Shree H. N. Shukla Institute of Pharmaceutical Education and Research, Rajkot

B. Pharm
Semester-VII

Subject Name: Novel Drug Delivery System
Subject Code: BP704TT

CHAPTER-4-TARGETED DRUG DELIVERY SYSTEM

SYLLABUS:

Targeted drug delivery system:

Concepts and approaches advantages and disadvantages, introduction to liposomes, niosomes, nanoparticles, monoclonal antibodies and their Applications

This subject is designed to impart basic knowledge on the area of novel drug delivery systems.

Learning objectives

Upon completion of the course the student shall be able to

1. To understand various approaches for development of novel drug delivery systems.
2. To understand the criteria for selection of drugs and polymers for the development of Novel drug delivery systems, their formulation and evaluation.

Targeted Drug Delivery System

What is Targeted Drug Delivery System (TDDS)

- 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 preidentified target(s) in therapeutic concentration, while restricting its access to non-target(s) normal cellular linings, thus minimizing toxic effects and maximizing the therapeutic index.
- 'Targeted drug delivery system is a special form of drug delivery system where the medicament is selectively targeted or delivered only to its site of action or absorption and not to the non-target organs or tissues or cells.'
- It is a method of delivering medication to a patient in a manner that increases the concentration of the medication in some parts of the body relative to others.
- Targeted drug delivery seeks to concentrate the medication in the tissues of interest while reducing the relative concentration of the medication in the remaining tissues.
- This improves efficacy and reduce side effects.

THE DRUG MAY BE DELIVERED:

- To the capillary bed of the active sites.
- To the specific type of cell (or) even an intracellular region. Ex: Tumour cells but not to normal cells.
- To a specific organ (or) tissues by complexion with the carrier, that recognizes the target.

OBJECTIVE:

- To achieve a desired pharmacological response at a selected sites without undesirable interaction at other sites, there by the drug have a specific action with minimum side effects & better therapeutic index.

- Ex- In cancer chemotherapy and enzyme replacement therapy.

REASON FOR DRUG TARGETING:

- In the treatment or prevention or diseases.
- Pharmaceutical drug instability in conventional dosage form solubility, biopharmaceutical low absorption, high- membrane bounding, biological instability, pharmacokinetic / pharmacodynamic short half-life, large volume of distribution, low specificity, clinical, low therapeutic index.

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 4^0 C.
- Drug loading is usually law. E.g. As in micelles. Therefore, it is difficult to predict /fix the dosage regimen.

- **One Word Question Answer**

SR NO.	QUESTION	ANSWER
1	What is a special form of drug delivery system where the medicament is selectively targeted or delivered only to its site of action or absorption and not to the non-target organs or tissues or cells is called?	Targeted Drug Delivery System
2	Which drug delivery system improves efficacy and reduce side effects?	Targeted Drug Delivery System
3	How the drug is delivered?	To a specific organ (or) tissues by complexion with the carrier, that recognizes the target
4	Which drug delivery enhances of the absorption of target molecules such as peptides and particulates	Targeted Drug Delivery System
5	The key disadvantage of TDDS?	Low drug loading
6	How much dose of TDDS as required to Conventional system?	Low Dose

CARRIER OR MARKERS:

- Targeted drug delivery can be achieved by using carrier system.
- Carrier is one of the special molecules or system essentially required for effective transportation of loaded drug up to the pre selected sites.
- They are engineered vectors, which retain drug inside or onto them either via encapsulation and/ or via spacer moiety and transport or deliver it into vicinity of target cell.

PHARMACEUTICAL CARRIERS:

- Polymers
- Microcapsules
- Microparticles
- Lipoproteins
- Liposomes
- Micelles

REASONS FOR DRUG TARGETING

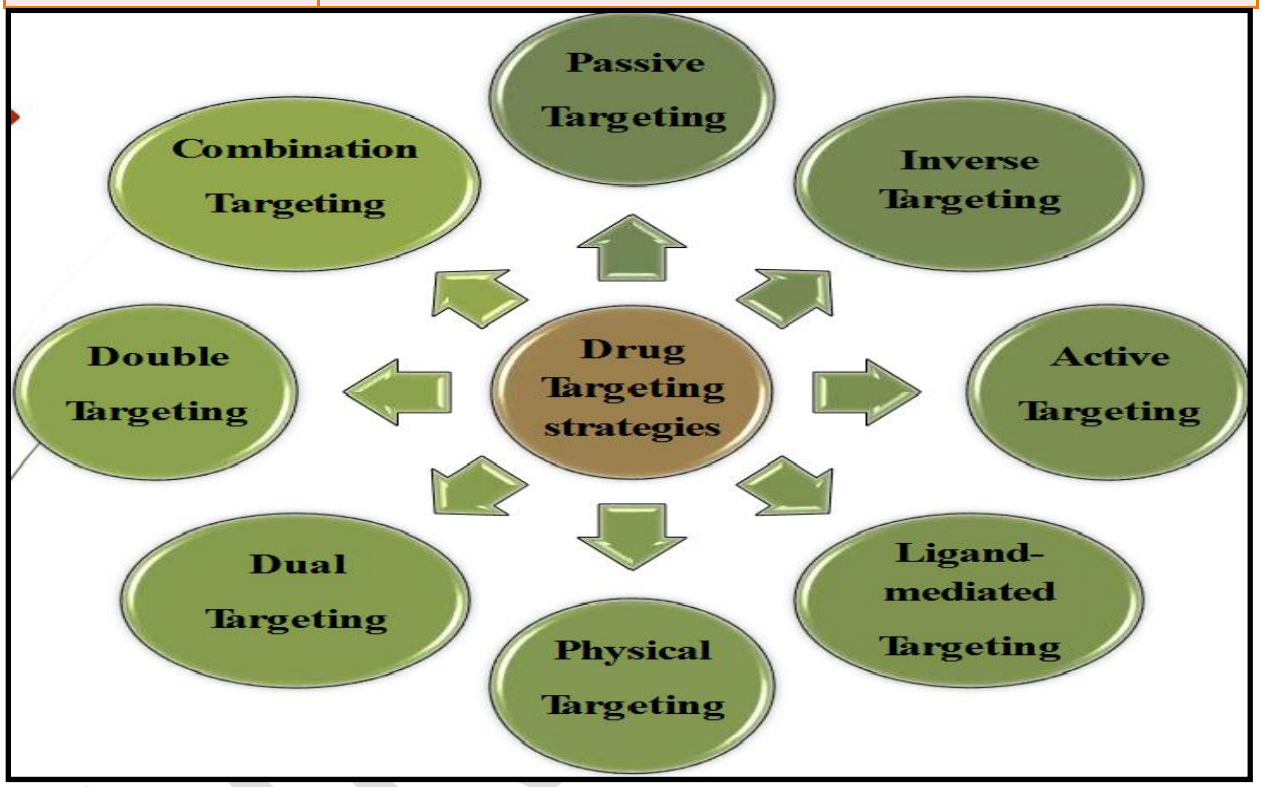
- Drug instability
- Low absorption Short half-life
- Large volume of distribution
- Low specificity
- Low therapeutic index
- Common Approaches of Targeted Drug Delivery
- Controlling the distribution of drug by incorporating it in a carrier system
- Altering the structure of the drug at molecular level
- Controlling the input of the drug into bio environment to ensure a programmed and desirable bio distribution

PROPERTIES OF IDEAL TARGETED DRUG DELIVERY

- Nontoxic, biocompatible and physicochemical stable *in-vivo* and *in-vitro*.
- Restrict drug distribution to target cells or tissue or organ or should have uniform capillary distribution.
- Controllable and predictable rate of drug release.
- Minimal drug leakage during transit.
- Carrier used must be biodegradable or readily eliminated from the body without any problem.
- Its preparation should be easy or reasonably simple, reproductive and cost effective.

Important Properties Influencing Drug Targeting

Drug	Concentration, 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, Temperature, Enzyme, Electric Field



PASSIVE DRUG 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 delivery of anti-infective agents.
- Inverse Targeting
- It is a result of the avoidance of passive uptake of colloidal carriers by the RES.
- It can be achieved by suppressing the function of RES by pre- junction of a large amount of blank colloidal carriers or macromolecules like dextran sulphate.

- **One Word Question Answer**

SR NO.	QUESTION	ANSWER
1	Targeted drug delivery can be achieved by using	Carrier system
2	Which is one of the special molecules or system essentially required for effective transportation of loaded drug up to the pre selected sites?	Carrier
3	What is properties of Nontoxic, biocompatible and physicochemical stable *in-vivo* and *in-vitro* ?	Targeted Drug Delivery System
4	Which system utilizes the natural course of bio distribution of the carrier?	Passive drug targeting
5	Passive system is one type of ?	Inverse Targeting
6	Ideal properties of targeting system is?	Controllable and predictable rate of drug release

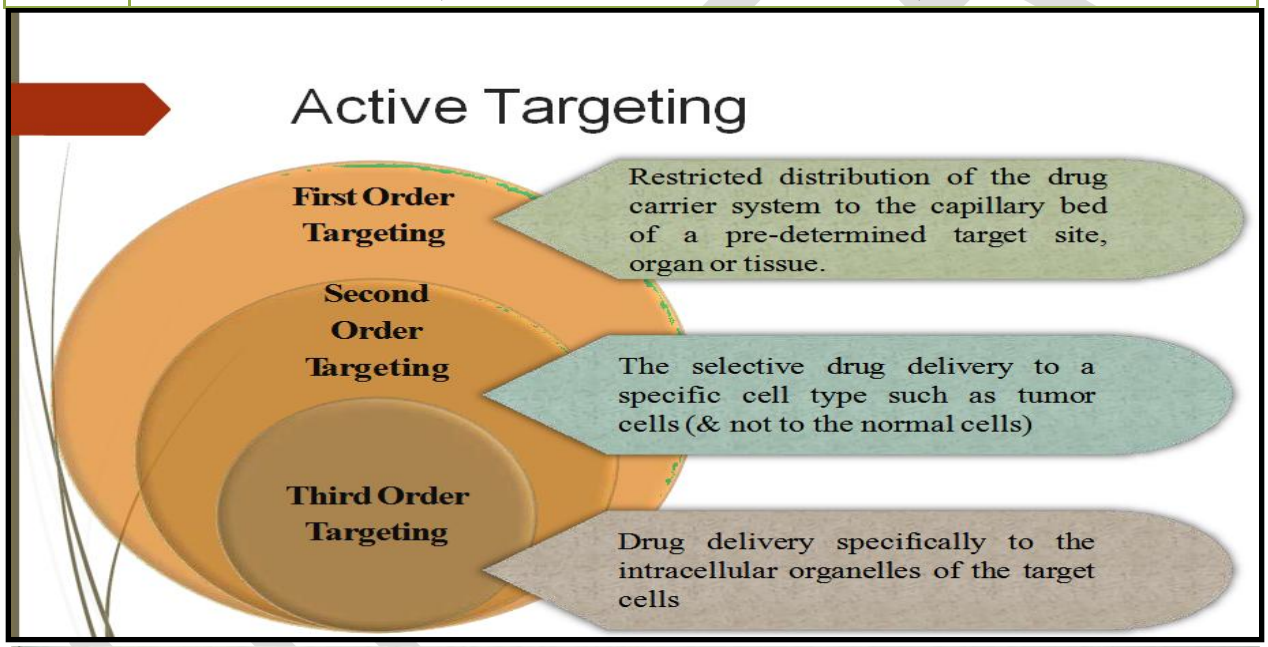
- Other strategies include modification and defined manipulation of the size, surface charge, composition, surface rigidity & hydrophilicity characteristics of carriers for desirable biofate.

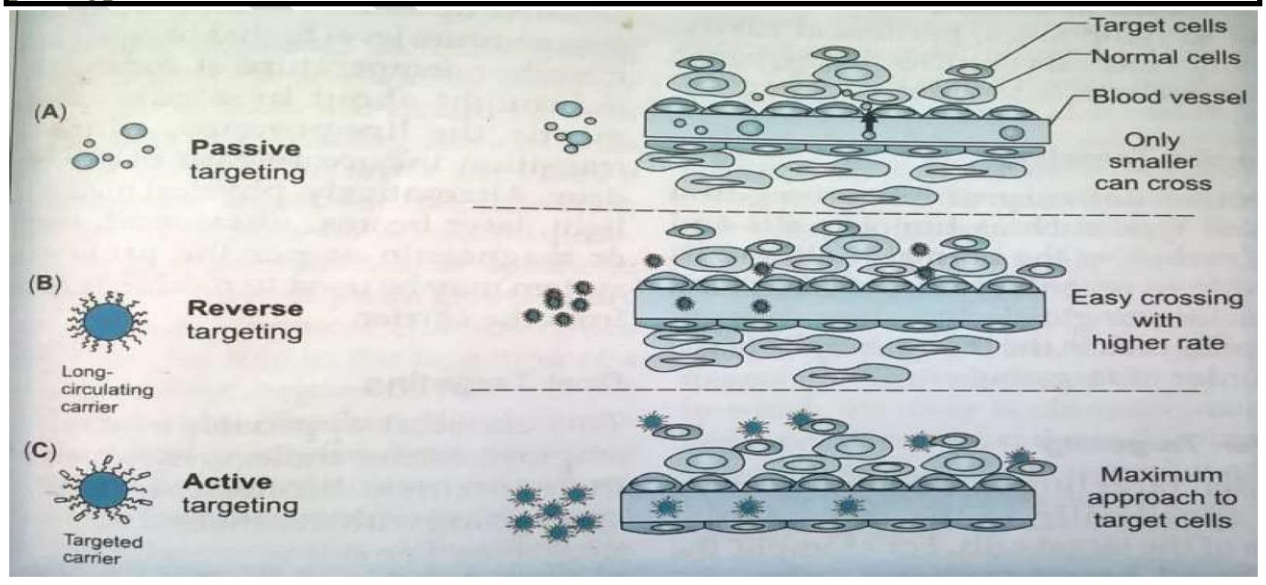
Active Targeting

- It involves the modification or fictionalization of the drug carriers so that the contents are delivered exclusively to the site corresponding to which the carrier is architected.

➨ Active targeting can be affected at different levels –

1.	First order targeting (organ compartmentalization)
2.	Second order targeting (cellular targeting)
3.	Third order targeting (intercellular organelles targeting)





STRATEGY OF DRUG TARGETING

Ligand mediating targeting

- Ligands are carrier surface group(s), which can selectively direct the carrier to the pre-specified site(s) housing the appropriate receptor units to serve as 'homimg device' to the carrier/drug.
- Most of the carrier systems are colloidal in nature & can be specifically functionalized using various biologically relevant molecular ligands including antibodies, polypeptides, oligosaccharides, viral proteins & fusogenic residues.
- The ligands confer recognition & specificity upon drug carrier & endow them with an ability to approach the respective target selectivity & deliver the drug.

Examples of Ligands

Ligands	Target	Tumor target
Folate	Folate receptor	Overexpression of folate receptor
Transferrin	Transferrin receptor	Overexpression of transferrin receptor
Galactosamine	Galactosamine receptors on hepatocytes	Hepatoma

PHYSICAL TARGETING

- Characteristics of environment changes like pH, temperature, light intensity, electric field, and ionic strength.
- This approach was found exceptional for tumor targeting as well as cytosolic delivery of entrapped drug or genetic material.

Physical Targeting	Formulation System	Mechanism for Drug Delivery
Heat	Liposome	Change in Permeability
Magnetic Modulation	Magnetically Responsive Microspheres Containing Iron oxide	Magnetic Field can retard fluid Flow of particles.
Ultrasound	Polymers	Change in Permeability
Electrical Pulse	Gels	Change in Permeability
Light	Photo responsive Hydro gels Containing Azo-Derivatives	Change in Diffusion Channels, Activated by Specific Wavelength

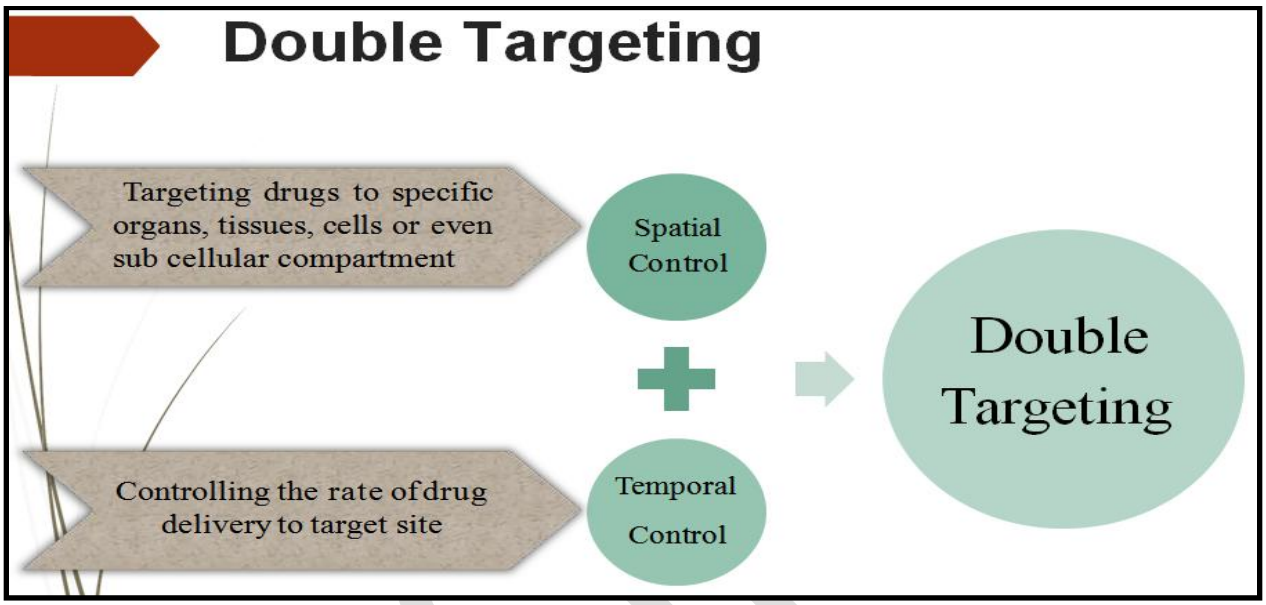
- **One Word Question Answer**

SR NO.	QUESTION	ANSWER
1	Which involves the modification or fictionalization of the drug carriers so that the contents are delivered exclusively to the site corresponding to which the carrier is architected?	Active targeting
2	First order targeting for?	Organ compartmentalization
3	Second order targeting for?	Cellular
4	Third order targeting for?	intercellular organelles
5	What are carrier surface group(s), which can selectively direct the carrier to the pre-specified site(s) housing the appropriate receptor units to serve as 'homimg device' to the carrier/drug.	Ligands
6	Most of the carrier systems are in which nature?	colloidal

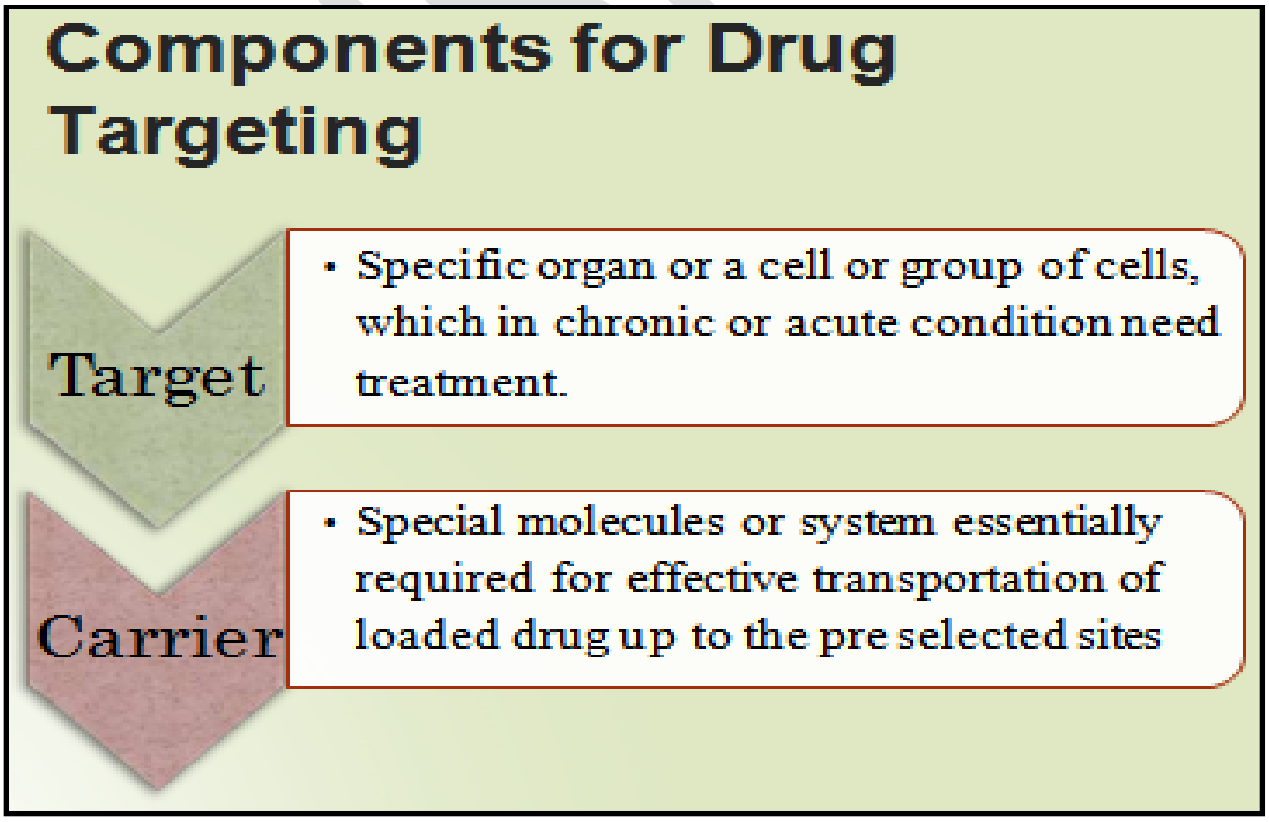
DUAL TARGETING

- In this targeting approach, carrier molecule, itself have their own therapeutic activity and thus increase the therapeutic effect of drug.
- A carrier molecule having its own antiviral activity can be loaded with antiviral drug and for the synergistic effect of drug conjugate.

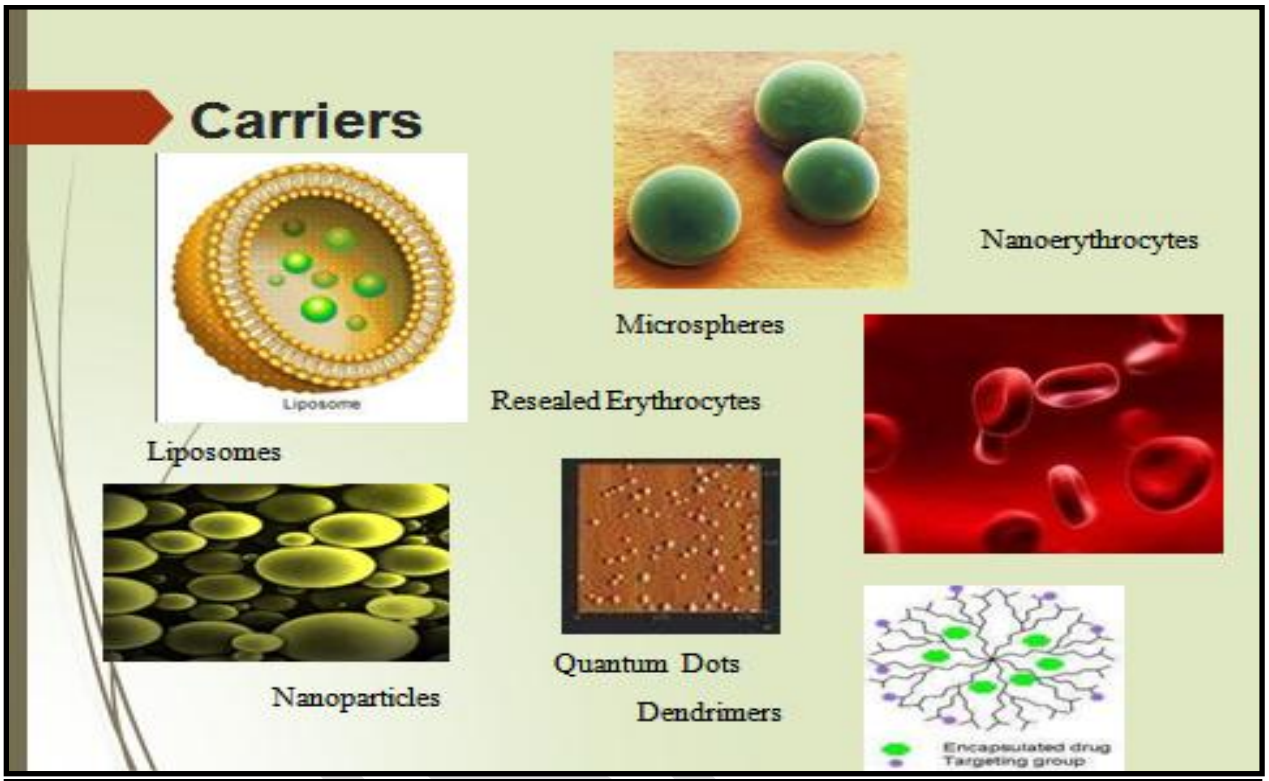
DOUBLE TARGETING



COMBINATION TARGETING



- These targeting systems are equipped with carriers, polymers and homing devices of molecular specificity that could provide a direct approach to target site.



Targeted Nanoparticles

Platform	Targeting ligand	Drug	Stage
PEGylated liposome	F(ab ¢) 2 fragment of human antibody GAH	Doxorubicin	Phase I
NGPE liposome	Transferrin	Oxaliplatin	Phase I/II
Liposome	Single-chain antibody fragment	p53 gene	Phase I
PEGylated PLGA NP	Peptide	Docetaxel	Phase I

- **One Word Question Answer**

SR NO.	QUESTION	ANSWER
1	In which targeting approach, carrier molecule, itself have their own therapeutic activity and thus increase the therapeutic effect of drug.	Dual targeting
2	Targeting drugs to specific organs, tissues, cells or even sub cellular compartment is called?	Double Targeting
3	Combination targeting is composed of?	Carrier, Polymers and home coming
4	What are the components of targeting delivery system?	Target and carrier
5	Niosome, Liposome are examples of?	Carrier

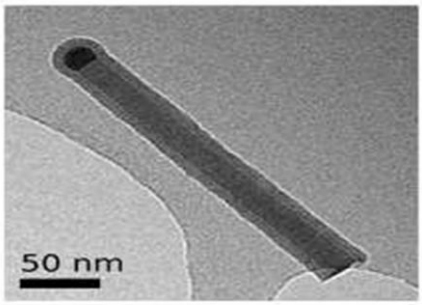
Applications of Resealed Erythrocytes

Diseases	Name of Drug(s)	Purpose
Liver tumors	Bleomycin, Adriamycin, Carboplatin, Gentamycin	Targeting to hepatic carcinoma
Parasitic diseases	Pentamidine loaded, IgG coated erythrocytes, Glutaraldehyde treated erythrocytes	Macrophage containing leshmania, liver targeting of primaquine phosphate, metronidazole

TYPES OF TARGETED DRUG DELIVERY SYSTEM

Nano Tubes :

- They are hollow cylinder made of carbon, atoms that can be filled and sealed for potential drug delivery.



Nanotube

Application:

- Cellular scale needle for attaching drug molecule to cancer cells.
- As an electrode in thermo cells.

Nano wires:

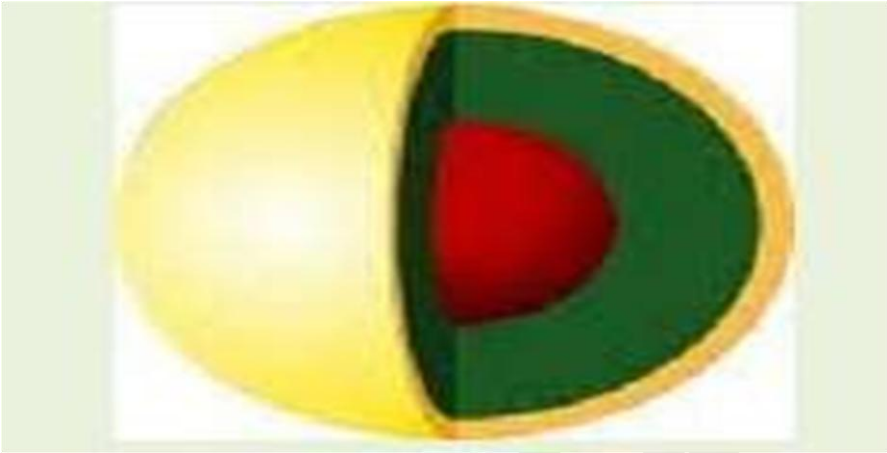
- The nanowire pinpoint damage from injury and stroke, localize the cause of seizures, and detect the presence of tumors and other brain abnormalities.

Application:

- Technique has potential as a treatment for Parkinson's and similar diseases.

Nanoshells

- Nanoshells are hollow silica spheres hollow silica spheres covered with gold. Scientist can attach with antibodies to their surfaces, and enabling the shells to target certain shells such as cancer cells?

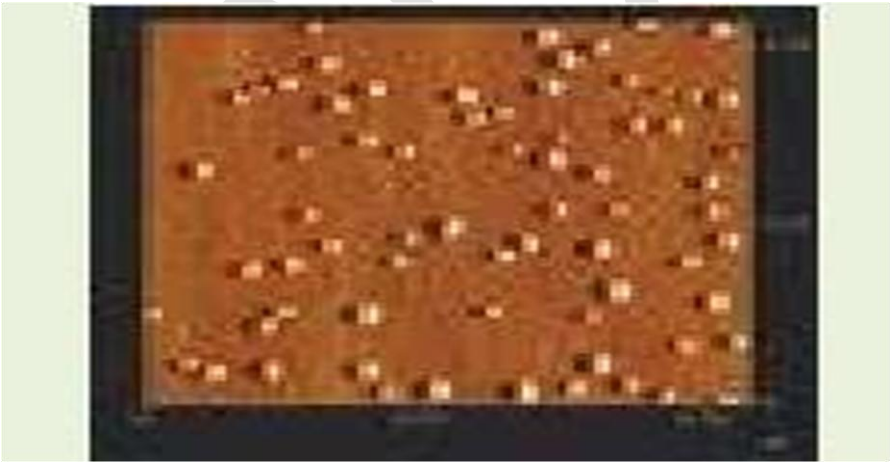


Applications

- Technique has potential for targeting cancerous cell

QUANTUM DOTS

- Quantum dots are miniscule semiconductor particles that can serve as signposts of certain types of cells or molecules in the body.



Application

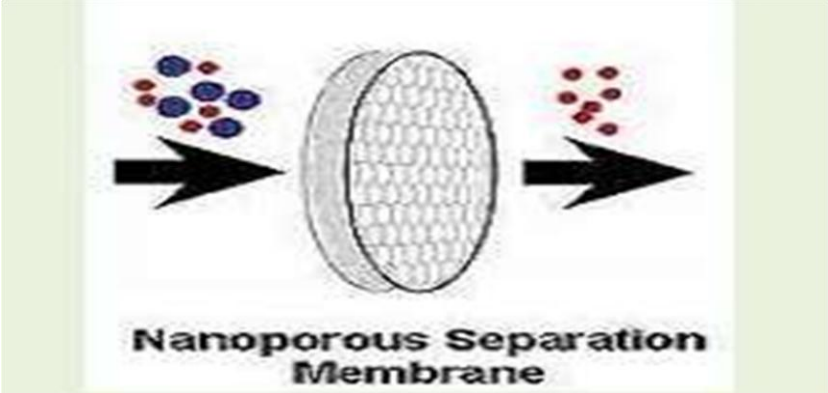
- Technique has potential for targeting cencerous cells

NANO PORES:

- Engineered into particles, they are holes that are so tiny that DNA molecules can pass through them one strand at a time, allowing for highly precise and efficient DNA sequencing.

- **One Word Question Answer**

SR NO.	QUESTION	ANSWER
1	Bleomycin is used for?	Targeting to hepatic carcinoma
2	What are hollow cylinder made of carbon, atoms that can be filled and sealed for potential drug delivery?	Carbon nano tube
3	Which nano system damage from injury and stroke, localize the cause of seizures, and detect the presence of tumors and other brain abnormalities	Nanowires
4	Which technique has potential as a treatment for Parkinson's and similar diseases.	Nanowires
5	Engineered into particles, they are holes that are so tiny that DNA molecules can pass through them one strand at a time, allowing for highly precise and efficient DNA sequencing is called?	Nanopores
6	Which are hollow silica spheres covered with gold. Scientist can attach with antibodies to their surfaces, and enabling the shells to target certain shells such as cancer cells?	Nanoshells
7	What are miniscule semiconductor particles that can serve as signposts of certain types of cells or molecules in the body.	Quantum dots

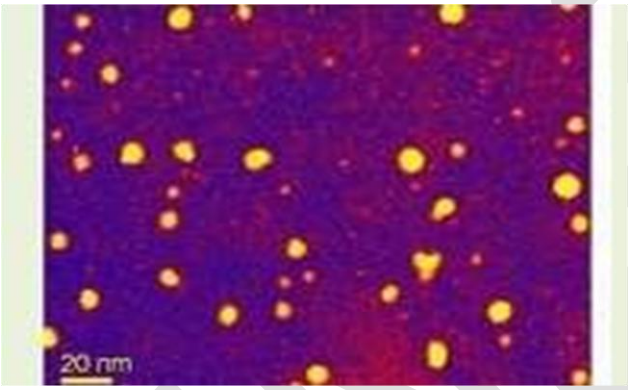


Application:

- Potential in genetic engineering and biotechnology.

GOLD NANO :

- Particle Scientist uses gold nanoparticle to develop ultrasensitive detection system for DNA and protein markers associated with many forms of cancer, including breast prostate cancer.



Application: In cancer Treatment and Genetic engineering.

DENDRIMERS:

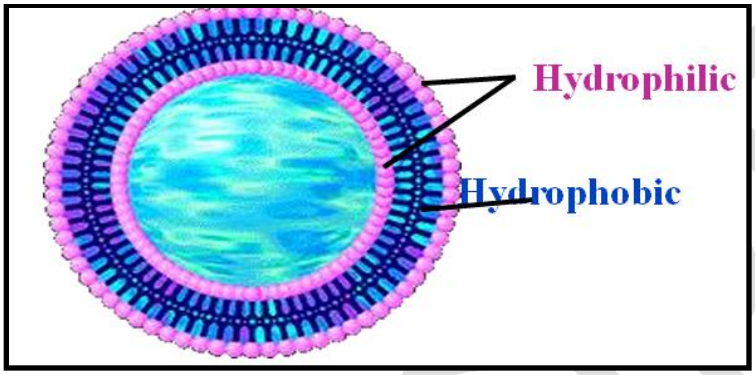
- Dendrimers precisely defined, synthetic nanoparticles that are approximately 510 nm in diameter.
- They are made up of layers of polymer surrounding a control core.
- The dendrimers surface contains many different sites to which drugs may be attach.

Application:

In Gene transfection, medical imaging

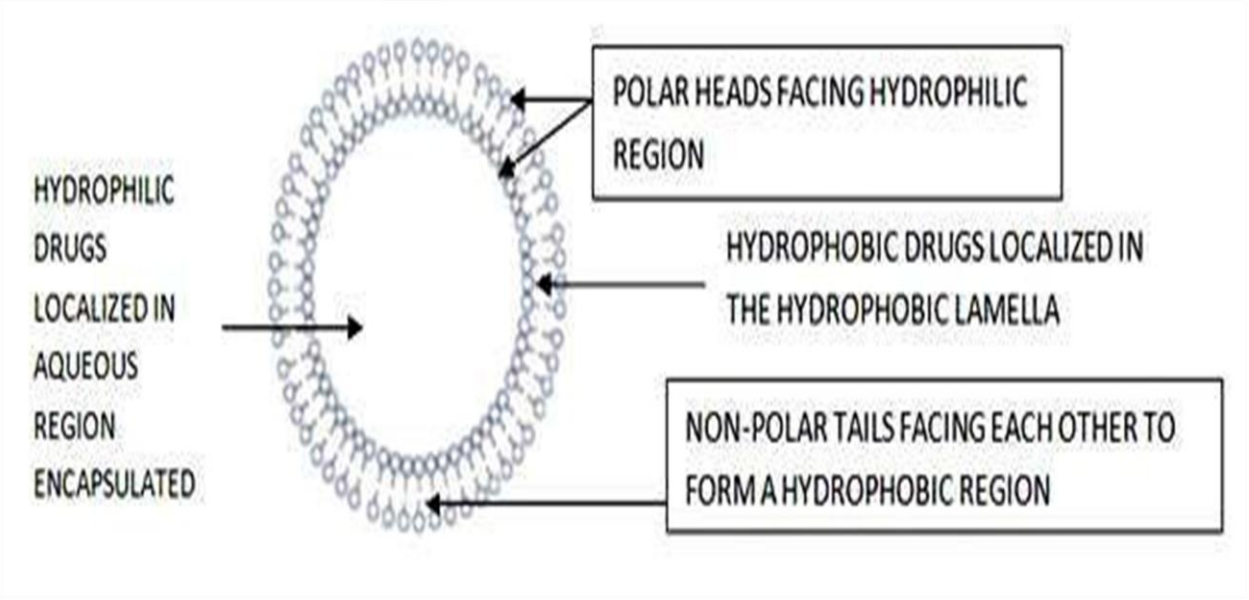
LIPOSOMES:

- Liposomes are simple microscopic vesicles in which an aqueous volume is entirely composed by membrane of lipid molecule various amphiphilic molecules have been used to form liposome.
- The drug molecules can either be encapsulated in aqueous space or intercalated into the lipid bilayers.
- The extent of location of drug will depend upon its physicochemical characteristics and composition of lipids.



NIOSOMES:

- Niosomes are non-ionic surfactant vesicles, which can entrap both hydrophilic and lipophilic drugs either in aqueous phase or in vesicular membrane made up of lipid materials.
- It is reported to attain better stability than liposomes.
- It may prove very useful for targeting the drugs for treating cancer, parasitic, viral and other microbial disease more effectively.

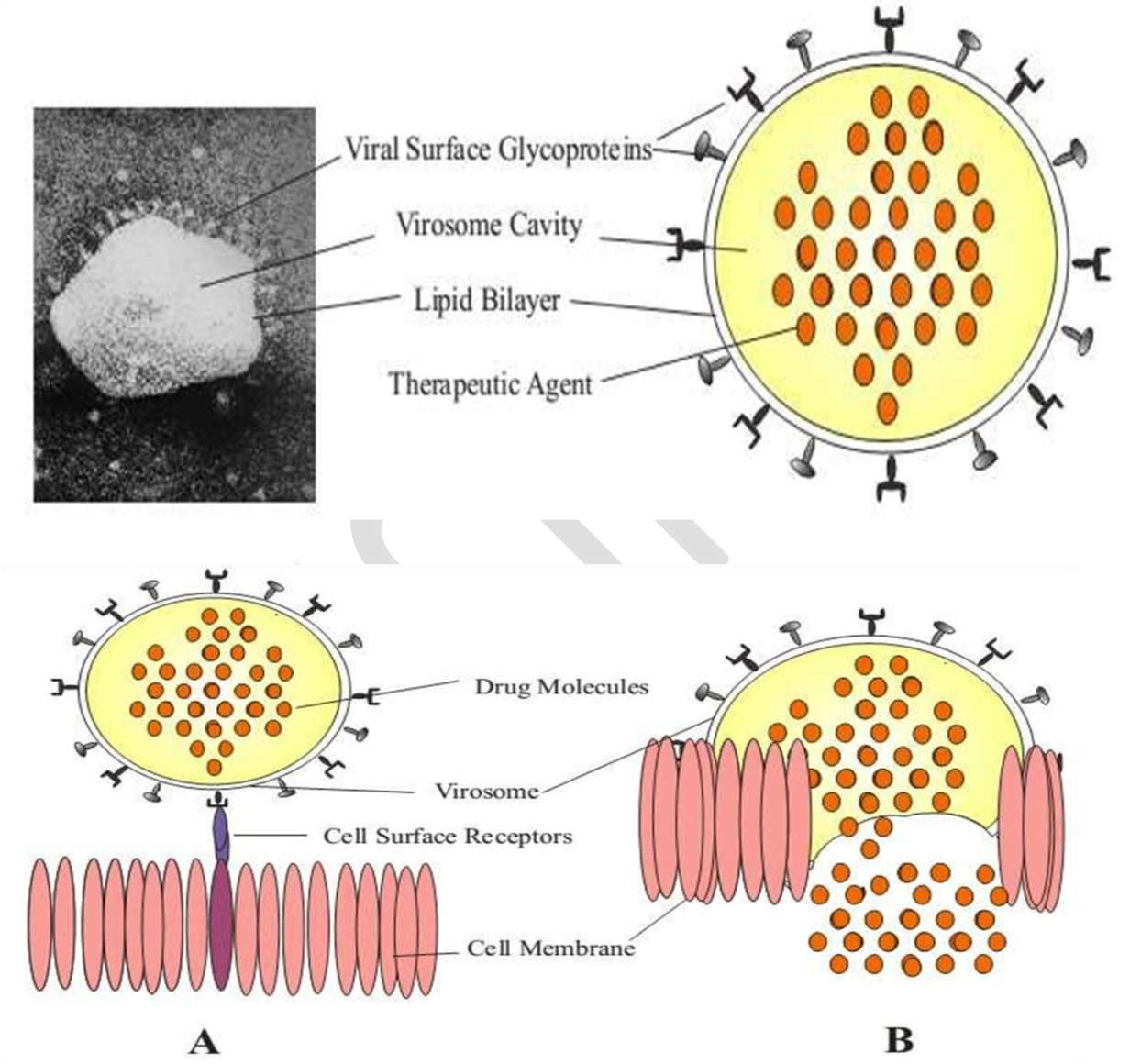


- **One Word Question Answer**

SR NO.	QUESTION	ANSWER
1	Which system is ultrasensitive detection system for DNA and protein markers associated with many forms of cancer, including breast prostate cancer.	Gold Nano
2	Cancer Treatment and Genetic engineering are application of?	Gold Nano
3	Which system involves synthetic nanoparticles that are approximately 510 nm in diameter?	Dendrimers
4	Structure of dendrimers is?	layers of polymer surrounding a control core
5	The structure contain microscopic vesicles in which an aqueous volume is entirely composed by membrane of lipid molecule is called?	Liposome
6	What are non-ionic surfactant vesicles, which can entrap both hydrophilic and lipophilic drugs either in aqueous phase or in vesicular membrane made up of lipid materials is called?	Niosomes

VIROSOMES :

- Virosomes are immuno-modulating liposomes consisting of surface glycoprotein of influenza virus (immune stimulating reconstituted influenza virosome) muramyl dipeptide etc.
- Virosomes must be target oriented and their fusogenic characteristics could be exploited in genome grafting and cellular microinjection.



A. Interaction of the virosomes with cell surface recepters.
B. Release of the encapsulated drug molecules in the target cell.

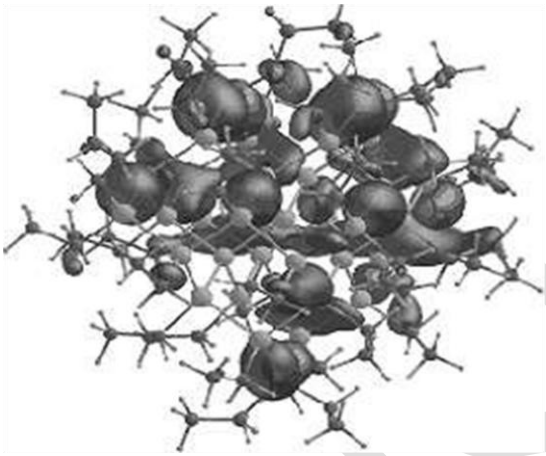
Targeted drug delivery system

CUBOSOMES:

- Cubosomes are liquid crystalline phase forming small cubic particles suitable for injection.

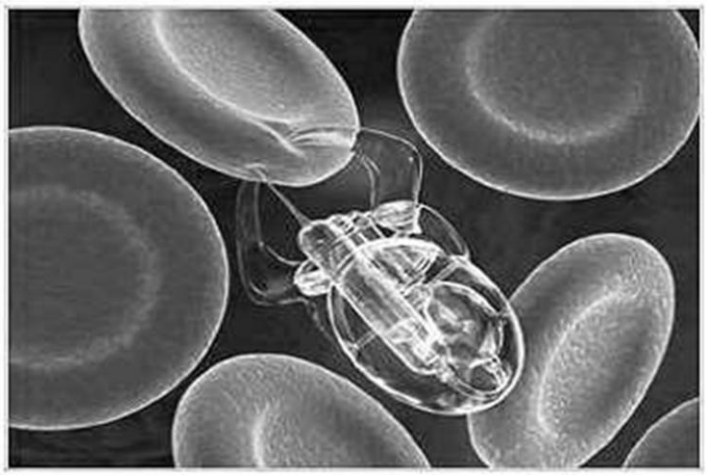
NANOCRYSTALS :

- Nanocrystal is any Nano material with at least one dimension≤ 100 nm and that is single crystalline.
- More properly, any material with a dimension of less than 1 micrometre, i.e., 1000 nanometers, should be referred to as a nanoparticle, not a Nanocrystal. For example, any particle which exhibits regions of crystallinity should be termed nanoparticle or nanocluster based on dimensions.



NANROBOTS

- Nanorobotics is the technology of creating machines or robots at or close to the microscopicscale of a nanometer (10^{-9}meters).
- More specifically, nanorobotics refers to the still largely hypothetical nanotechnology engineering discipline of designing and building nanorobots, devices ranging in size from 0.1-10 micrometers and constructed of nano scale or molecular components.



- **One Word Question Answer**

SR NO.	QUESTION	ANSWER
1	Whatare immuno modulating liposomes consisting of surface glycoprotein of influenza virus (immune stimulating reconstituted influenza virosome) muramyl dipeptide etc	Virosomes
2	Virosome is applied in?	Genome grafting and cellular microinjection
3	What are liquid crystalline phase forming small cubic particles suitable for injection ?	Cubosomes
4	What is any Nano material with at least one dimension≤ 100 nm?	Nanocrystals
5	Which technology is creating machines or robots at or close to the microscopic scale of a nanometer (10^{-9} meters)?	Nanorobotics
6	Which devices ranging in size from 0.1-10 micrometers and constructed of nano scale or molecular components	Nanorobotics

TRANSFEROSOMES:

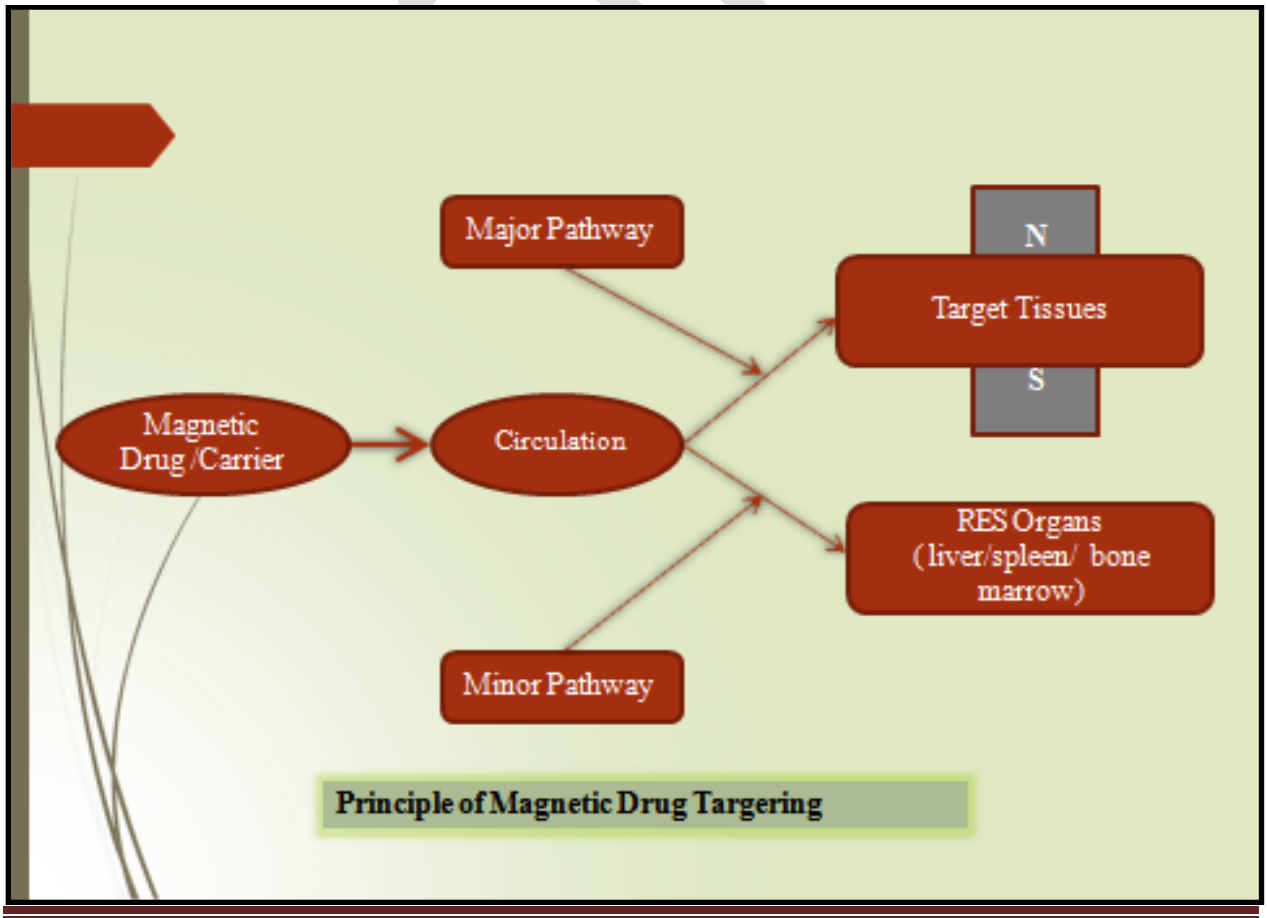
- A transferosomes, in functional terms, may be described as lipid droplets of such deformability that permits its easy penetration through the pores much smaller than the droplets size.
- Transferosomes is a supramolecular entity that can pass through a permeability barrier and there by transport material from the other, site.
- These are more elastic than standard liposomes.

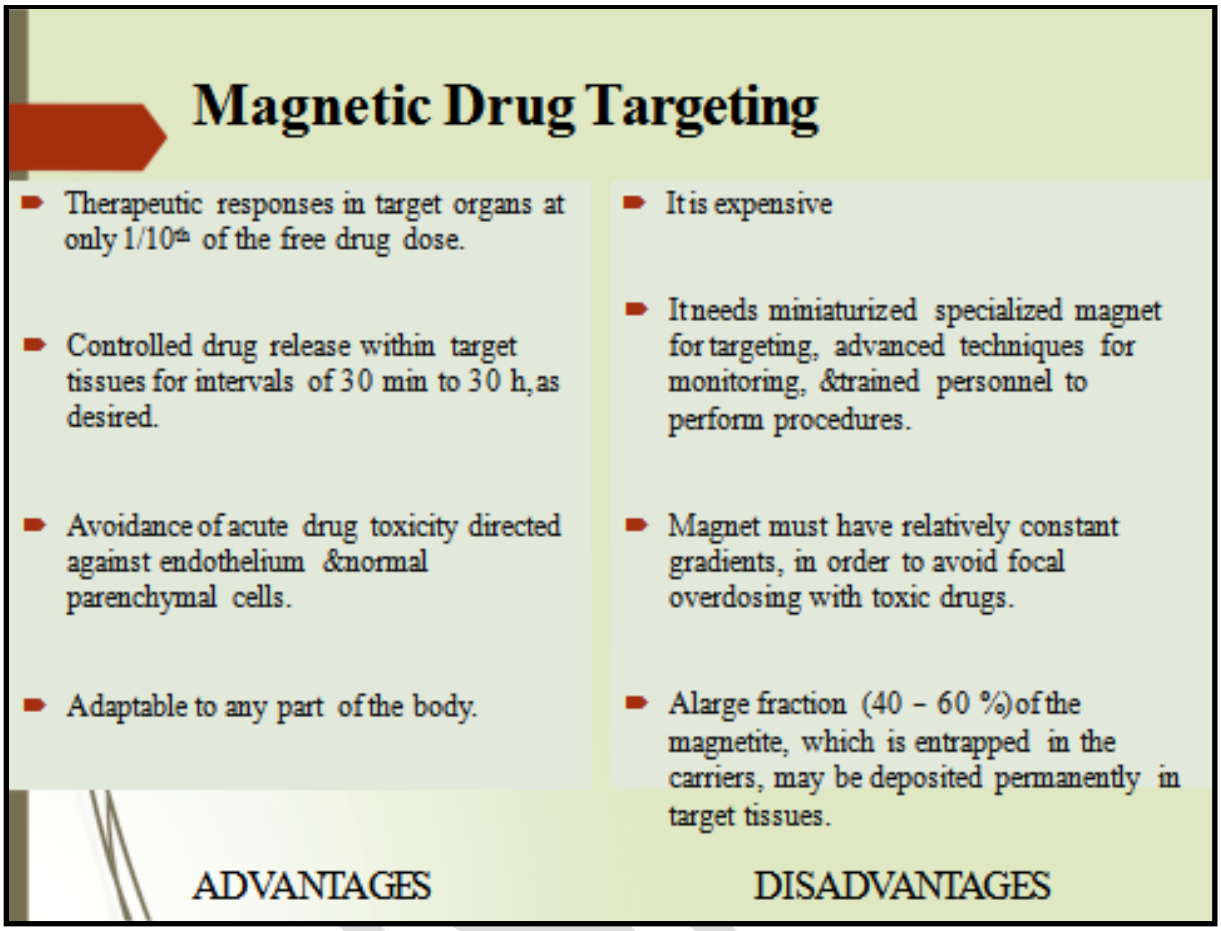
Other approaches of drug targeting

1. Magnetically modulated drug targeting
2. Monoclonal antibody based targeted drug delivery
3. Prodrug

MAGNETICALLY MODULATED DRUG TARGETI

- An interesting approach of targeting carrier system has been to magnetize the carrier so that these particles can be retained at or guided to the target site by the application of an external magnetic field of appropriate strength.
- Retention of magnetic carrier at the target site will delay reticuloendothelial clearance, facilitate extravasations & thus prolong the systemic action of drug.





MAGNETIC DELIVERY SYSTEM

1. Magnetic microspheres
2. Magnetic nanoparticles
3. Magnetic liposomes
4. Magnetic emulsion
5. Magnetic resealed erythrocytes

MONOCLONAL ANTIBODY BASED TARGETED DRUG DELIVERY

- The recognition site for the monoclonal antibody should be located on the surface of the cell.
- The antibodies should have sufficient tumor tissue specificity.
- The extent of localization of the antibody at the target site. Biodistribution of the drug–antibody conjugate in the body relative to that of the parent antibody.
- Stability of the drug–antibody conjugates in blood.
- The host toxicity of the conjugate.
- The conjugate must be biodegradable and non-immunogenic.
- Drugs should be released upon interaction between the carrier molecule and the cell.

- **One Word Question Answer**

SR NO.	QUESTION	ANSWER
1	The lipid droplets of such deformability that permits its easy penetration through the pores much smaller than the droplets size is called?	Transferosomes
2	Which is more elastic than standard liposomes?	Transferosomes
3	In which system the particles can be retained at or guided to the target site by the application of an external magnetic field of appropriate strength?	Magnetically modulated delivery system
4	magnetic carrier at the target site will delay reticuloendothelial clearance, facilitate extravasations & thus prolong the systemic action of drug this mechanism for?	Magnetically modulated delivery system
5	Which is expensive system?	Magnetically modulated delivery system
6	In which system contain Bio distribution of the drug–antibody conjugate in the body relative to that of the parent antibody.	Monoclonal antibody targeting system

APPROVED MONOCLONAL ANTIBODIES

Antibody	Target	Indication
Trastuzumab	HER2	Breast Cancer
Bevacizumab	VEGF	Lung Cancer
Cetuximab	EGFR	Colorectal carcinoma
Panitumumab	EGFR	Colorectal carcinoma

IMMUNOCONJUGATES

- The possibility of raising monoclonal antibodies against cell surface markers allow tumor site targeting discretely.
- Many cytotoxic drugs have been conjugated with monoclonal antibodies.
- These conjugates have been used to study drug localization in tumours and modulation of drug toxicity.
- They have been found to be useful in the management of various types of carcinomas.
- The conjugation of antibodies developed against a specific tumor determinant with another recognition component provides them dual specificity to target the drug or toxin intracellular.

BISPECIFIC ANTIBODIES

- The approach has been mainly suggested for immunotherapy of immunological disorders especially those related to lack of MHC restricted recognition by immune effectors cells.
- Bispecific antibodies against tumour endothelium & tissue factors (the initiator of the intrinsic pathway of blood conjugation) have also been proposed for synergistic effects.

IMMUNOTOXINS

- These are conjugates of antibody (Mab & Fab) fragments & toxins, in which cell binding moieties of the toxins are replaced with specific binding chain of the antibodies.

Advantages

- The naturally occurring toxins used have very specific biological pathways in producing their cytocidal effects.
- The cytotoxic activity of the toxin that is conjugated to the antibody does not involve any other secondary agent(s).
- Theoretically, immunotoxins should not bind to non-malignant cells, and even if they do bind, the internalization of the agent should not be sufficient to neutralize the therapeutic effect.

IMMUNOTOXINS UNDER CLINICAL TRIALS

Immunotoxin	Target antigen	Target malignancy	Stage
LMB-2	CD25	Leukemia	Phase II
SSIP	Mesothelin	Pancreatic cancers	Phase I
UCHT1	CD3ε	Leukemia	Phase II
RFT5-dgA	CD25	Melanoma	Phase I/II

PRODRUG

- Prodrug is an inactive pharmacological moiety developed to optimize pharmacokinetics or site selectivity of a drug.
- Since the prodrug has low cytotoxicity prior to its activation, it has very few chances of its encounter with healthy cells.
- In general, selective enzyme expression, hypoxia, & low extracellular pH at tumor site is utilized for prodrug activation.
- ADEPT has been investigated in the treatment of tumours, where an antibody-enzyme conjugate is administered systemically, where it clears from the circulation & localizes to its target by virtue of the antibody binding to its specific biomarker on the tumour.

One Word Question Answer

SR NO.	QUESTION	ANSWER
1	When the drug release in monoclonal antibody system?	interaction occurs between the carrier molecule and the cell
2	The possibility of raising monoclonal antibodies against cell surface markers allow tumor site targeting discretely is called?	Immunoconjugates
3	Which system has been found to be useful in the management of various types of carcinomas?	Immunoconjugates
4	Which are conjugates of antibody (Mab & Fab) fragments & toxins, in which cell binding moieties of the toxins are replaced with specific binding chain of the antibodies?	Immunotoxins
5	The system in which naturally occurring toxins used have very specific biological pathways in producing their cytocidal effects, this is the properties of?	Immunotoxins
6	What is an inactive pharmacological moiety developed to optimize pharmacokinetics or site selectivity of a drug is called?	Prodrug