UNIT-4

TARGATED DRUG DELIVERY

Points to be covered in this topic

- ❑ INTRODUCTION
- ❑ APPROACHES
- ❑ ADVANTAGES
- ❑ DISADVANTAGES
- ❑ LIPOSOMES
- ❑ NIOSOMES
- ❑ NANOPARTICLES
- ❑ MONOCLONAL ANTIBODIES

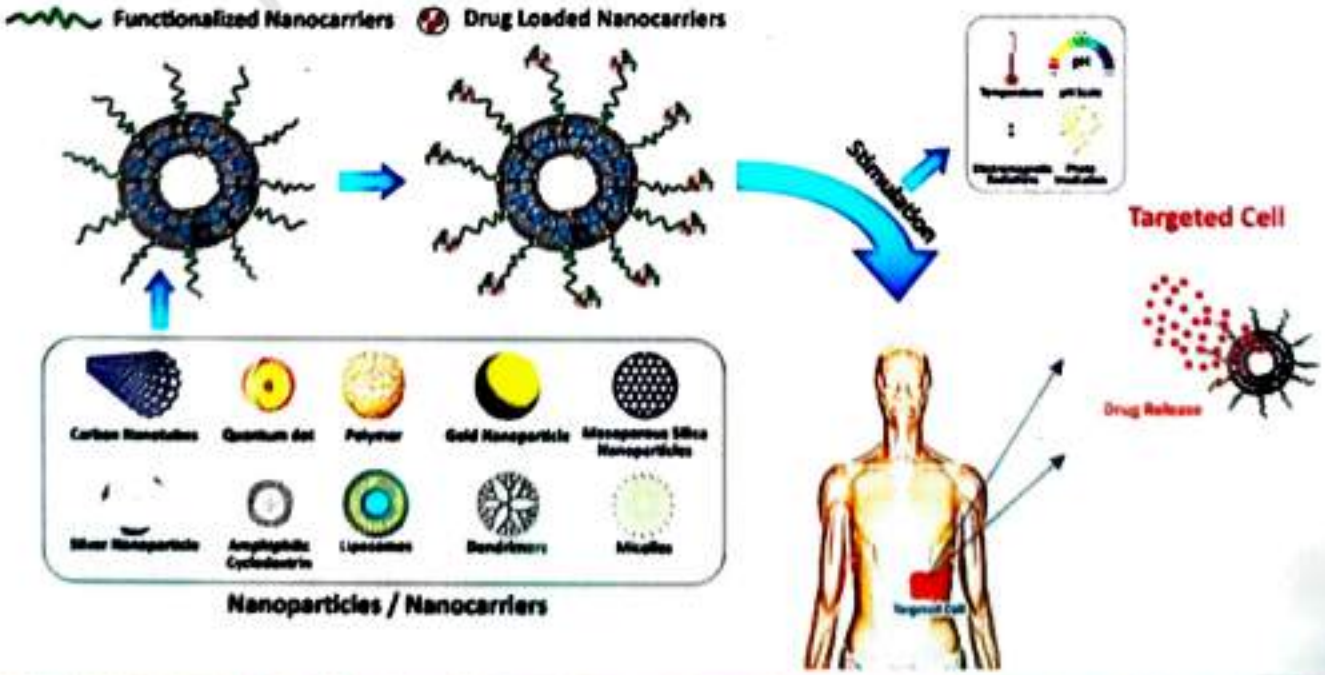
TARGATED DRUG DELIVERY

❑ INTRODUCTION:

- In conventional drug delivery systems such as oral ingestion or intravascular injection, The medication is distributed throughout the body by means of systemic blood circulation.

- For most therapeutic agents, only a small portion of the medication reaches the affected organ or tissue,
- Targeted drug delivery sue to **deliver medication in the tissues of interest** while **reducing the relative concentration of the medication** in the remaining tissues.
- For example, by avoiding the host's defence mechanisms and inhibiting non-specific distribution in the liver and spleen, a system can reach the intended site of action in higher concentrations.
- Targeted delivery is believed to **improve efficacy while reducing side-effects.**

Targeted Drug Delivery System



What is drug targeting?

- ✓ The therapeutic response of a drug depends upon the interaction of drug molecules with cell on cell membrane related biological events at receptor sites in concentration dependent manner.
- ✓ **Selective and effective** localization of the pharmacologically-active moiety at pre-identified target in therapeutic concentration, While **restricting** its access to non-target normal cellular linings, Thus minimizing toxic effects and maximizing the therapeutic index.

❑ APPROACHES

- The basic approaches for targeting the drug to specific site based on different research outcomes may be categorized broadly in to followings,

I. Controlling the distribution of drug by incorporating it in a carrier system

II. Altering the structure of the drug at molecular level

III. Controlling the input of the drug into bioenvironment to ensure a programmed and desirable biodistribution

❑ ADVANTAGES

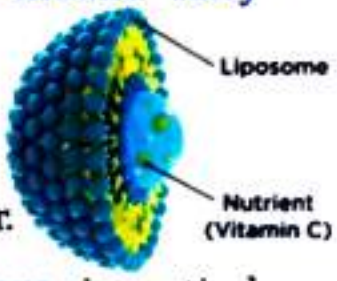
- Drug administration protocols may be simplified.
- Toxicity is reduced by delivering a drug to its target site, thereby reducing harmful systemic effects.
- Drug can be administered in a smaller dose to produce the desire effect.
- Avoidance of hepatic first pass metabolism.
- Enhancement of the absorption of target molecules such as peptides and particulates.
- Dose is less compared to conventional drug delivery system.
- No peak and valley plasma concentration.
- Selective targeting to infections cells that compare to normal cells.

❑ DISADVANTAGES

- Rapid clearance of targeted systems.
- Immune reactions against intravenous administered carrier systems.
- Insufficient localization of targeted systems into tumour cells.
- Diffusion and redistribution of released drugs.
- Requires highly sophisticated technology for the formulation.
- Requires skill for manufacturing storage, administration.
- Drug deposition at the target site may produce toxicity symptoms.
- Difficult to maintain stability of dosage form. E.g.: Resealed erythrocytes have to be stored at 4°C.

❑ LIPOSOMES

- Liposome is derived from the Greek word, where **lipo means "fatty"** constitution and **soma means "structure"**.



- Liposome are relatively **small in size** and it ranges from **50 nm to several micrometres** in diameter.
- These are **spherical vesicle** in which **aqueous core** is entirely **enclosed** by one or more **phospholipid bilayers.**
- It having the unique ability to **entrap both lipophilic and hydrophilic compounds.**
- The hydrophobic or lipophilic molecules are inserted into the bilayer membrane,
- Whereas hydrophilic molecules can be entrapped in the aqueous centre.

Liposome
(hydrophobic load)

Liposome
(hydrophilic load)

❖ Advantages:

- ✓ Suitable for delivery of hydrophobic (e.g. amphotericin B) hydrophilic (e.g. cytrabine) and amphipathic agents.
- ✓ Liposome increases efficacy and therapeutic index of drug (actinomycin-D)
- ✓ Liposome increase stability via encapsulation
- ✓ Suitable for targeted drug delivery
- ✓ Suitable to give localized action in particular tissue
- ✓ Suitable to administer via various routes
- ✓ Liposomes help to reduce the exposure of sensitive tissue to toxic drug.

❖ Disadvantages:

- ✓ Once administrated, liposome cannot be removed.
- ✓ Possibility of dumping, due to faulty administration.
- ✓ Leakage of encapsulated drug during storage.
- ✓ Low solubility
- ✓ Production cost is high.

❖ Applications:

➢ **Cancer chemotherapy:**

- ✓ Liposome are successfully used to entrap anticancer drugs.
- ✓ This increases circulation life time, protect from metabolic degradation.

➢ **Liposome as carrier of drug in oral treatment:**

- ✓ Steroids used for arthritis can be incorporated into large MLVs.
- ✓ Alteration in blood glucose levels in diabetic animals was obtained by oral administration of liposome encapsulated insulin.

➢ **Liposome for topical application:**

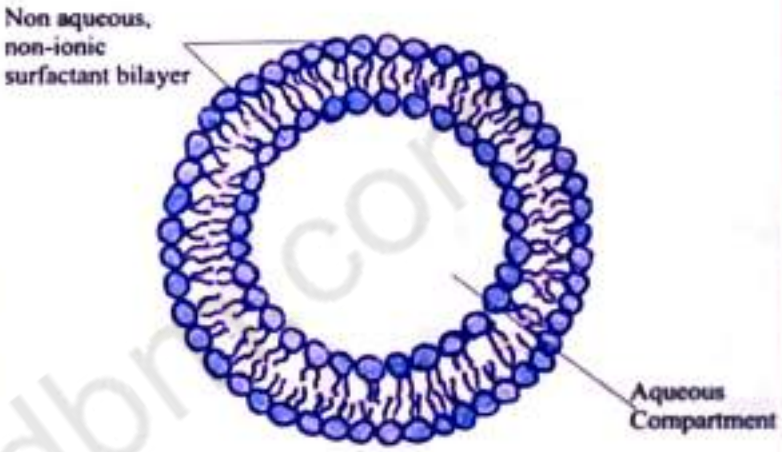
- ✓ Drug like triamcinolone, methotrexate, benzocaine, corticosteroids etc. Can be successfully incorporated as topical liposome.

➢ **Liposome for pulmonary delivery:**

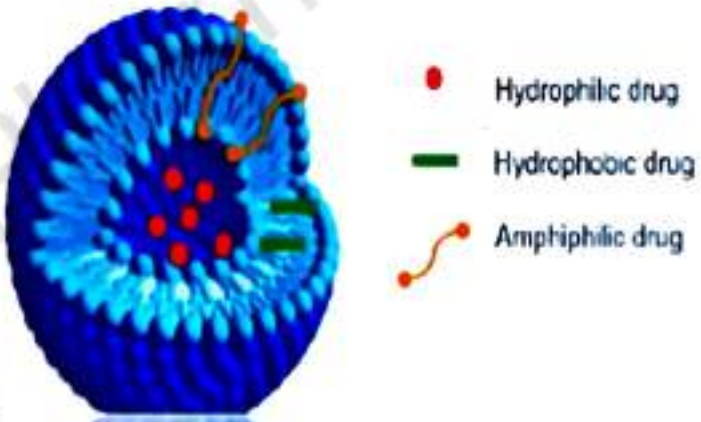
✓ Inhalation devises like nebulizers are used to produce an aerosol of droplets containing liposome.

❑ NIOSOMES

- Niosomes are one of the novel drug delivery system of **encapsulating the medicament in a vesicular system.**
- The vesicle composed of a **bilayer of non-ionic surfactants** and hence the name niosomes.
- The niosomes are very small, and **microscopic in size** (in nanometric scale).
- Although being **structurally similar to liposomes**, they have several advantages over them.



Structure of Niosome



❖ Advantages:

✓ The vesicles may act as a depot, releasing the drug in a controlled manner,

✓ They are osmotically active and stable,

✓ They improve the therapeutic performance of the drug molecules by delayed clearance from the circulation,

✓ Protecting the drug from biological environment,

- ✓ They improve oral bioavailability of poorly absorbed drugs.
- ✓ Niosomal dispersion in an aqueous phase can be emulsified in a non-aqueous phase to regulate the delivery rate of drug and administer normal vesicle in external non-aqueous phase.

❖ Disadvantages

- ✓ Physical instability of the noisome vesicles is major disadvantage of the noisome drug delivery system.

  Aggregation: Aggregation of the noisome vesicles can be another disadvantage to be considered.

  Fusion: Fusion of the niosomal vesicles to form loose aggregates
- ✓ Leaking of entrapped drug: affect the intended properties of the niosomes.
- ✓ Hydrolysis of encapsulated drugs which limiting the shelf life of the dispersion.

❖ Applications

➢ Anti-neoplastic Treatment:

- ✓ Niosomes can alter the metabolism, prolong circulation and half-life of the drug, thus decreasing the side effects of the drugs.

➢ Use in Studying Immune Response:

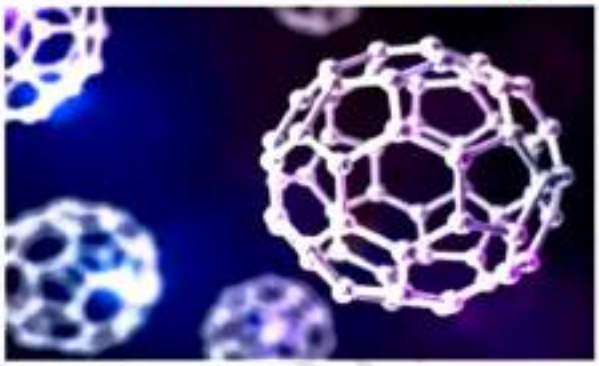
- ✓ Due to their immunological selectivity, low toxicity and greater stability.

➢ Niosomes as Carriers for Haemoglobin:

- ✓ The niosomal vesicle is permeable to oxygen and hence can act as a carrier for haemoglobin in anaemic patients.

❑ NANOPARTICLES

- A site specific drug delivery system consisting of **poly metacryclic nanoparticles.**
- The main goal in designing nanoparticles as a delivery system is to **control size of particle, surface characteristics and discharge of pharmacologically active agents.**



- In order to achieve the site-specific action of the drug at the therapeutically **optimal rate and dose regimen.**

❖ Advantages:

- ✓ Increases the stability of any volatile pharmaceutical agents.
- ✓ They offer a significant improvement over traditional oral and intravenous methods of administration in terms of efficiency and effectiveness.
- ✓ Delivers a higher concentration of pharmaceutical agent.
- ✓ The choice of polymer and the ability to modify drug release from polymeric nanoparticles have made them ideal candidates for cancer therapy, delivery of vaccines, contraceptives and delivery of targeted antibiotics.

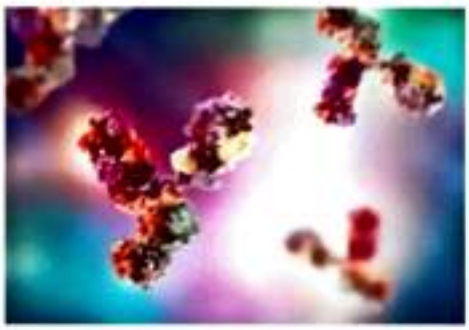
❖ Disadvantages:

- ✓ Small size & large surface area can lead to particle aggregation.
- ✓ Physical handling of nano particles is difficult in liquid and dry forms.
- ✓ Limited drug loading.
- ✓ Toxic metabolites may form. Etc.

❖ Application

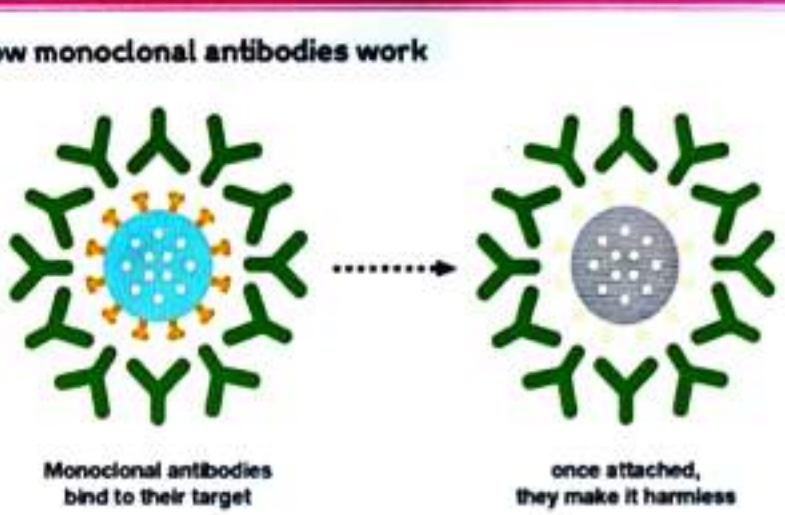
- **Internalization:** Internalization within mammalian cells can be achieved by surface functionalized carbon nanotubes
- **Vaccine delivery:** Conjugation with peptides may be used as vaccine delivery structures.
- **Gene delivery:** carbon nanotubes has been modelled in such a way so that they can be conveniently utilized as small molecule transporters in transporting DNA, indicating potential use as a gene delivery tool.
- **Transport of peptides,** nucleic acids and other drug molecules Incorporation of carboxylic or ammonium groups to carbon nanotubes enhances their solubility.
- **Cancer therapy:** This technology is being evaluated for cancer therapy..
- **Diagnostic purposes:** In whole blood immunoassays e.g. coupling of gold nanoshells to antibodies to detect immunoglobulins in plasma and whole blood. etc.

❑ MONOCLONAL ANTIBODIES



- An antibody is a protein used by immune system to identify and neutralize foreign objects like bacteria and viruses.
- Each antibody recognizes a specific antigen unique to its target.
- The **high specificity of antibodies** makes them an excellent tool for detecting and quantifying a broad array of targets, from drugs to serum proteins to microorganisms.
- With in-vitro assays, antibodies can be used to precipitate soluble antigens, agglutinate (clump) cells, opsonize.

- Kill bacteria with the assistance of **complement, and neutralize drugs, toxins, and viruses.**



❖ Advantages

- ✓ Though expensive, monoclonal antibodies are cheaper to develop than conventional drugs because it is based on tested technology.
- ✓ Side effects can be treated and reduced by using mice-human hybrid cells or by using fractions of antibodies.
- ✓ They bind to specific diseased or damaged cells needing treatment.
- ✓ They treat a wide range of conditions.

❖ Disadvantages

- ✓ Time consuming project - anywhere between 6 -9 months.
- ✓ Very expensive and needs considerable effort to produce them.
- ✓ Small peptide and fragment antigens may not be good antigens- monoclonal antibody may not recognize the original antigen.
- ✓ Hybridoma culture may be subject to contamination.
- ✓ System is only well developed for limited animal and not for other animals.
- ✓ More than 99% of the cells do not survive during the fusion process reducing the range of useful antibodies that can be produced against an antigen
- ✓ It is possibility of generating immunogenicity.

❖ Application

➢ Diagnostic Applications:

- Monoclonal antibodies have revolutionized the laboratory diagnosis of various diseases.
- For this purpose, MAbs may be employed as diagnostic reagents for biochemical analysis or as tools for diagnostic imaging of diseases.

(A) MAbs in Biochemical Analysis:

- ✓ Diagnostic tests based on the use of MAbs as reagents are routinely used in radioimmunoassay (RIA) and enzyme-linked immunosorbent assays (ELISA) in the laboratory.
- ✓ These assays measure the circulating concentrations of hormones (insulin, human chorionic gonadotropin, growth hormone, progesterone, thyroxine, triiodothyronine, thyroid stimulating hormone, gastrin, renin), and several other tissue

(B) MAbs in Diagnostic Imaging:

- ✓ Radiolabeled—MAbs are used in the diagnostic imaging of diseases, and this technique is referred to as immunoscintigraphy.
- ✓ The radioisotopes commonly used for labelling MAb are iodine—131 and technetium—99.

2. Therapeutic Applications:

(A) Cardiovascular diseases:

- **Myocardial infarction:**
  - ✓ The cardiac protein myosin gets exposed wherever myocardial necrosis (death of cardiac cells) occurs. Antimyosin MAb labelled with radioisotope indium chloride (111 In) is used for detecting myosin and thus the site of myocardial infarction.

- ✓ Imaging of radiolabeled MAb, is usually done after 24-48 hours of intravenous administration.

- **Deep vein thrombosis (DVT):**
  - ✓ DVT refers to the formation of blood clots (thrombus) within the blood veins, primarily in the lower extremities.
  - ✓ For the detection of DVT, radioisotope labelled MAb directed against fibrin or platelets can be used.
  - ✓ The imaging is usually done after 4 hours of injection. Fibrin specific MAbs are successfully used for the detection of clots in thigh, pelvis, calf and knee regions.