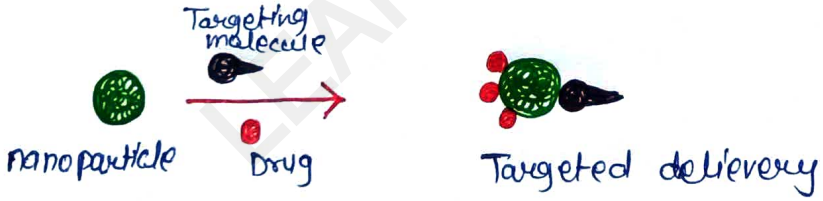
UNIT-4 TARGETED DRUG DELIEVERY SYSTEM (TDDS)

Introduction

- Targeted Drug Delievery System is a special form of drug delievery System where the medicaments is selectively targeted or delievered only to its site of action or absorption and not to the non-target organs or tissues or cells.
- It is a method of delievering medication to a patient in a manner that increases the conc^{n} of the medication in some parts of the body relative to others.
- Targeted drug delievery seeks to concentrate the medication in the tissues of interest while reducing the relative conc^{n} of the medication in the remaining tissues.
- This improves efficacy and reduce side effects.



Reasons for drug Targeting

- Drug instability
- Low absorption
- Short half-life
- Large volume of distribution
- Low specificity
- Low Therapeutic Index.

Approaches

⇒ Controlling the distribution of drug by incorporating it in a carrier system.
⇒ Altering the structure of the drug at molecular level.
⇒ Controlling the Input of the drug into bio-environment to ensure a programmed and desirable biodistribution.

Properties

→ Non-toxic, biocompatible and physicochemical stable in vivo and invitro.
→ Restrict drug distribution to target cells or tissue or organ or should have uniform capillary distribution.
→ Controllable and pridictable rate of drug release.
→ minimal drug leakage during transit.
→ Carrier used must be biodegradable or readily eliminated from the body without any problem.
→ It's preperation should be easy or reasonably simple, reproductive and cost effective.

Components of Targeted Drug delievery

① **Target** → Target means specific organ or a cell or group of cells, which in chronic or acute condition need treatment.

② **Carrier or marker** →

- Carrier is one of the special molecule or system essentially required for effective transportation of loaded drug upto the pre selected sites.
- They are engineered vectors, which retain drug inside or onto them either via encapsulation and/or via spacer moeity and transport or delievery it into vicinity of target cell.

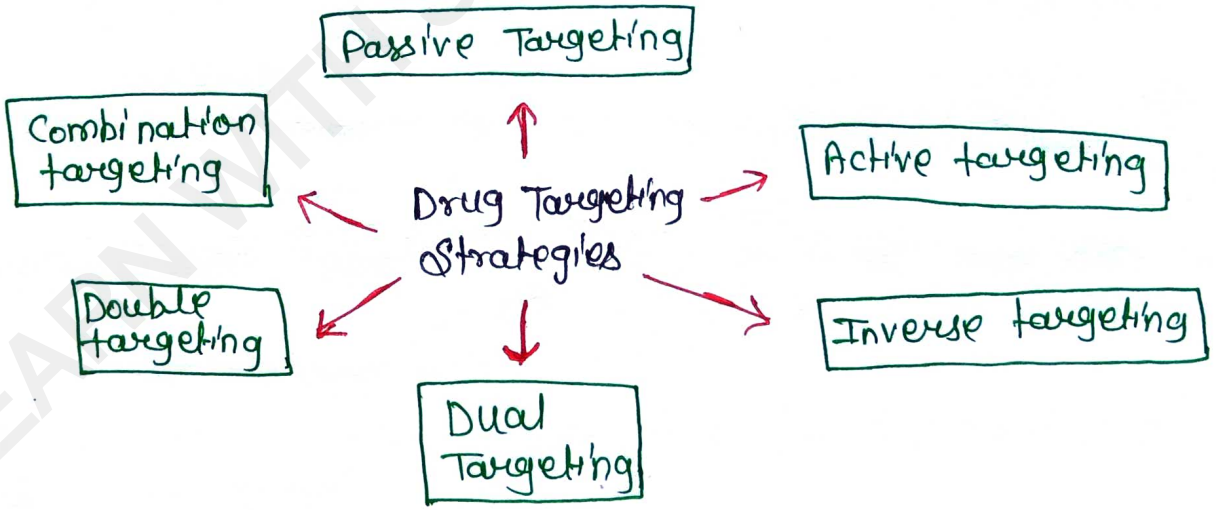
③ Drug

Properties influencing Drug Targeting

Drug →
- Conc^n, Particulate location and distribution.
- molecular weight, physiochemical properties Drug Carrier interaction.

Carrier →
- Type, amount of Excipients, surface characteristics, size.
- Density.

In vivo environment →
- pH, polarity, ionic strength, surface tension, viscosity
- Temp., Enzyme, Electric field.



① Passive targeting

- it utilizes the natural course of biodistribution of the carrier.
- The colloids which are taken up by the Reticulo-endothelial System (RES) can be ideal vectors for passive targeting of drugs to RES predominant compartments.
- Passive capture of colloidal carriers by macrophages offers therapeutic opportunities for the delievery of anti-infective agents.

② Inverse targeting

- It is a result of the avoidance of passive uptake of colloidal carriers by the RES.
- It can be achieved by repressing the role of RES by pre-function of a large amount of blank colloidal carriers or macromolecules like dextran sulphate.
- other strategies like modification and defined manipulation of the size surface change, composition, surface rigidity and hydrophilicity characteristics for desirable biofate.

③ Active Targeting

- It involves the modification or frictionalization of the drug carriers so that the contents are delievered exclusively to the site corresponding

to which the carrier is targeted.

- Active targeting can be affected at diff. levels -
  - (a) First order targeting (organ compartmentalization)
  - (b) Second order targeting (cellular targeting)
  - (c) Third order targeting (intercellular organelles targeting)

(4) Dual Targeting

- In this targeting, carrier molecules itself has its own therapeutic activity thus enhancing the therapeutic action of the drug.

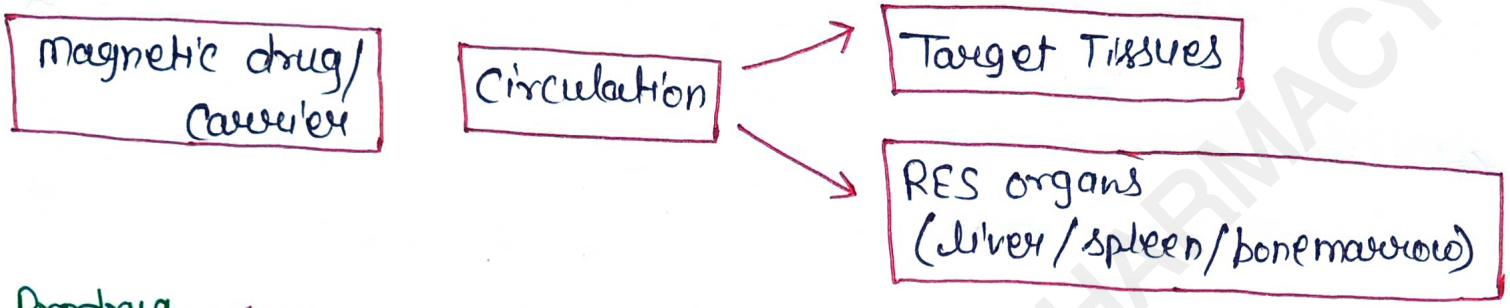
(5) Combination Targeting

- This system includes carriers, polymers homing device of molecular specificity with the drug to direct towards the specific target site.

Other approaches

- magnetically modulating drug targeting.
- prodrug.
- monoclonal antibody based drug targeting.

- Magnetically Modulating Drug Targeting



- Prodrug ✓
- monoclonal antibodies. ✓

Advantages of TDDS

- The duration of extension of action. ✓
- Improved drug bioavailability.
- Reduction of drug degradation/loss. ✓
- Reduce adverse effects. ✓
- Reduce dosing frequency. ✓
- Minimize drug conc^{n} fluctuations in plasma level. ✓
- Improved drug utilization and patient compliance.
- Improved stability. ✓

Disadvantages of TDDS

- Possible toxic agents and degraded products.
- Patients discomfort with device usage.
- High cost of final product.
- Requires skill for manufacturing storage, administration.
- Rapid clearance of targeted systems.

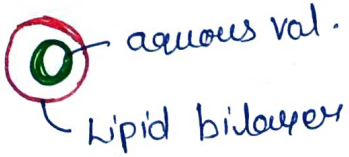
LIPOSOMES

Imp

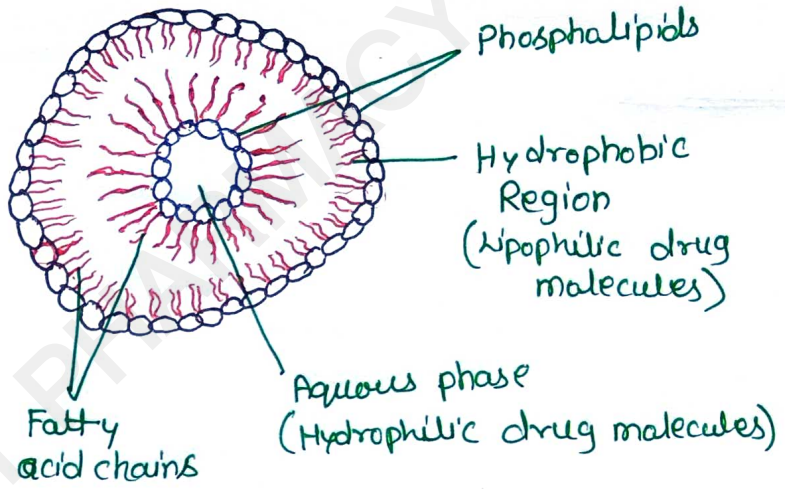
→ Carrier

Intro

- Concentric (circular) bilayered (double layer) vesicles. → Container like.
- In which an aqueous volume is entirely enclosed by a membranous lipid bilayer.
- Lipid bilayer is mainly composed of natural / synthetic phospholipids.



Structure



Composition of Liposomes

Liposomes has been composed of 2 components :-

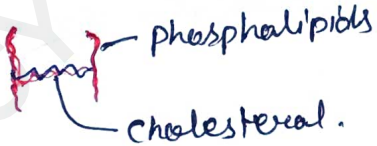
1. Phosphalipids
2. Cholesteral.

① Phosphalipids

- Phospholipids are amphiphatic in nature. (having affinity for both aqueous and polar moieties).
- Phosphalipids molecules has hydrophobic tail and hydrophilic polar head.
- The hydrophobic tail is composed of 2 fatty acid chains containing 10-24 Carbon atom & 0-6 double ~~bond~~ bonds in each chain.
- The hydrophobic tail and hydrophilic polar head is linked by a glyceral bridge.

② Cholesteral – Stable the structure.

- It is useful in stabilizing the membrane.
- It can interdigitized in the phospholipids
- cholesteral enhances the rigidity of the phospholipids bilayer.
- It can reduces the permeability of water soluble substance.



Mechanism of Liposomes formation

- In aqueous medium, polar portion of the molecule remains in contact with the polar environment at the same time shields the polar part.
- In aqueous media phospholipids are not soluble, they align themselves closely in planar bilayer sheets or lipid cakes which is thermodynamically stable.
- In which polar head groups face outwards into the aqueous medium, and the lipid chains turns inwards to avoid the water phase giving rise to double layer or bilayer.
- Liposomes are formed when thin lipid films or lipid cakes

are hydrated and stacks of liquid crystalline bilayer become fluid and swell.

- The hydrated lipid sheets detach during agitation and self close to form large, multicellular vesicles.
- These vesicles are called liposomes.

Classification of liposomes

① Based on structural parameters :-

- MLV - Multilamellar large vesicles.
- OLV - Oligolamellar vesicles.
- UV - Unilamellar vesicles.
- SUV - Small Unilamellar vesicles.
- MUV - Medium Unilamellar vesicles
- LUV - Large Unilamellar vesicles.
- GUV - Giant Unilamellar vesicles.
- MV - Multi Vesicular vesicles.

② Based on Liposomes method of preperation

- REV - Prepared By Reverse phase Evaporation method.
- MLV-REV - " " " " "
- SPLV - Stable Plurilamellar vesicles.
- FATMLV - Frozen and Thawed MLV.
- VET - Prepared by Extrusion Technique.
- DRV - " " Dehydration - Rehydration method.

③ Based Upon Composition and Application

- Conventional Liposomes - Neutral and Negatively charged phospholipids & cholesterol
- Fusogenic Liposomes - Reconstituted Sendai virus Envelopes
- ph sensitive Liposomes - Liposomes are sensitive to pH.
- Cationic Liposomes - Cationic Lipids with DOPE.
- Long Circulatory Liposomes - Neutral High Transition Temperature.
- Immuno - Liposomes - Attached with monoclonal Antibodies.

Methods of Liposome preperation.

Passive loading Techniques

Mechanical Dispersion

- Lipid film hydration
  - Hand shaking
  - Non-Hand Shaking
  - Freeze drying.
- Microemulsification
- Sonification.
- French pressure cell.
- membrane extrusion
- Dried reconstituted vesicles
- Freeze-thawed liposomes.

Solvent dispersion

- Ethanol injection
- Ether injection
- Double emulsion vesicles.
- Reverse phase evaporation vesicles
- Stable plurilamellar vesicles.

Active loading Techniques

Detergent Removal

- Detergent removal from mixed micelles by ↓
  - Dilution
  - column chromato.
  - Rec. Sandai vesicles.

① Mechanical Dispersion methods

- Lipid is solubilized in organic solvent, drug to be entrapped in solubilized in aqueous solvent, the lipid phase is hydrated at high speed stirring.
- Due to affinity of aqueous phase to polar head, it is entrapped in lipid vesicles.

ex → Lipid film hydration, micro-emulsification, sonification, Dried reconstituted vesicles.

② Solvent dispersion methods

- In this method, lipids are first dissolved in organic solvent, which is then brought into contact with aqueous phase containing material which is to be entrapped in liposome under rapid dilution at rapid evaporation of organic solvent.

ex → Ethanol injection, Ether injection, De-emulsification.

③ Detergent removal method

- In this method, phospholipids are brought into intimate contact with the aqueous phase via detergent which associate with phospholipids molecule and serve to screen the hydrophobic portions of the molecules from water.

Advantages

- Provide selective passive Targeting to tumor tissues.
- ↑ efficacy and therapeutic index.
- ↑ stability.
- ↓ toxicity.
- Site avoidence effect.
- Improved pharmacokinetic effects.

Disadvantages

- production cost is high.
- Leakage and fusion of encapsulated drug.
- Short half-life.
- Low solubility.

Applications

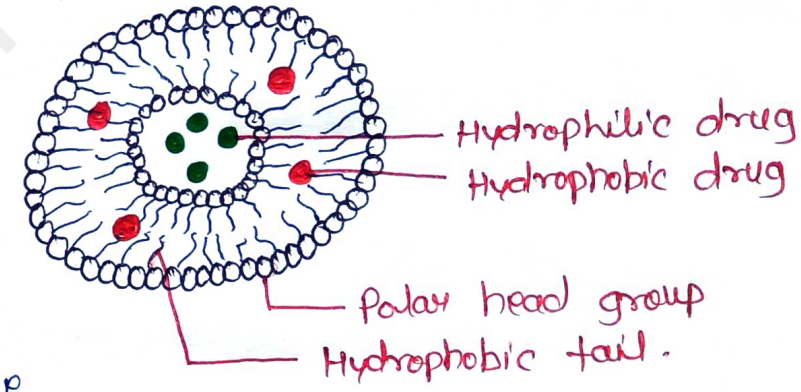
- Liposomes as drug or protein delievery vehicles.
- In tumor therapy.
- In gene therapy.
- In immunology.
- Liposomes are artificial blood surrogates.
- Liposomes in Cosmetics and dermatology.

NIOSOMES

Short note

Definition • Niosomes are non-ionic surfactant based multilamellar or unilamellar vesicles in which an aqueous solution of solute(s) is entirely enclosed by a membrane resulted from the organization of surfactant macromolecules as bilayers.

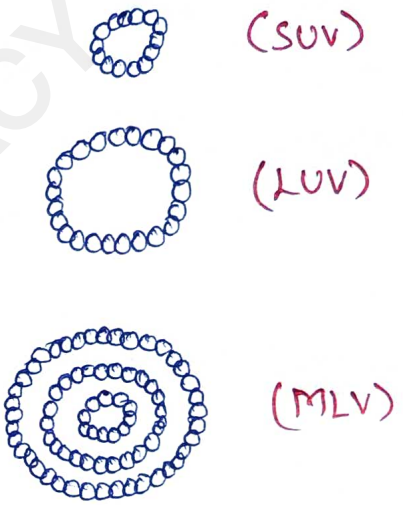
Characteristics



- Biocompatible, Biodegradable, non-toxic, non immunogenic and non-carcinogenic.
- The ability of non-ionic surfactant to form bilayer vesicles is dependent on the HLB value of the surfactant, the chemical structure of the components and the critical packing parameter.
- Niosomes can be characterized by their size distribution studies.
- High resistance to hydrolytic degradation.
- The properties of niosome depends both on composition of the bilayer and on method of their production.

Types of Niosomes ⇒

① Small unilamellar vesicles (10-100 nm) → (SUV)
② Large unilamellar vesicles (100-3000 nm) → (LUV)
③ multi lamellar vesicles (>1 bilayer) → (MLV)



Structure of Niosomes

- Niosomes are microscopic lamellar structures.
- Basic structural components are -
  - Non ionic surfactant.
  - Cholesterol.
  - Charge inducing molecule.
- A number of non-ionic surfactants used are :- Polyglyceral alkyl ether, glucosyl dialkyl etheres, crown etheres, ester linked surfactants, polyaxyethylene alkyl ether and a series of spans and tweens.

Characterization of Niosomes →
- Physical characterization ✓
- Chemical characterization ✓
- Biological characterization ✓

① Physical characterization

Parameters	Analytical methods/instruments
- Vesicles shape and surface morphology	Transmission electron microscopy, Freeze-fracture electron microscopy.
- mean vesicle size and size distribution.	Dynamic light scattering, zetasizer, Photocorrelation spectroscopy, laser light scattering, gel permeation and gel exclusion.
- Surface charge	Free flow electrophoresis.

② Chemical characterization

- Cholesterol conc^{n}.	cholesterol oxidase assay and HPLC.
- Cholesterol auto-oxidation	HPLC and TLC
- osmolarity	osmometer.

③ Biological characterization

- Sterility	Aerobic or anaerobic cultures.
- Pyrogenicity	Limulus Amebocyte Lysate (LAL) Test.
- Animal toxicity	monitoring survival rates, histology and pathology.

Applications of Niosomes

1. Gene delievery
2. Drug Targeting
3. Antineoplastic treatment
4. Delievery of peptide drugs.
5. Studying immune response
6. Transdermal Drug Delievery System.
7. Cosmetics.

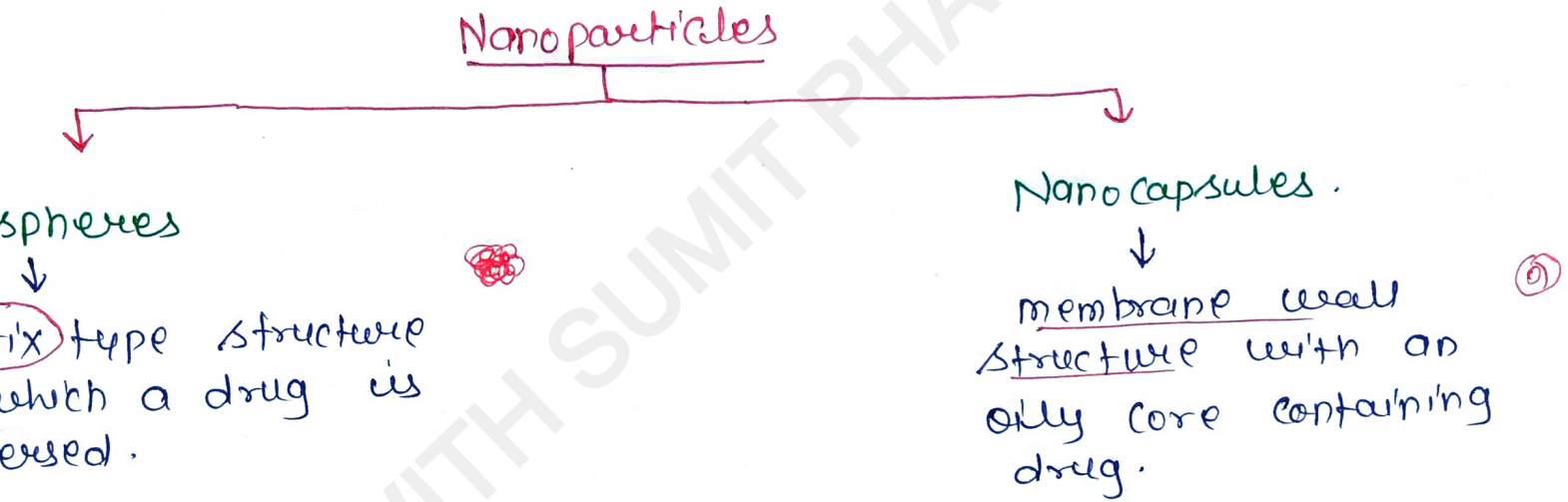
Nanoparticles

Short note

- Nanoparticles are particles b/w 1 nm and 100 nm in size with a surrounding interfacial layer.
- Interfacial layer is an integral part of nanoscale matter, fundamentally affecting all of its properties.
- The Interfacial layer typically consists of ions, inorganic and organic molecules.
- Organic molecules coating inorganic nanoparticles are known as stabilizers, capping and surface ligands, or passivating agents.
- In Nanotechnology, a particle is defined as a small object that behaves as a whole unit with respect to its transport and properties.

Nanocapsules :- In which the drug is confined to an aqueous or oily core surrounded by a shell-like wall.

Alternatively, the drug can be covalently attached to the surface or into the matrix.



Methods used for nanoparticle preperation

1. Emulsion polymerization
2. Dispersion polymerization
3. Interfacial polymerization
4. Interfacial complexation.

Applications

1. In Cosmetics
2. Tumar targeting delievery System
3. Vaccines
4. molecular diagnostic
5. Drug discovery
6. Implantable drug delievery system.
7. oral delievery of peptide/proteins.
8. For gene delievery.
9. As brain targeting.
10. Bio-sensors and bio-labels.

Monoclonal Antibodies

short note

- An Antibody is a protein used by the immune system to identify and neutrilize foreign objects like bacteria and viruses. Each antibody recognises a specific antigen unique to its target.
- Monoclonal Antibodies (mAb or moAb) are antibodies that are made by identical immune cells that are all clones of a unique parent cell.

- Polyclonal antibodies are antibodies that are derived from diff. cell lines. They differ in amino acid sequence.

Monoclonal Antibodies are made of :-

- mAb are man made proteins that act like human antibodies in the immune system.
- There are 4 diff. way they can be made and are named based on what they are made of.
  - Murine They are made from mouse proteins and the names of the treatments end in -omab.
  - Chimeric These proteins are combination of part mouse and part human and the names of the treatments end in -ximab.
  - Humanized These are made from small parts of mouse proteins attached to human proteins and the names of the treatments end in -zumab.
  - Human These are fully human proteins and the names of treatments end in -umab.

Production

① Immunization of mice and selection of mouse donors for generation of Hybridoma cells.

② Screening of mice for antibody production.

③ Fusion of myeloma cells with immune spleen cells.

④ Selection of hybridoma cells.

⑤ Checking for hybridoma cells.

⑥ Clone of ~~Hyp~~ Hybridoma cell lines.

Application

① In Diagnosis

- Cardiovascular diseases
- Deep vein thrombosis
- Immuno suppressive therapy
- Pregnancy testing kits.

② Therapeutic

- Radioisotope @ immunoconjugates. - In cancer
- Toxin and drug immunoconjugates
- Immunoliposome based kits