycerin, Nicotine, Estradiol, Hyoscine, Fentanyl

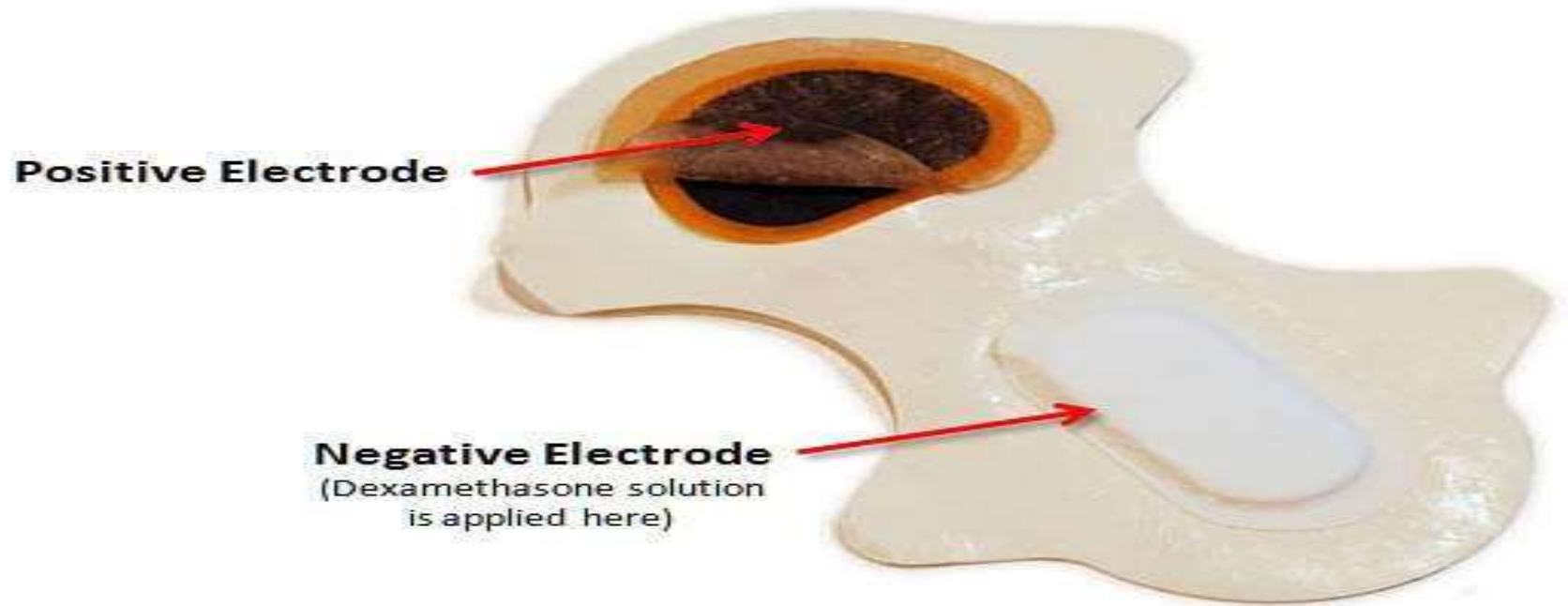


Transdermal Adhesive Patch cont...

- ▶ **Adv.** - more convenient and better patient compliance
- ▶ **ADR** : Local Irritation, Erythema
- ▶ **Disadvantage** : Drug delivery is slow & passive, large molecular wt drugs cannot be delivered, lack of dosage flexibility.



Transdermal Drug delivery...



Recent advances in TDD

▶ Iontophoresis

▶ **Galvanic current** allows the penetration of drug applied to the skin into deeper tissues.

▶ **Anode iontophoresis** - compounds with positive charge

▶ **Cathode iontophoresis** - compounds with negative charge.

▶ E.g. **Salicylates**

- Enhance transport of charged LMW molecules through skin
- Involves application of low voltage electric impulses for long periods
- Used as therapy for hyperhidrosis and analgesics

▶ Electroporation

- High voltage pulses
- Allows systemic delivery of large, charged molecules
- Eg: heparin, oligonucleotides

► Sonophoresis

- Ultrasound enhancement of drug delivery
- For insulin, interferon, erythropoietin
- Ultrasound application → cavitation → tiny air filled spaces in lipid bilayers → diffusibility of drug through skin



Ethosomes

Ethosomes are the slight modification of well established drug carrier- liposome.

Ethosomes are lipid vesicles containing phospholipids with high concentrations of ethanol and water.

These are vesicles tailored for enhanced delivery of active agents

Mechanism of Action

Ethanol causes skin disruption



More permeability through skin



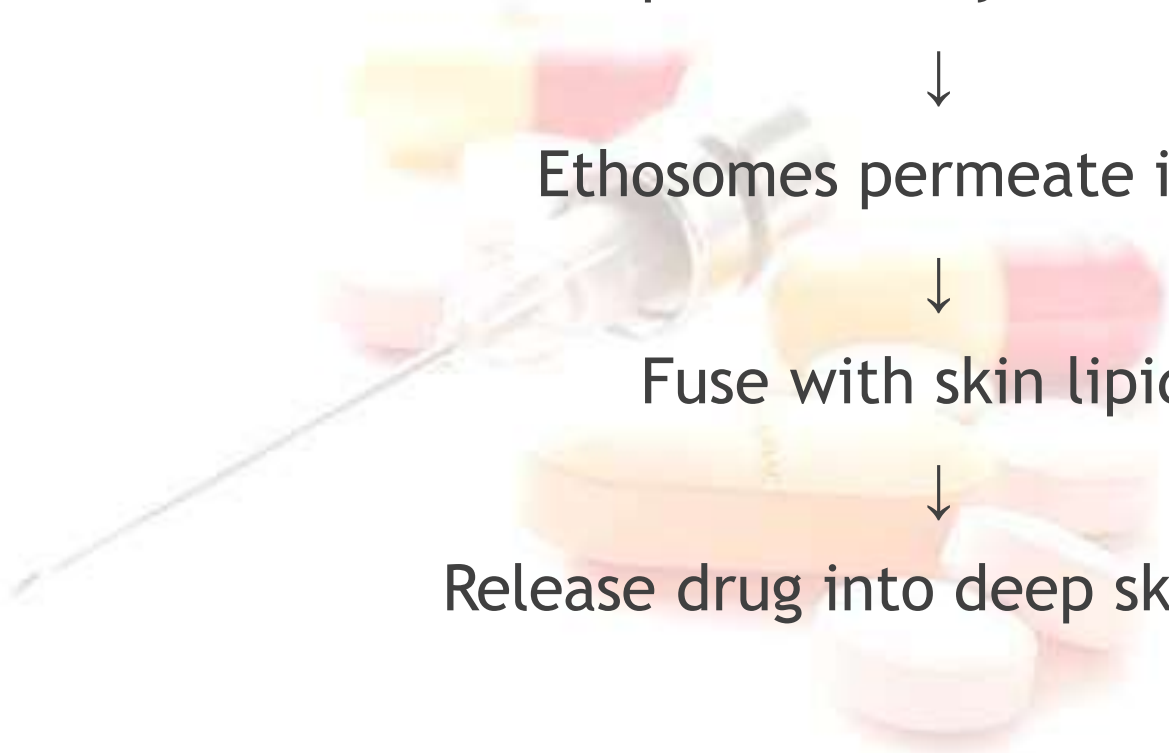
Ethosomes permeate inside



Fuse with skin lipids



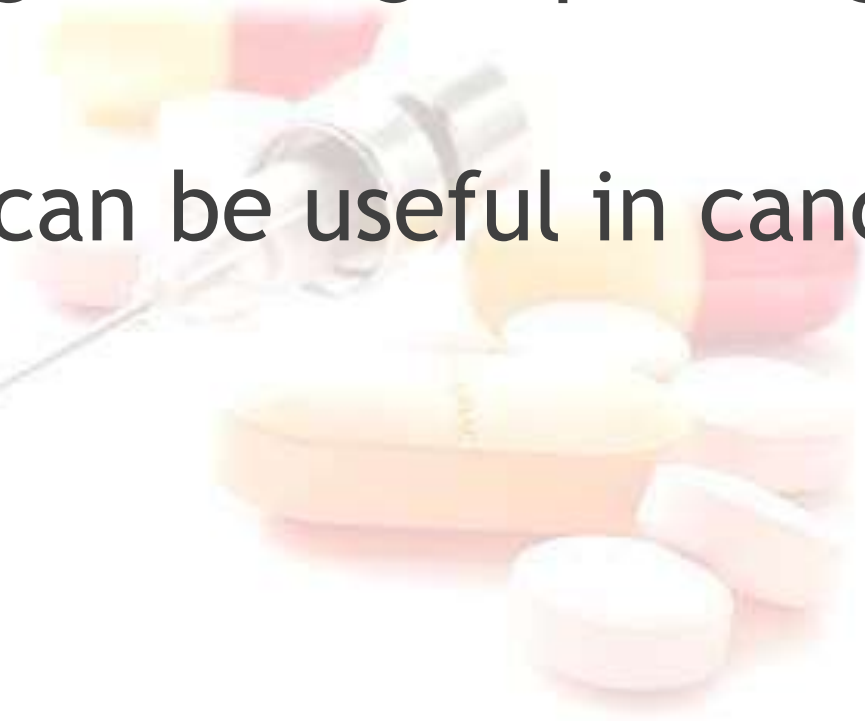
Release drug into deep skin layers



Patient Controlled Analgesia

Patient can control the release of analgesic drug depending on the pain

-
this can be useful in cancer pain

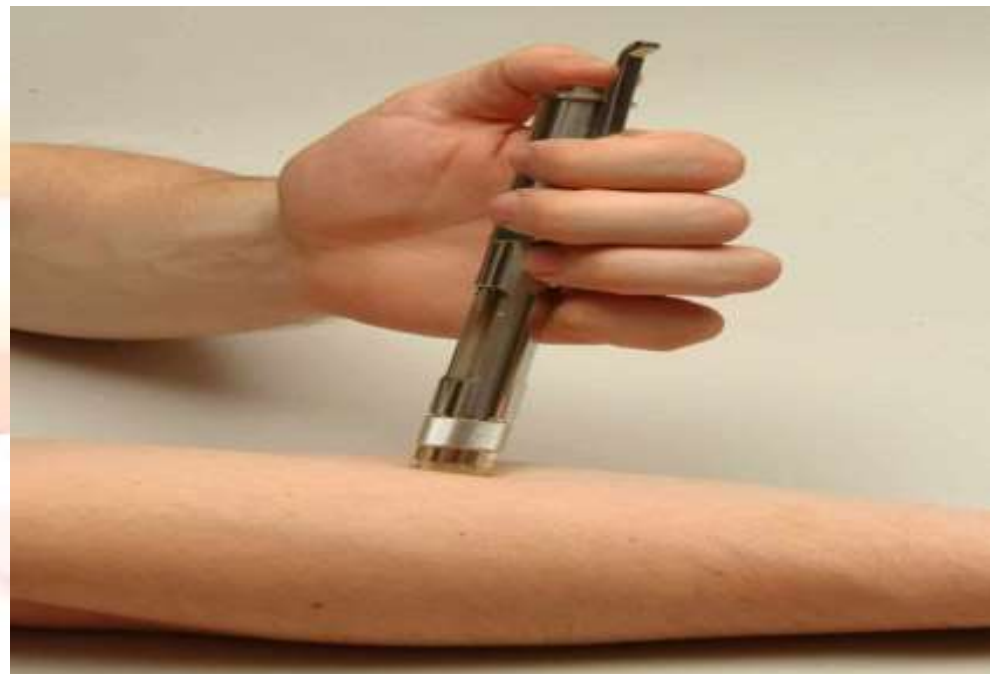


PCA



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.
 - ▶ Essentially painless and suited for mass inoculations.
 - ▶ Eg. **Insulin**



DERMAL

- ▶ Jet injector- medical injecting syringe that uses a high-pressure narrow jet of the injection liquid instead of a hypodermic needle to penetrate the epidermis.
- ▶ It is powered by compressed air or gas, either by a pressure hose from a large cylinder, or from a built-in gas cartridge or small cylinder.
- ▶ Eg: used for mass vaccination, and as an alternative to needle syringes for diabetics to inject insulin



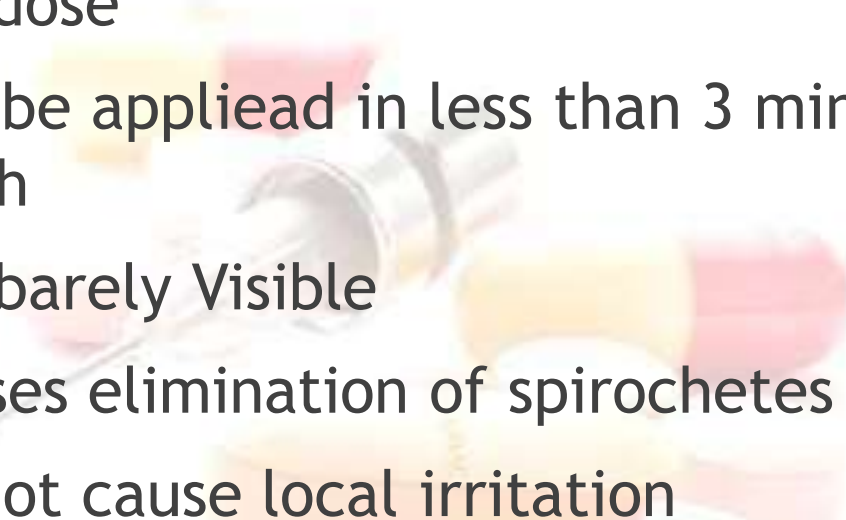
Periodontal Disease

- ▶ Percent with evidence of periodontal disease in 25%
- ▶ 2-3% requiring surgery

- ▶ **Advantages**

Surgery is painful and expensive
oral tetracyclines cause GI effects, nausea, diarrhea etc

Tetracycline Hollow Fibres

- ▶ Are effective with less than 1/1000th of the dose
 - ▶ Can be applied in less than 3 min per tooth
 - ▶ Are barely Visible
 - ▶ Causes elimination of spirochetes
 - ▶ Do not cause local irritation
- 

Special delivery forms in SC route

Pellet implantation : Drug in solid pellet form introduced with a trochar and canula.

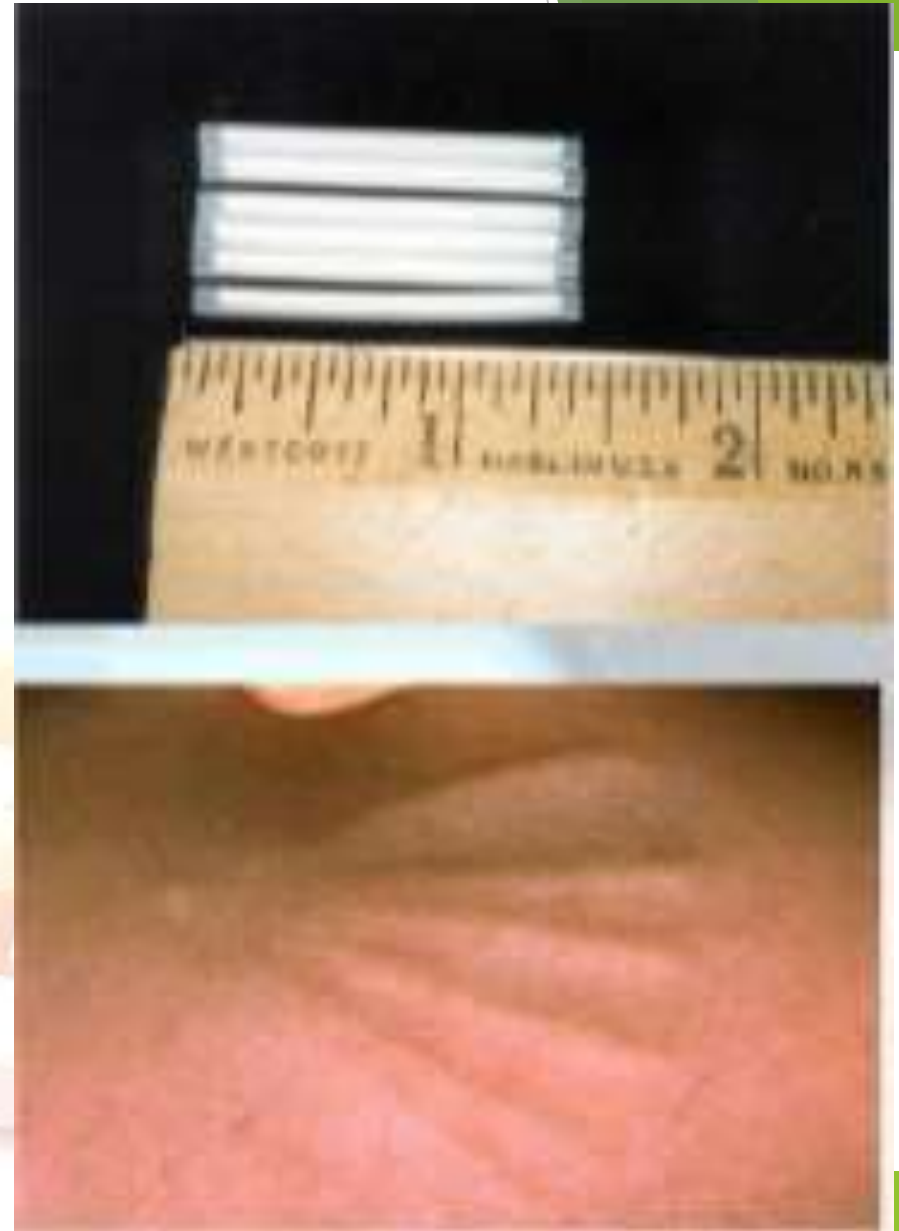
- ▶ Provides sustained release of drug over weeks and months. Eg. DOCA, Testosterone



Special delivery forms in SC route cont...

- ▶ **Sialistic (Non biodegradable) and Biodegradable implants :**
Crystalline drug is packed in tubes or capsules made of suitable materials and implanted under skin.
- ▶ **NORPLANT - Levonorgestrel**
subdermally implanted provides contraception for a period of 5 yrs.

ADV. : No missing of dose



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.



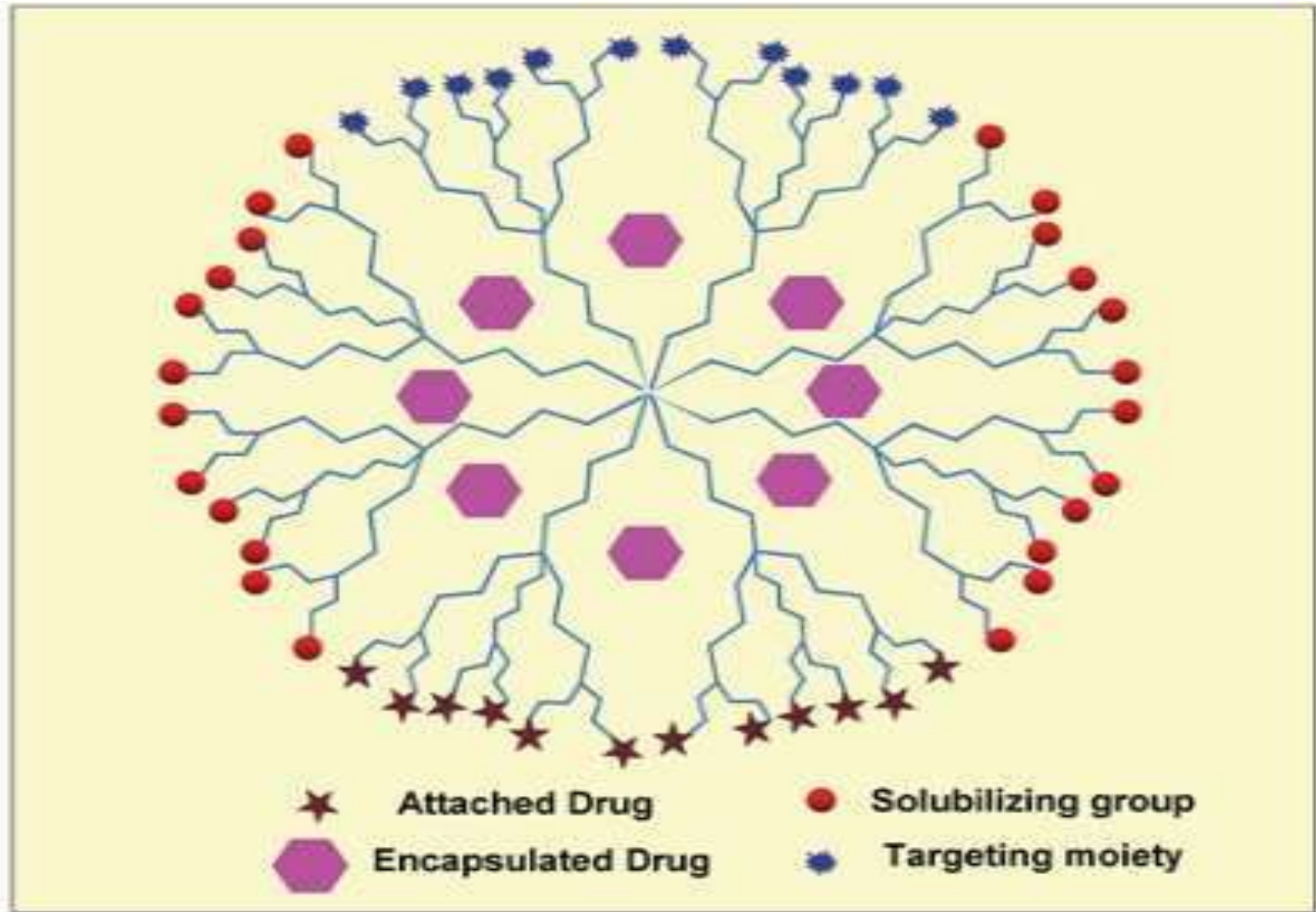
MAbs cont...

- ▶ **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)

Dendrimers

- ▶ Dendritic macromolecules (highly branched, globular) :
- ▶ Used to **encapsulate individual small drug molecules** (unimolecular nanocapsule)
- ▶ Can also serve as “**hubs**” onto which large numbers of drug molecules can be attached via covalent bonds.
- ▶ Eg. : **Anticancer agents 5-fluorouracil** to polyaminoamine dendrimers
- ▶ **Methotrexate** to hydrazide-terminated dendrimers formed from poly aryl ether.

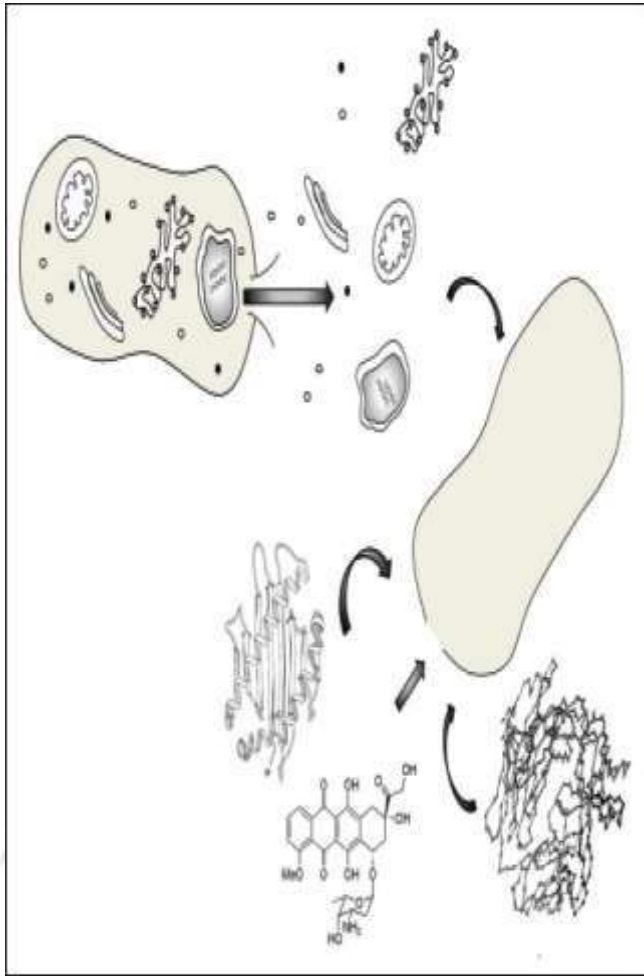
Dendrimer...



Bacterial ghosts/Artificial cells as carriers

- ▶ Different species of microorganisms have been used to produce ghosts like *Salmonella*, *Pasteurella hemolytica*, *Actinobacillus pleuropneumoniae*, *E.coli*
- ▶ **Artificial Cells** : Size & structure same as biological cell with some functional property of biological cells.
- ▶ E.g. **Microencapsulation of islets of pancreas, hepatocytes, cholesterol removing microorganisms- *Pseudomonas pictorum* & Urea removal - *E.Coli***

Bacterial Ghost



bacterial ghost platform technology



INFECTIOUS DISEASES

- Human Vaccines
- Veterinary Vaccines
- Adjuvants
- Innate Immunity

TUMORS

- DC Cell Therapy
- Tumor Vaccines
- Drug Delivery

Hydrogel carriers

- ▶ Hydrogels are **hydrophilic, polymeric networks** capable of **imbibing large amounts of water or biological fluids**.
- ▶ Hydrogels are **stimuli-sensitive gel systems** modulate release **in response to pH, temperature, ionic strength, electric field, or specific analyte concentration differences**.

Micro Electro Mechanical System (MEMS)

- ▶ Dorian Liepmann and Boris Stoeber developed MEMS syringe, the size of a fingernail.
- ▶ It is 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.

MEMS

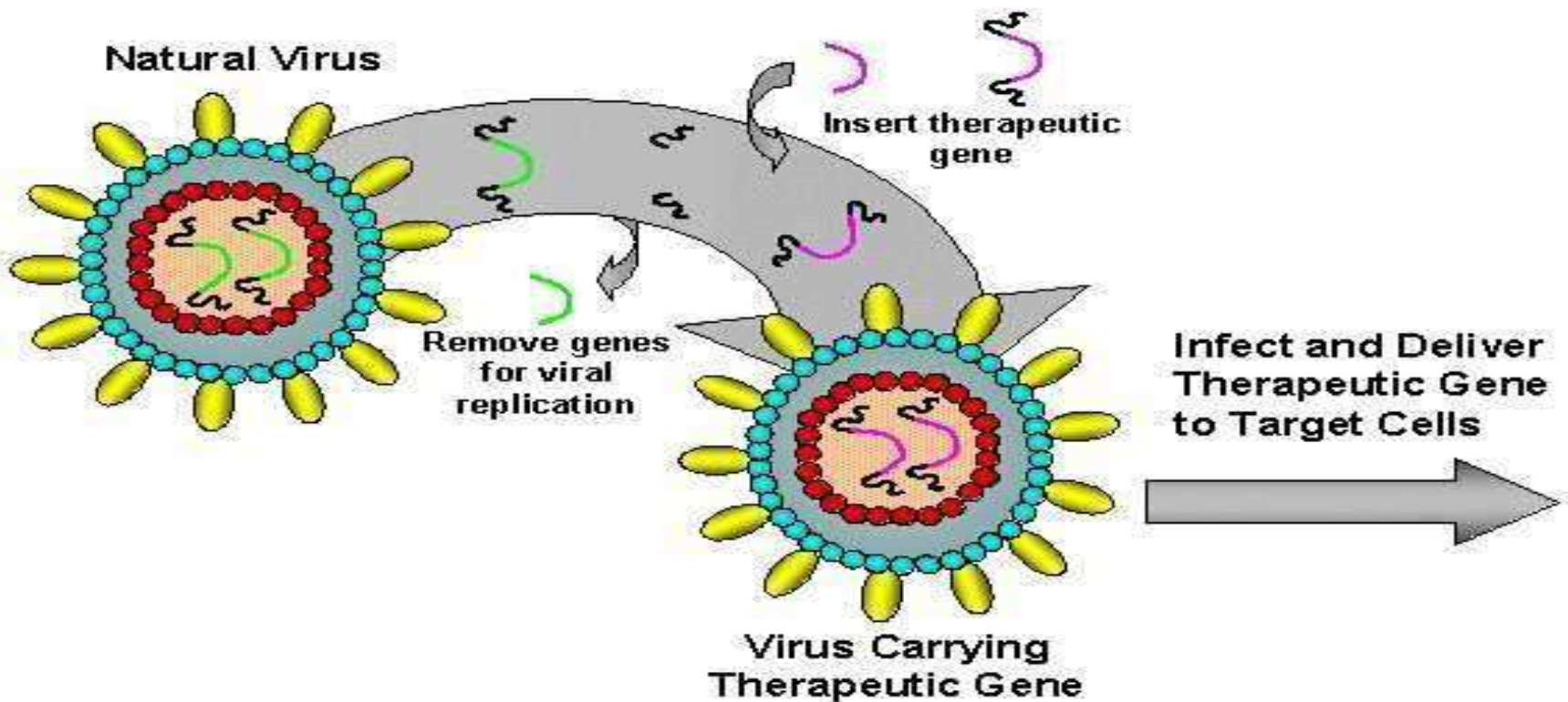


Gene Therapy

- ▶ Gene therapy is an experimental/therapeutic technique that uses genes to treat or prevent disease. In the future ,this technique may allow doctors to treat a disease by inserting a gene(nucleic acid polymer) into a patient cells instead of using drugs or surgery.

- ▶ Under evaluation & III Phase clinical trials for Adenovirus & HIV

Viral Vectors for Gene Transfer

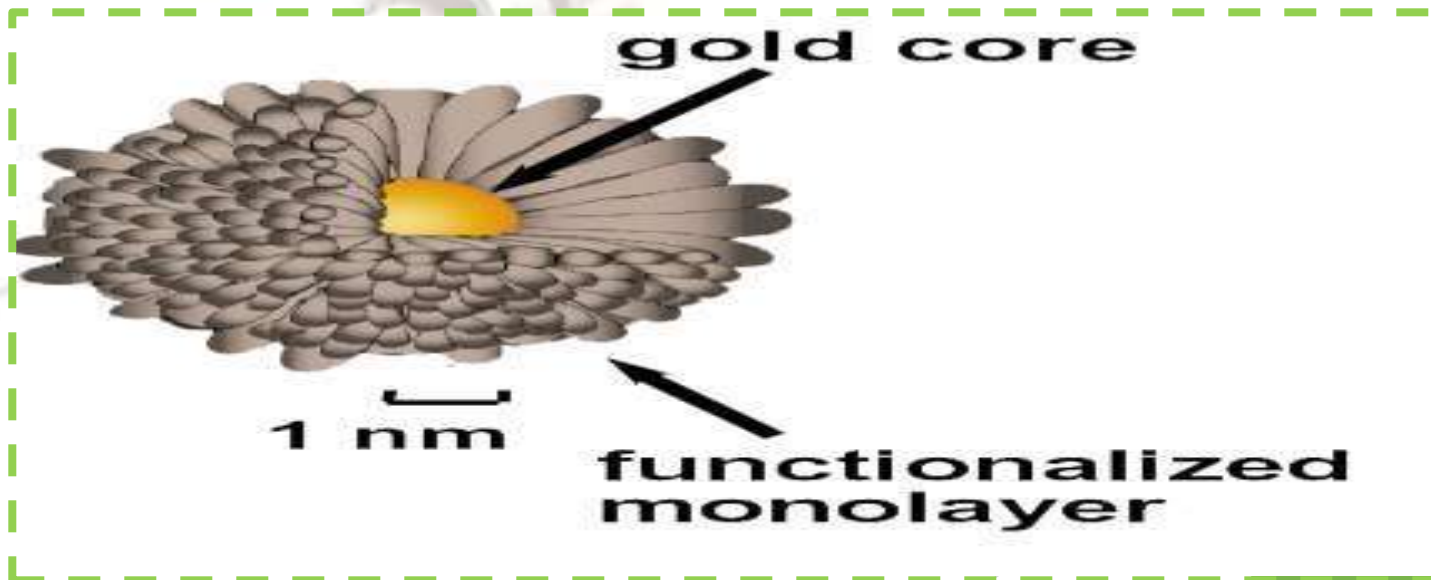


Nano particles

- ▶ Nanoparticles includes **Nanospheres and Nanocapsules** of size **10-200 nm** which are solid particles, either **amorphous or crystalline** formed from biodegradable or non biodegradable polymers.
- ▶ **Nanocapsules** : These are vesicular systems in which the drug is confined to a cavity surrounded by a unique polymer membrane
- ▶ **Nanospheres** : These are matrix systems in which the drug is physically and uniformly dispersed.

Nanoparticles as carriers

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



Nano - Erythroosomes as carriers

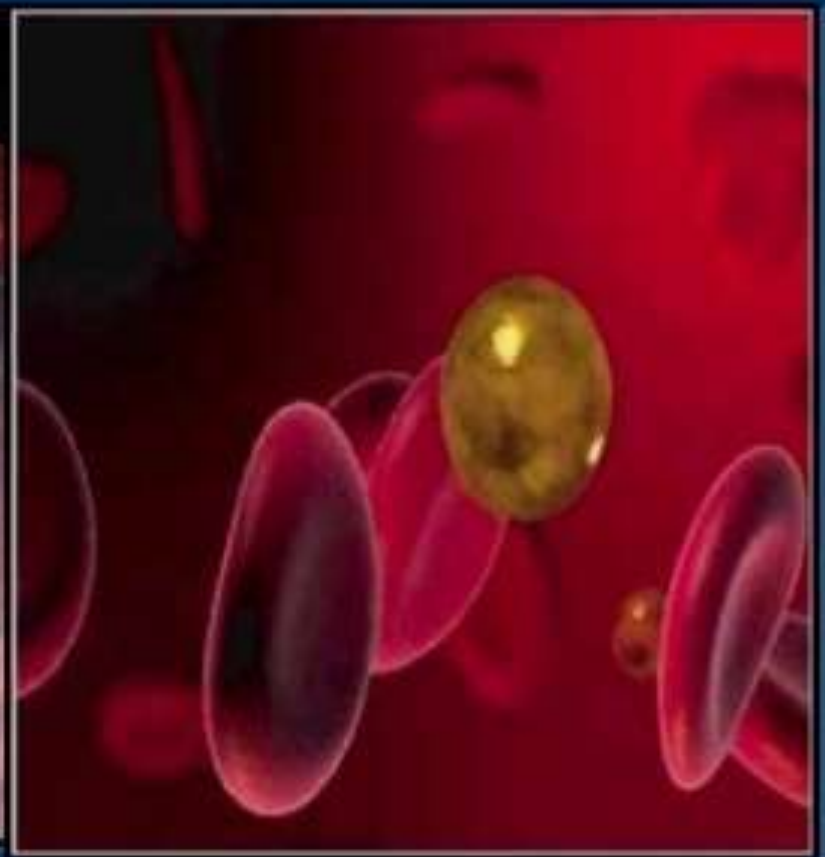
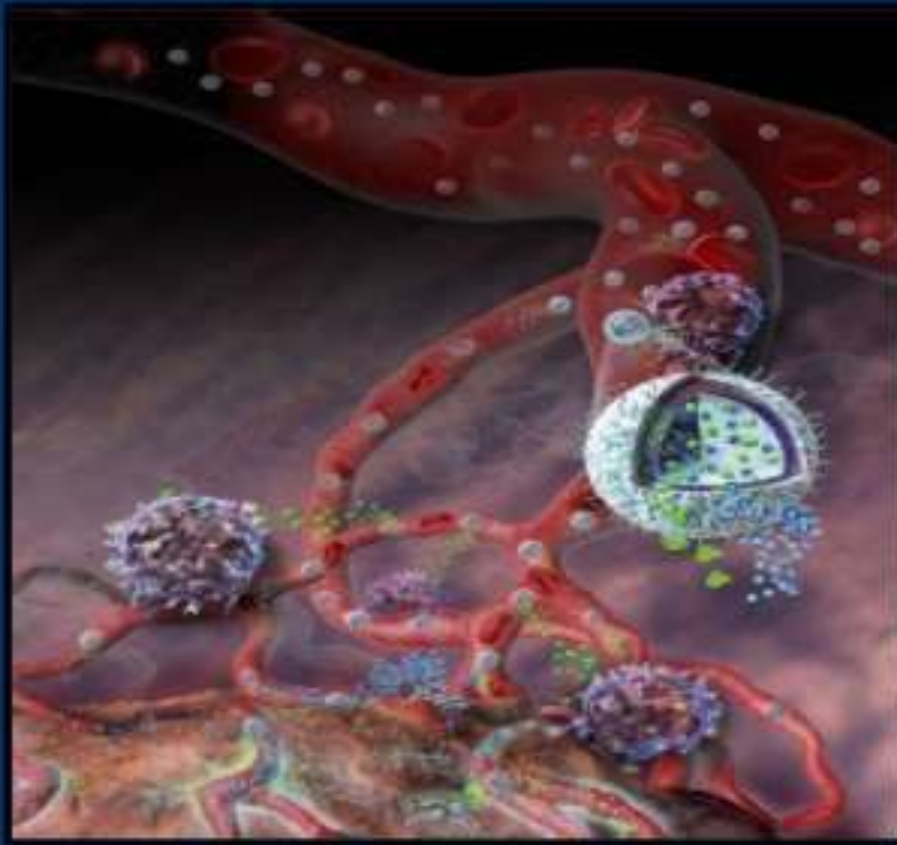
- ▶ Drug loaded in body's own erythrocytes.
- ▶ Also called **GOLDEN EGGS**.

ADVANTAGES:

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

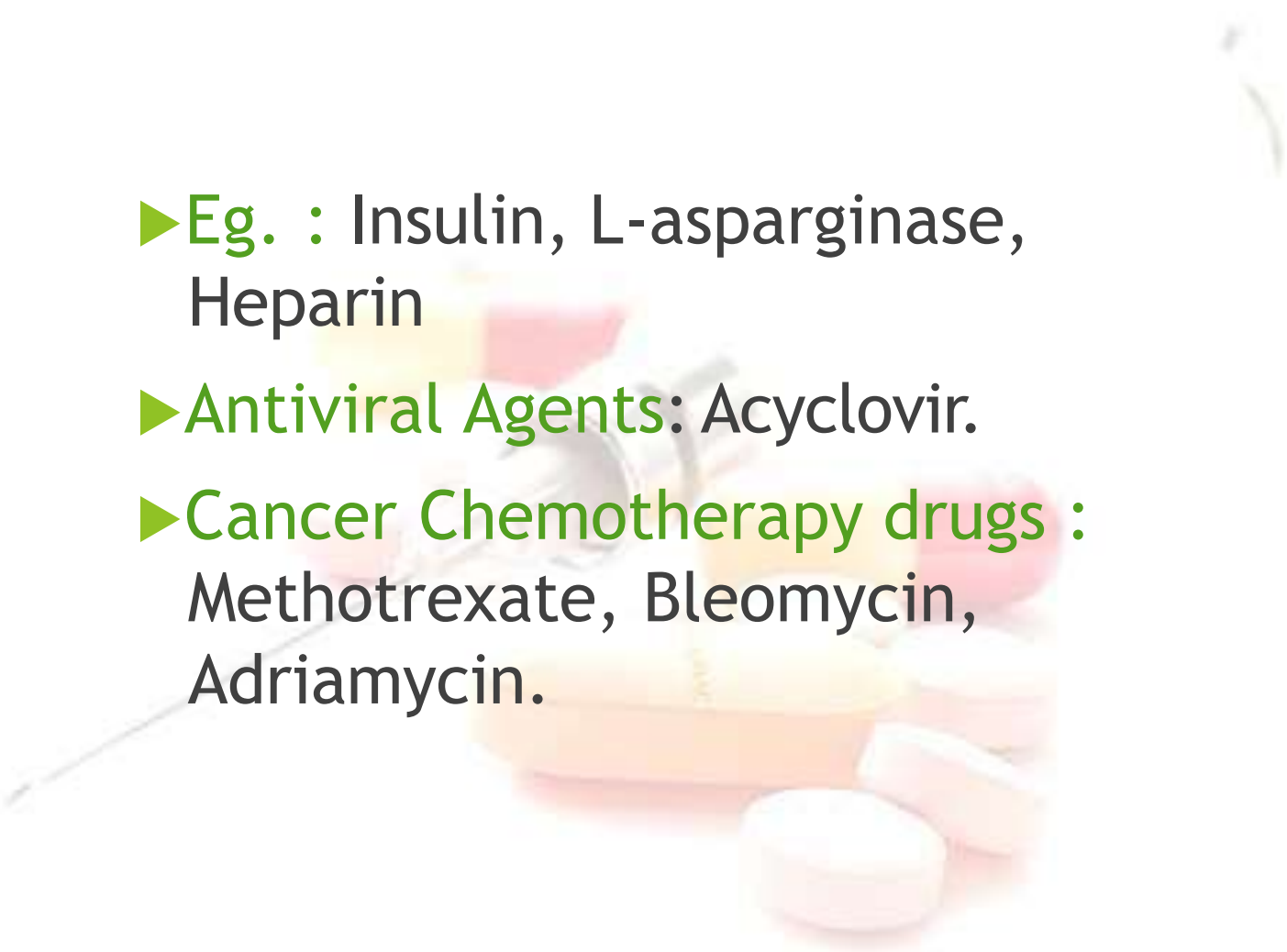


Nanoerythroosomes



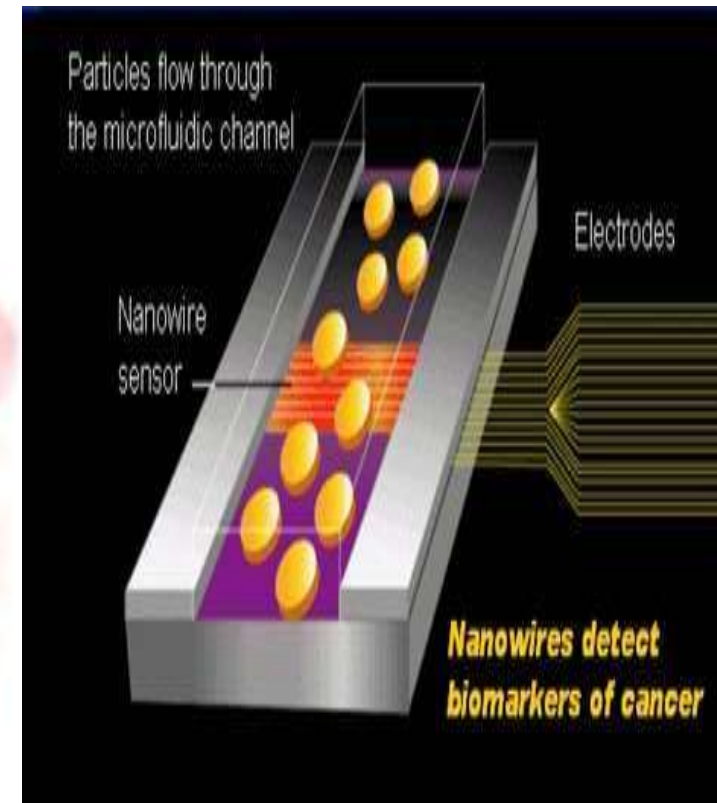
Nanoerythroosomes are resealed erythrocytes that can carry proteins, enzymes & macromolecules. They are used in the treatment of liver tumor, parasitic disease & enzyme disease

Nano - Erythroosomes as carriers

- ▶ **Eg. :** Insulin, L-asparaginase, Heparin
 - ▶ **Antiviral Agents:** Acyclovir.
 - ▶ **Cancer Chemotherapy drugs :** Methotrexate, Bleomycin, Adriamycin.
- 

Nanotechnology in healthcare...

- ▶ Nanotechnology offers tools and techniques for more effective detection, diagnosis and treatment of diseases
- ▶ Lab on chips help detection & diagnosis of diseases more efficiently
- ▶ Nanowire help in early detection of cancer biomarkers

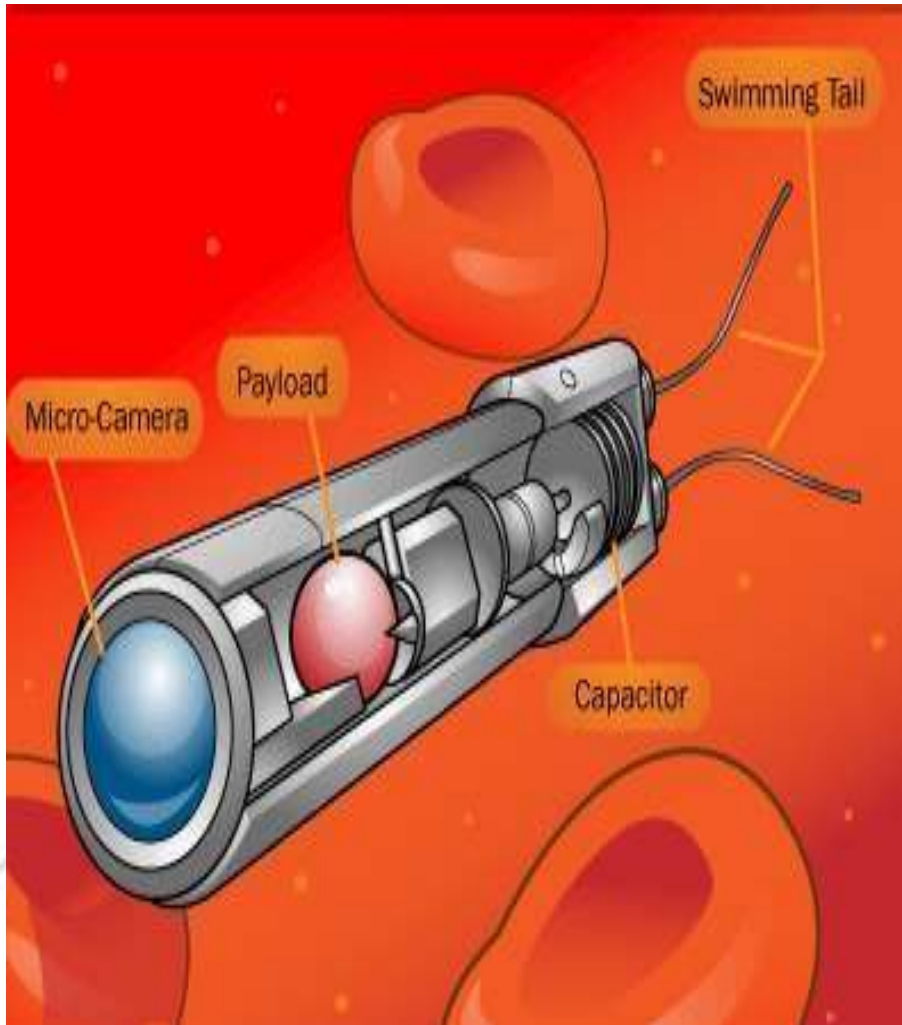


Nanotechnology in Cancer

- ▶ The mixture of two different-sized nanoparticles work with the body's bloodstream to seek out, stick to and kill tumors.
- ▶ One is designed to find the cancerous tumor and then adhere to it, while the second is designed to then kill the tumor cells.

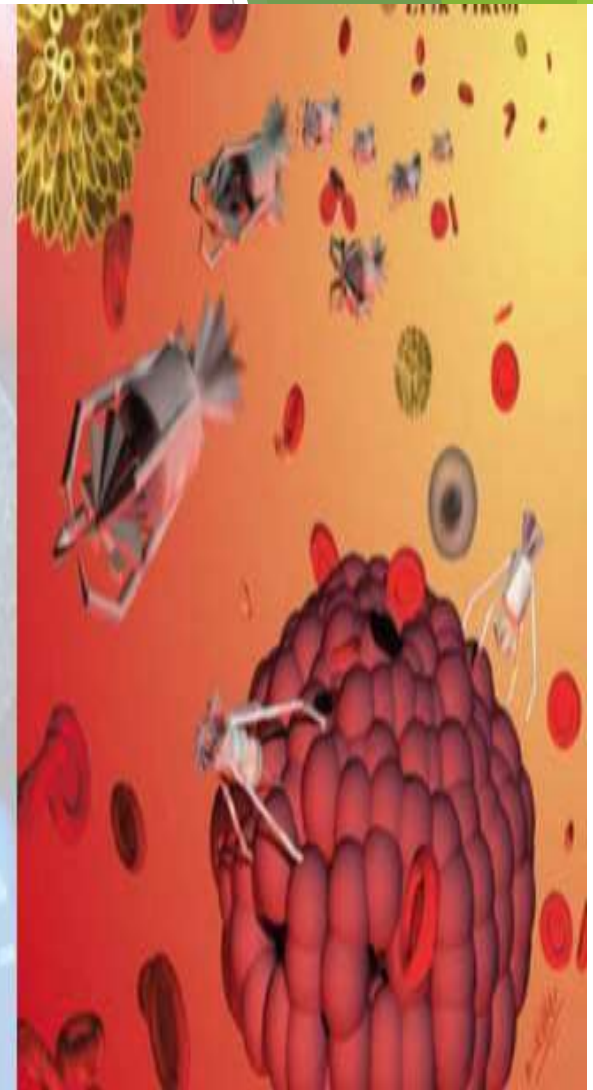


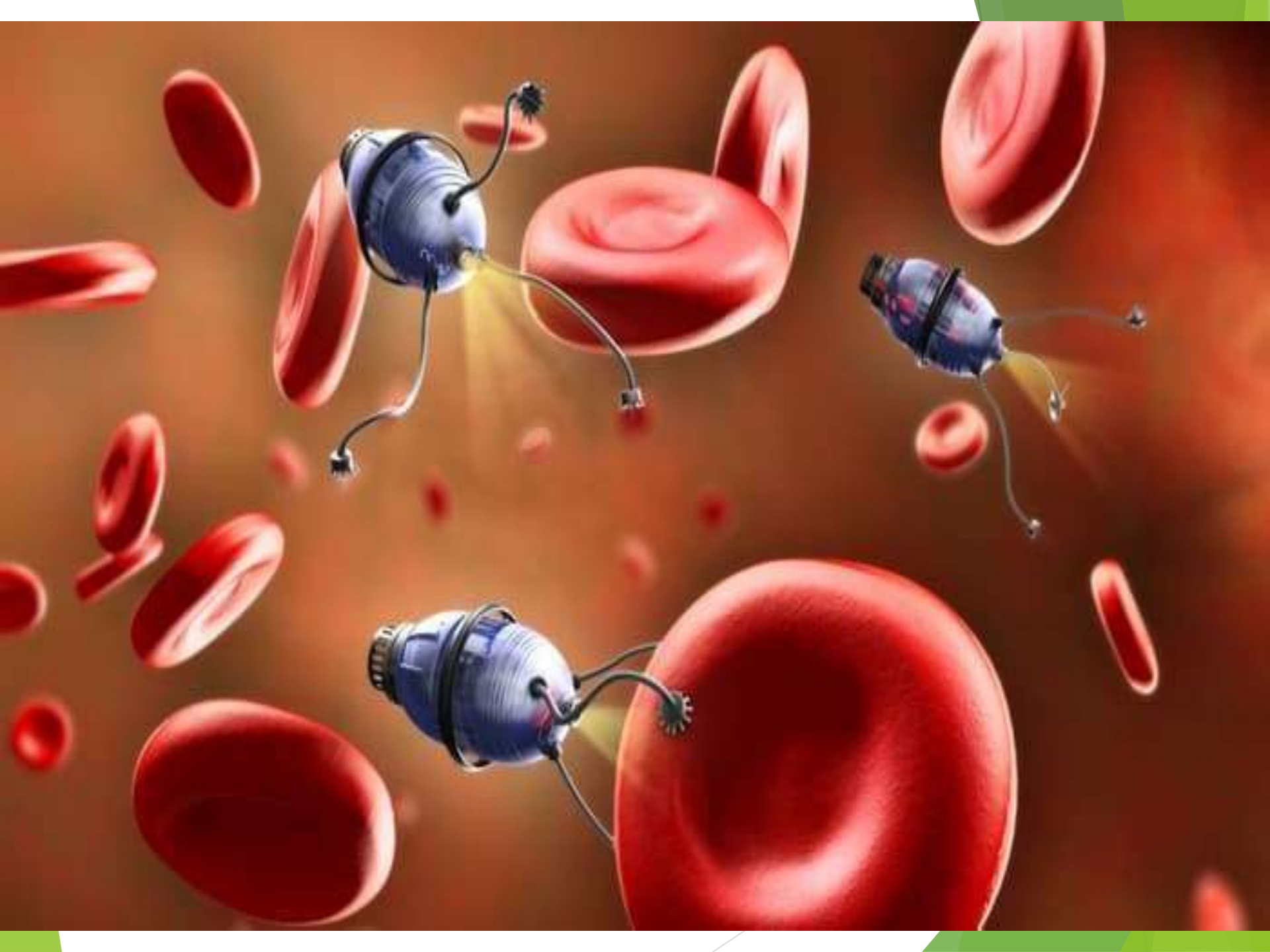
Nano-Robots



er.

**Mechanical
drilling of a
small tumor
mass by a
nanorobot**





Magnetic Micro carriers

- ▶ Include Magnetic Microspheres, Magnetic Liposomes, Magnetic Nanoparticles, Magnetic Resealed Erythrocytes, Magnetic Emulsion etc.
- ▶ Magnetic Micro/Nanoparticle & molecular magnetic labels have been used for great number of application in various areas of biosciences, targeted drug delivery, imaging & in bio separation technology.