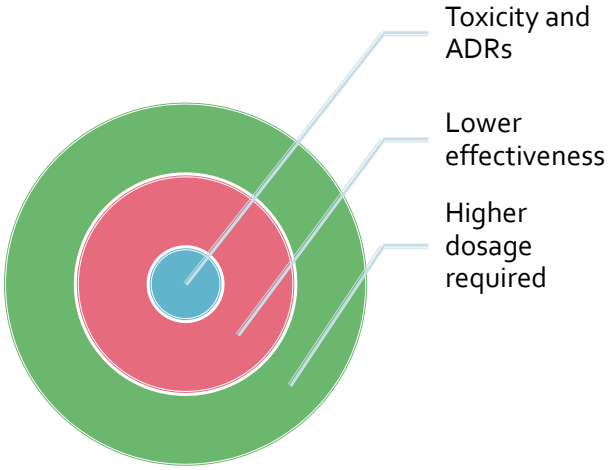
Introduction to NDDS

Disadvantages of conventional DDS



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Requirements of novelty

Temporal	• Drug delivery at a predetermined rate and for pre-determined span of time
Spatial	• Conveying the active entity to the target site.

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Economic requirements

21st century - Cost of innovation

NCE	NDDS	Generic competition
$2.6 billion; 10-12 years	$50 million; 3-4 years	

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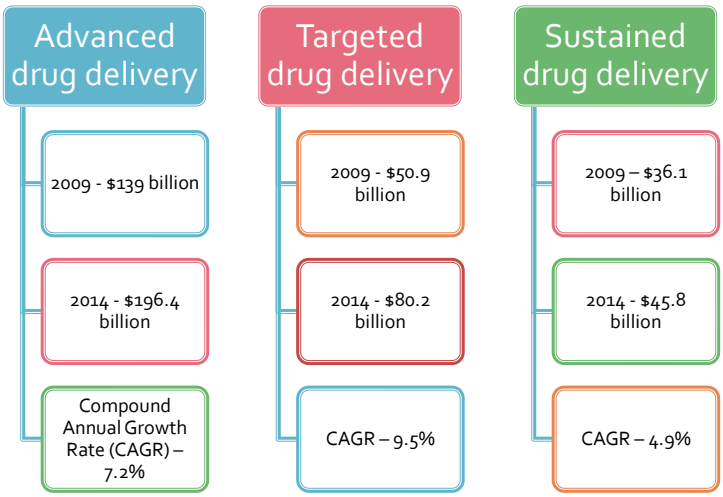

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Advantages of NDDS

1. Increased efficacy of the drug
2. Site specific delivery
3. Decreased toxicity/side effects
4. Increased convenience
5. Shorter hospitalizations
6. Viable treatments for previously incurable diseases
7. Potential for prophylactic applications
8. Lower healthcare costs - both short and long term
9. Better patient compliance.

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Limitations of NDDS

Variability

- Physiological factors such as gastro intestinal enzyme, activates pH /gastric and intestinal transit rates, food and disease which often influence drug bioavailability from conventional dosage forms may interfere with the accuracy of control release and absorption of drug from the system.

Local irritation

- The products which remain intact may become accommodates at some sites results slow release of drug from the dosage form may produce a high localized concentration of drug which produces local irritation.

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Short half life

- Drugs with half- life of 1hr or less are difficult to be formulated as sustained release formulation. The high rate of elimination of such drugs from the body requires an highly large maintenance dose which provides 8-12 hrs of continuous release.

Dose dumping

- Since these products contain a large amount of drug. There is a chance of unsafe over dosage, if the product is improperly made and the total drug contained there is released at one time or over too short time of interval

Cessation

- It is difficult to cease the therapy once after administration may be for reasons of toxicity or any other.

Potent drugs

- It may be not suitable to encompass potent drugs in such system

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Targeting of drug

- It is the delivery of drugs to receptors or organs or any other specific part of the body to which one wishes to deliver the drug exclusively.

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Why?????

To get desired therapeutic response (site specificity)

To reduce toxicities associated with a drug

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Reasons for Site specific delivery of drugs

- 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.

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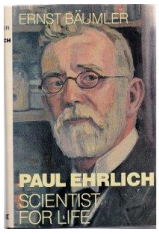
History

- Paul Ehrlich (1902) – "Magic Bullet"
- He described targeted drug delivery as an event where, " a drug –carrier complex/conjugate , delivers drug exclusively to the preselected target cells in a specified manner"



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Passive targeting

- Targets systemic circulation
- It is a passive process which utilises the natural course of biodistribution
- The ability of some colloids to be taken up by RES especially in liver and spleen – vectors for passive hepatic targeting
- Passive capture of carriers by microphage – can be used for delivery of anti-infective agent for disease conditions involving macrophages of RES eg. Leshmaniasis, brucellosis, candidiasis etc

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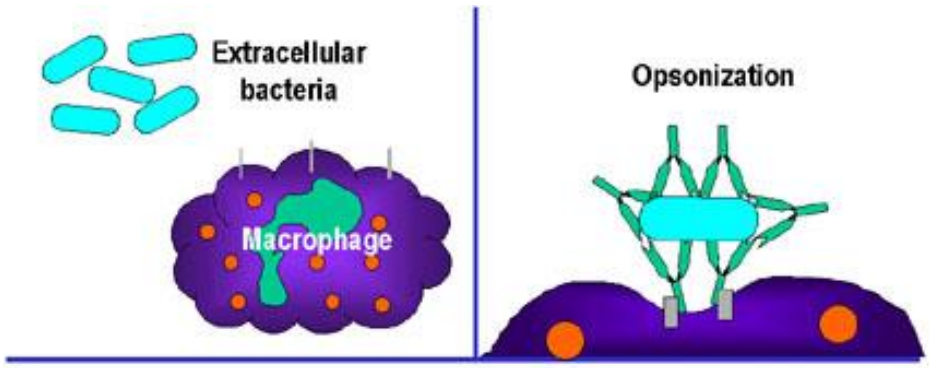

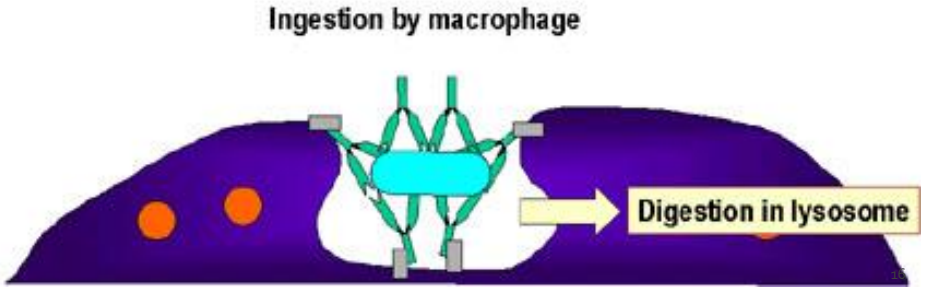

- Disadvantage – carriers cannot cross the endothelial barrier hence extravasation is poor
- Thus limited to intravascular targets
- Trials for targeting them to intravascular non RES cell lines

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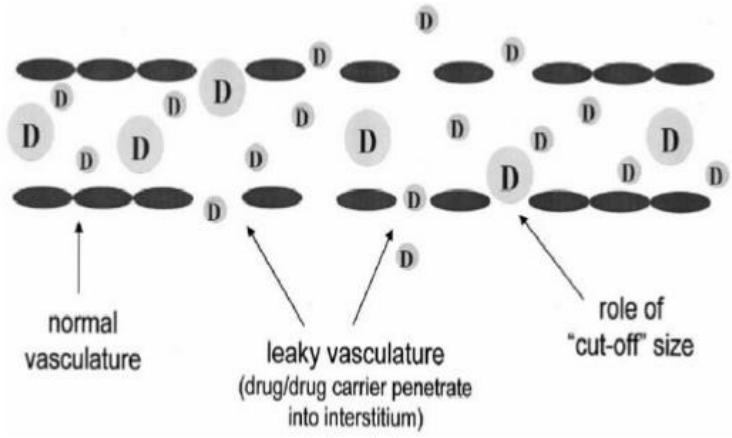

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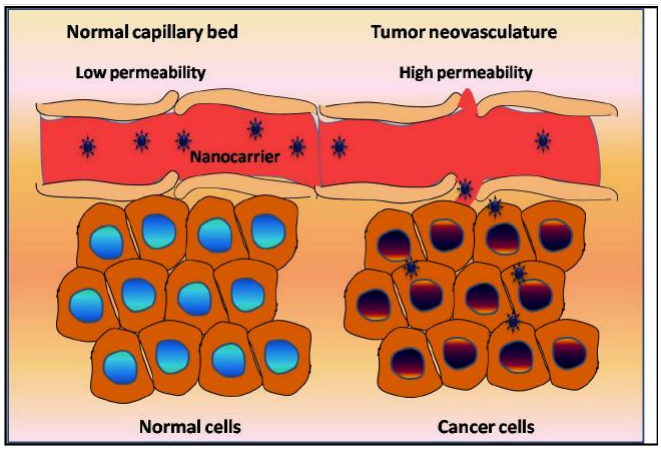

Enhanced Permeation & Retention (EPR) effect in cancer cells

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- Carriers for passive targeting:
  - Liposome
  - Microparticles
  - Cellular carriers
- Increasing circulation half life – modification of size, surface charge, composition, surface rigidity and surface hydrophilicity

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Inverse targeting

- Based on circumventing and avoiding passive uptake of colloidal carriers by RES
- This leads to reversion of biodistribution, hence inverse targeting

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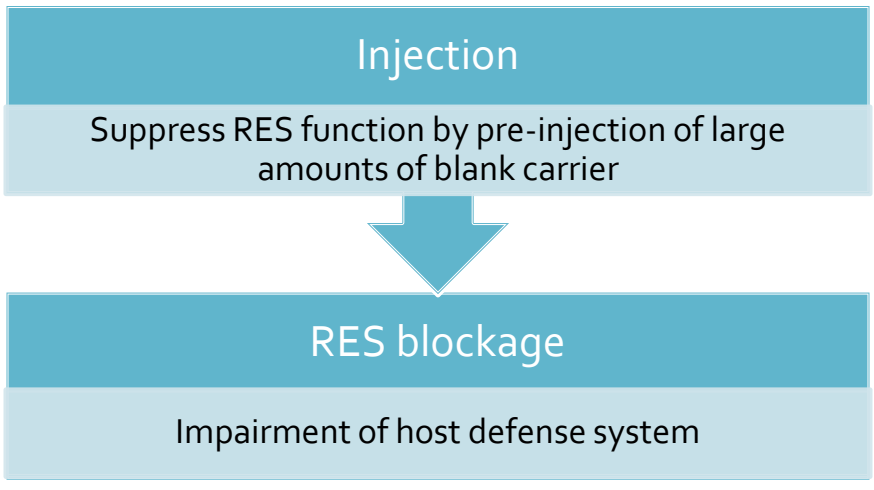
Approaches



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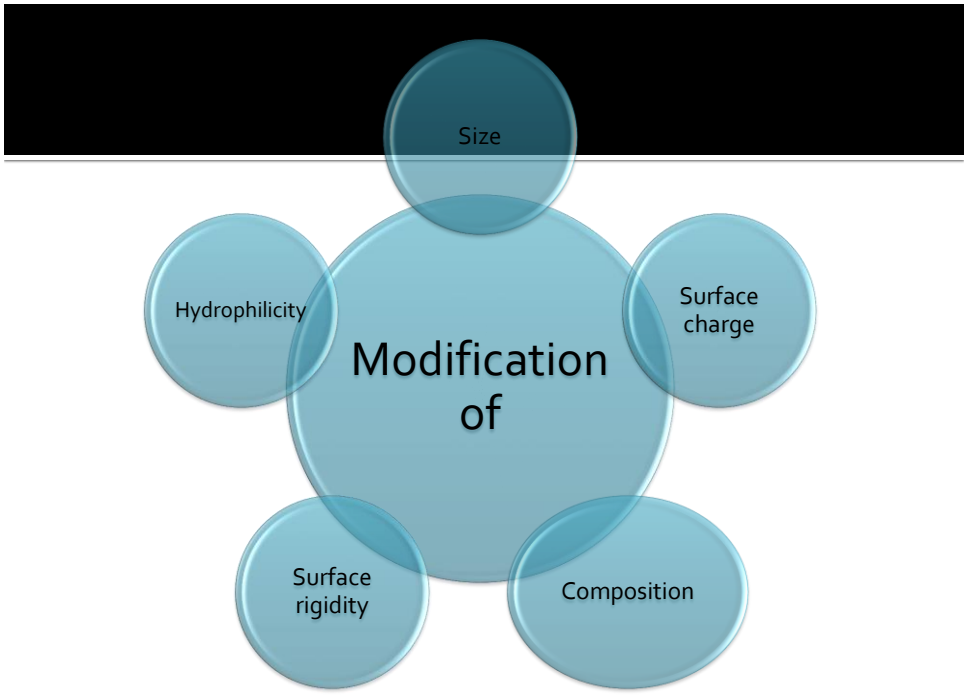

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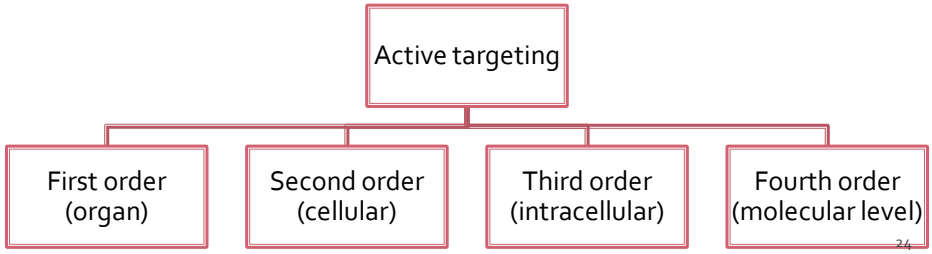
Active targeting

- Natural distribution pattern of drug carrier is enhanced using biological, chemical and physical means.
- Facilitation of binding of carrier to target cells by use of ligands



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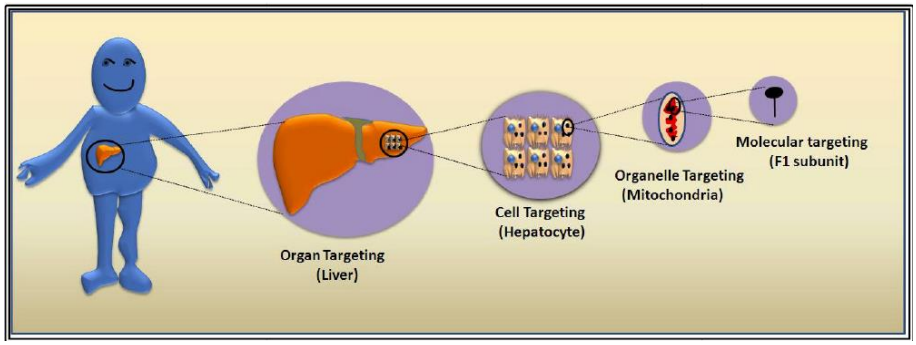

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First order active targeting – organ compartmentalisation

- Restricted distribution of carrier to capillary bed of pre-determined target site – organ or tissue
- Targeting to lymphatics, peritoneal cavity, plural cavity, cerebral ventricles, lungs, joints, eyes etc
- Drug eluting stents

drug eluting stents.flv

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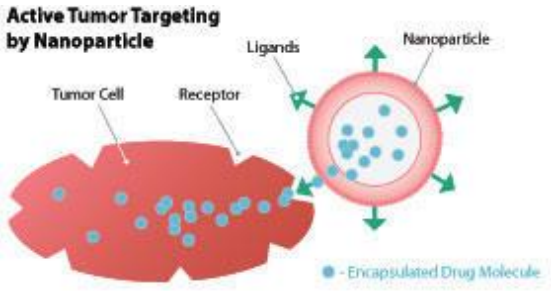
Second order active targeting – cellular targeting

- Targeting specific cell types
- Eg. Tumor cells



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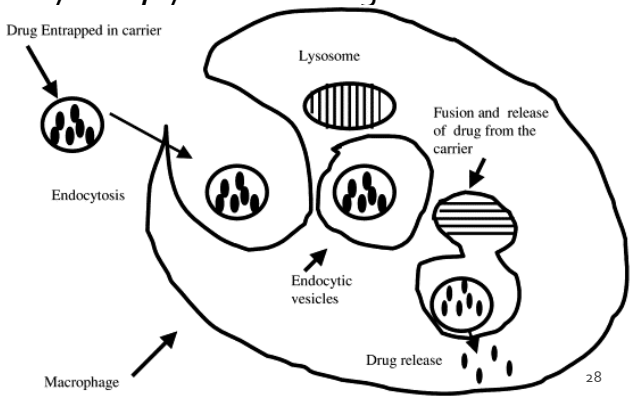
Third order active targeting – intracellular drug targeting

- Drug delivery specifically to intracellular target sites
- Eg. Receptor-based ligand mediated entry of drug complex by endocytosis, lysosomal degradation of carrier

tumortargeting.flv



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Fourth order active targeting – molecular level drug targeting

- Targeting a specific molecule in the cell.
- For example, in many gene delivery systems, the target is the DNA present in the nucleus.

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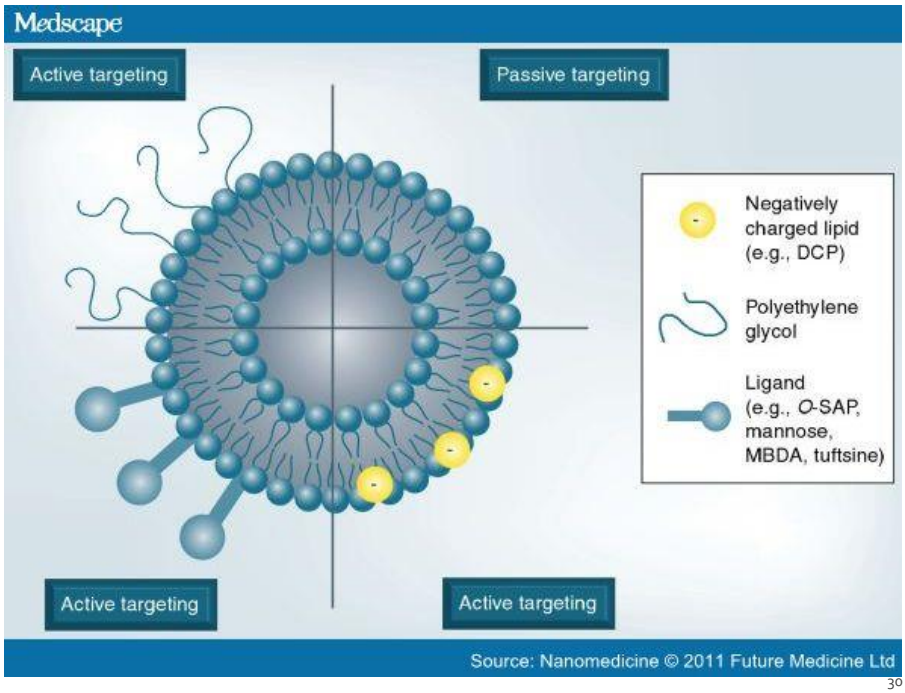

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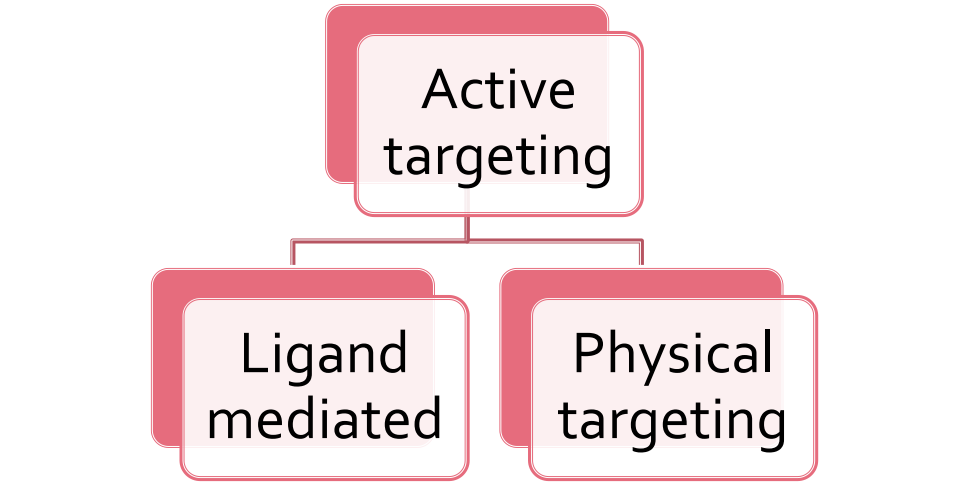

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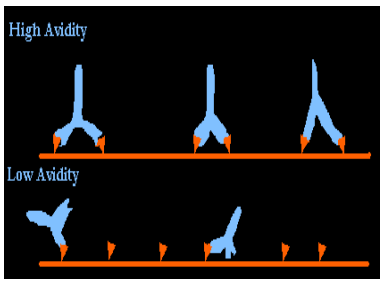
Ligand mediated targeting

- Carriers functionalised using various biologically relevant molecular ligands – antibodies, polypeptides, oligosaccharides, viral protein or fusogenic residues
- It confers avidity to drug carrier
- Avidity is the overall stability of the interaction and is determined by affinity, valency as well as the geometric arrangement of components



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- Can involve various uptake mechanisms
  - Receptor dependent uptake of LDL particles (liposomes)
  - Biotin-aveidin linkage; etc

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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

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Physical targeting

- Selective drug delivery programmed and monitored at external level (ex vivo) with the help of physical means
- Some characteristics of the bioenvironment are used to:
  - Direct the carrier to a particular location – magnetic fields for magno-responsive carriers
  - Cause selective release of its content – temperature sensitive liposomes

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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

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Reverse targeting

- In reverse targeting, instead of the drug delivery system seeking its target, the target cells are attracted to the drug delivery system.
- The inspiration for such concept is from the natural process of immune activation at the site of injury through secretion of signalling molecules known as chemokines

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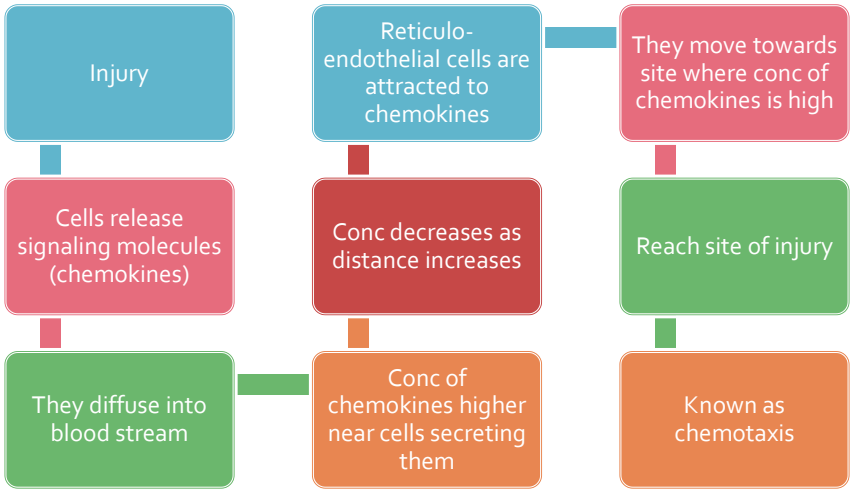

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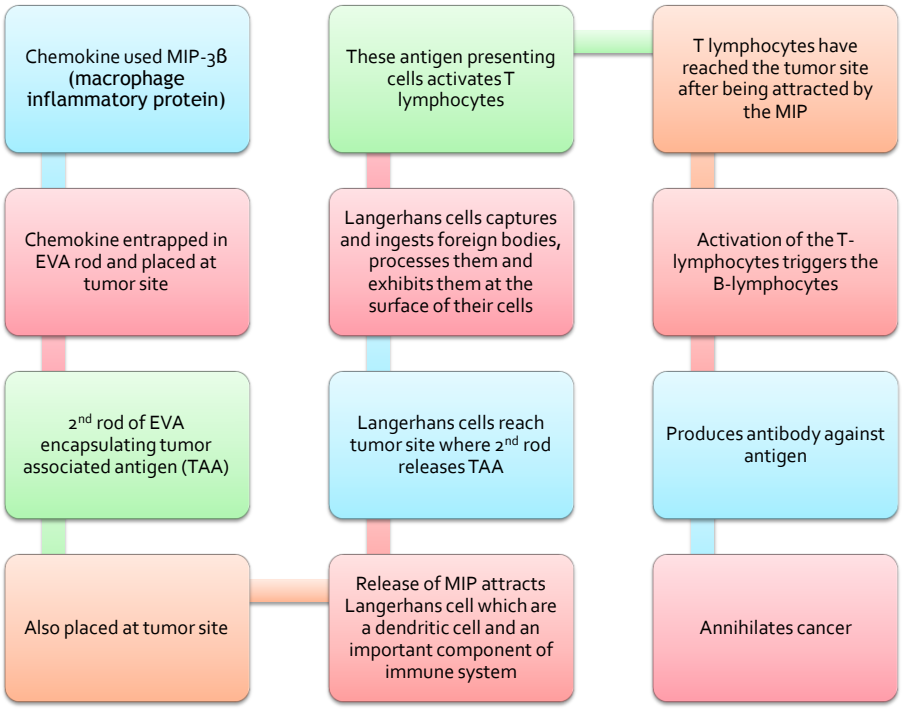
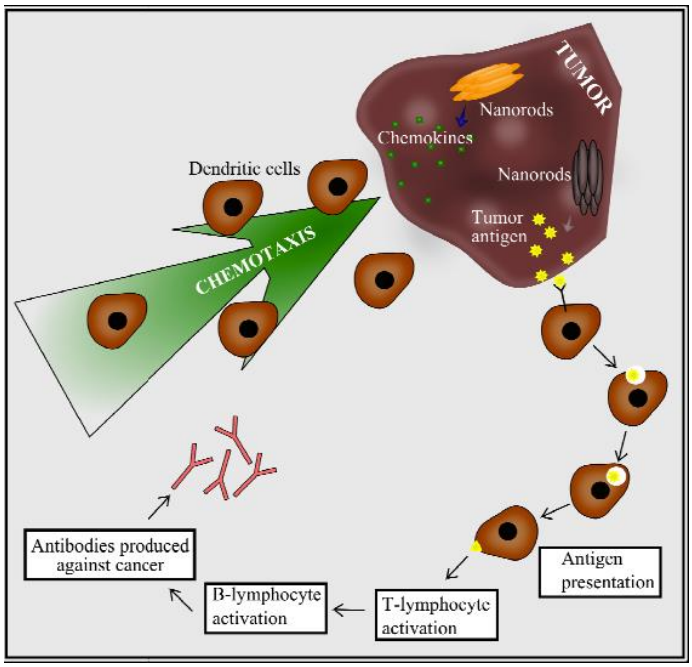

Chemokine used MIP-3β (macrophage inflammatory protein)
Chemokine entrapped in EVA rod and placed at tumor site
2nd rod of EVA encapsulating tumor associated antigen (TAA)
Also placed at tumor site
Release of MIP attracts Langerhans cell which are a dendritic cell and an important component of immune system
Langerhans cells reach tumor site where 2nd rod releases TAA
Langerhans cells captures and ingests foreign bodies, processes them and exhibits them at the surface of their cells
These antigen presenting cells activates T lymphocytes
T lymphocytes have reached the tumor site after being attracted by the MIP
Activation of the T-lymphocytes triggers the B-lymphocytes
Produces antibody against antigen
Annihilates cancer


TUMOR
Nanorods
Chemokines
Nanorods
Tumor antigen
Dendritic cells
CHEMOTAXIS
Antibodies produced against cancer
B-lymphocyte activation
T-lymphocyte activation
Antigen presentation

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Dual targeting

- Carrier molecules have their own effect like the drug, thus synergistic
- Eg. Anti-viral drug carriers fortified with their own anti-viral activity
- Advantage: drug resistance could be overcome

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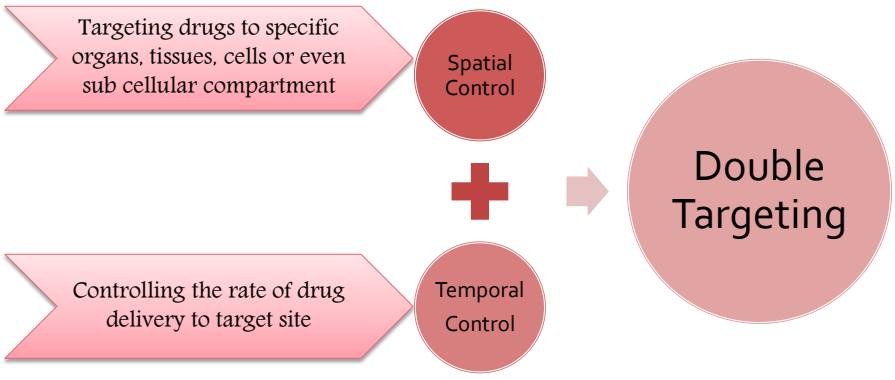
Double targeting



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Combination targeting

- Site specific delivery of proteins and peptides
- These systems are equipped with carriers, polymers or homing devices
- Modification of proteins with polymers alters their physical characteristics and favours targeting

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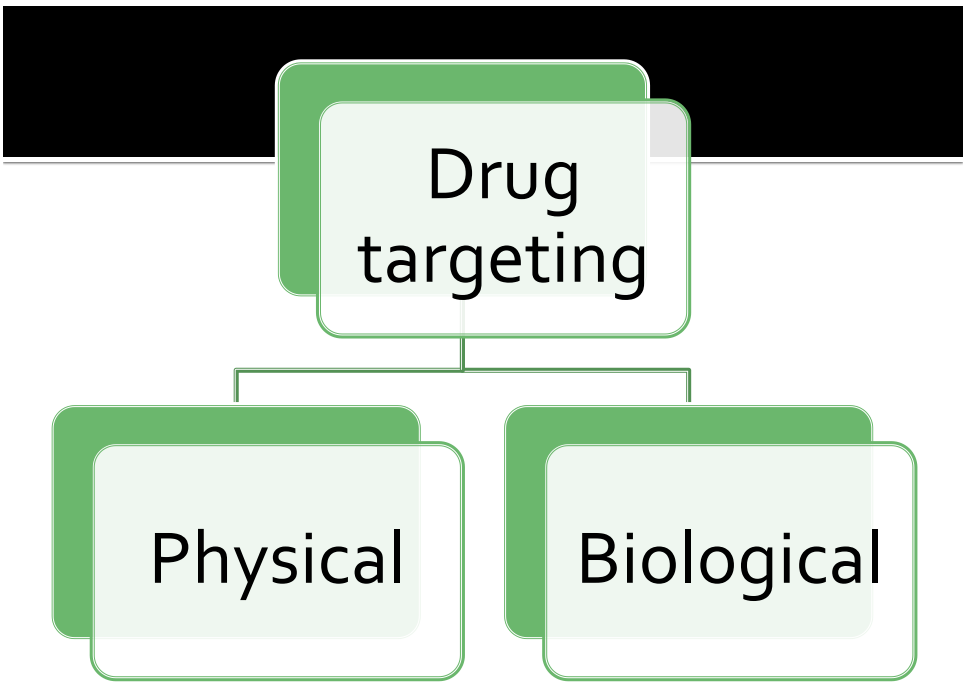

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Physical targeting

- Magnetic approach
- Localisation based on size
- Extra vascular delivery

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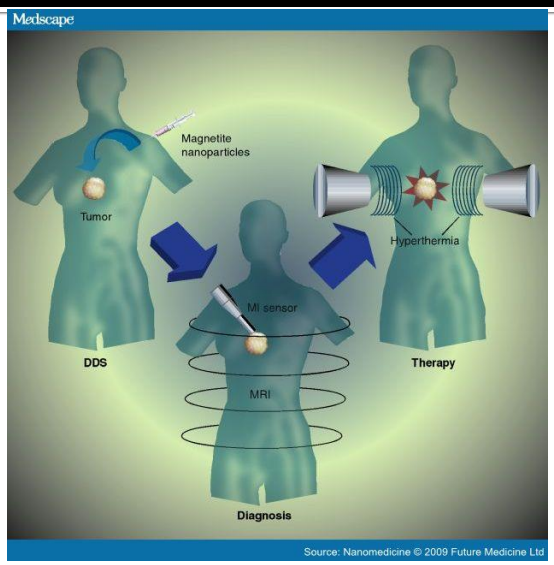
Magnetic approach



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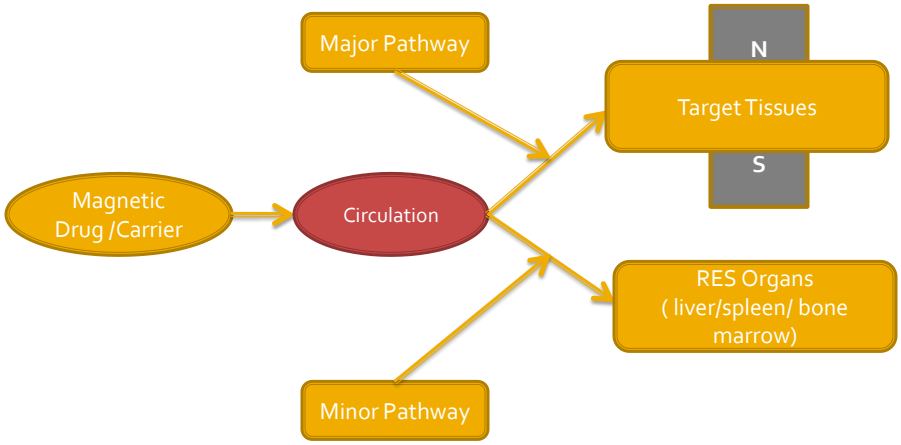
Principle of magnetic targeting



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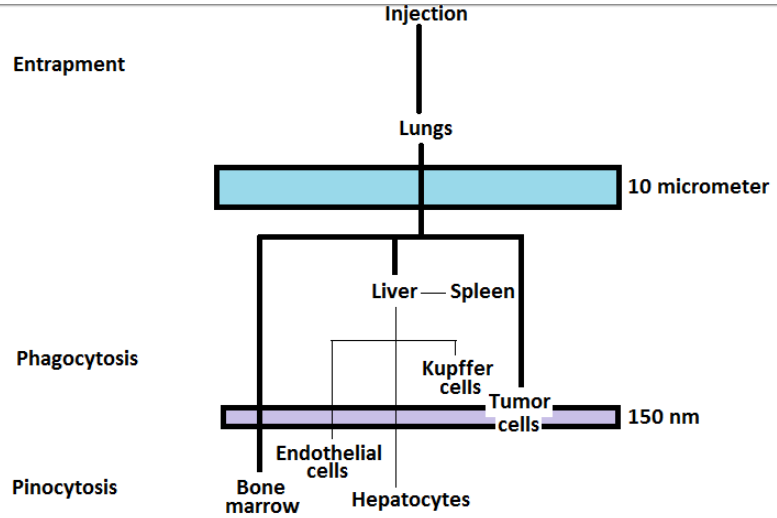
ADVANTAGES	DISADVANTAGES
▪ Therapeutic responses in target organs at only 1/10th of the free drug dose.	▪ It is expensive
▪ Controlled drug release within target tissues for intervals of 30 min to 30 h, as desired.	▪ It needs miniaturized specialized magnet for targeting, advanced techniques for monitoring, & trained personnel to perform procedures.
▪ Avoidance of acute drug toxicity directed against endothelium & normal parenchymal cells.	▪ Magnet must have relatively constant gradients, in order to avoid focal overdosing with toxic drugs.
▪ Adaptable to any part of the body.	▪ A large fraction (40 – 60 %) of the magnetite, which is entrapped in the carriers, may be deposited permanently in target tissues.

Localisation based on size



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Extravascular delivery

- In-situ opthalmic preparations
- Mucosal drug delivery
- Intra-articular delivery

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Biological approach

- Antibodies directed against surface antigens
- Endogenous carbohydrate binding proteins (lectins)
- Glycoconjugated
- Hormones

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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.

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Approved Monoclonal Antibodies

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

How should a targeted DDS be?

- Biochemically inert (non-toxic)
- Non-immunogenic.
- Both physically and chemically stable *in vivo* and *in vitro*.
- Restrict drug distribution to target cells or tissues or organs
- Should have uniform capillary distribution.
- Controllable and predicate rate of drug release.

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- Drug release does not effect the drug action.
- Therapeutic amount of drug release.
- Minimal drug leakage during transit.
- Carriers used must be bio-degradable or readily eliminated from the body without any problem and no carrier induced modulation of diseased state.
- The preparation of the delivery system should be easy or reasonably simple, reproductive and cost effective

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Basic 3 S

- **STABILITY** in blood
- **STEALTH** characteristics to retard immune recognition and
- **SPECIFICITY** towards the target!

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Biological processes and events involved in drug targeting

1. Transport across the epithelial barrier
2. Cellular Uptake and Processing
3. Extravasation
4. Lymphatic Uptake

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Transport across the epithelial barrier

The oral, buccal, nasal, vaginal and rectal cavities are internally lined with one or more layers of epithelial cells

Depending on the position and function in the body epithelial cells can be varied forms

Three layer physiology:

- Epithelium
- Lamina propria
- Basal lamina

Low molar mass drugs cross the above by passive difussion ,carrier mediated systems and selective and non-selective endocytosis

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The polar materials diffuse through tight junctions of epithelial cells

Passive transport is usually higher in damaged mucosa where as active transport depends on structural integrity of epithelial cells

Positively charged particles showed increased uptake than negatively charged counterparts.

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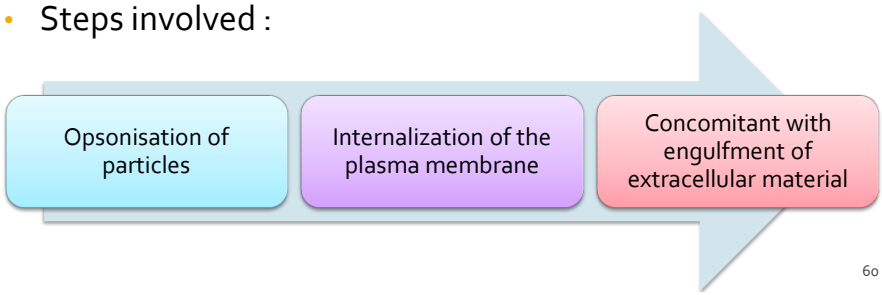
Cellular Uptake and Processing

- Following administration; low molar mass drugs can enter into or pass through various cells by simple diffusion process.
- Targeted drug delivery usually have macro molecular assemblies hence cannot enter by such simple process. Hence take up by a process called ENDOCYTOSIS
- Steps involved :



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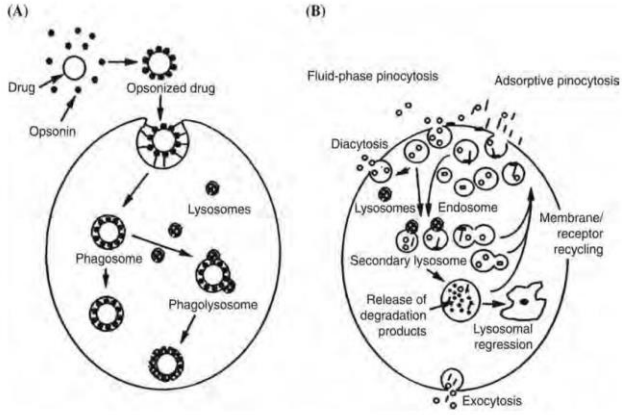

Figure 3 (A) Phagocytic and (B) pinocytic uptake of drugs.

- Phagocytes^^^^ rest of the cells
- opsosins immunoglobulin G complement C3b fibronectin
- dysopsonins IgA & sIgA impart degree of hydrophilicity>>>decrease the uptake

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Extravasation

Many diseases result from the dysfunction of cells located outside the cardiovascular system thus for a drug to exert its therapeutic effects it must exit from the central circulation this process of trans vascular exchange is called Extravasation which is governed by blood capillary walls

Factors that control permeability of capillaries are:	Structure of the capillary wall
	Pathological condition
	Rate of blood and lymph supply
	Physicochemical factors of drug

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The structure of the blood capillary varies in different organs tissues.

It consists of a single layer of endothelial cells joined together by intercellular junctions

Depending on the morphology and continuity of the endothelial layer and the basement membrane blood capillaries are divided into

- Continuous
- Fenestrated
- Sinusoidal

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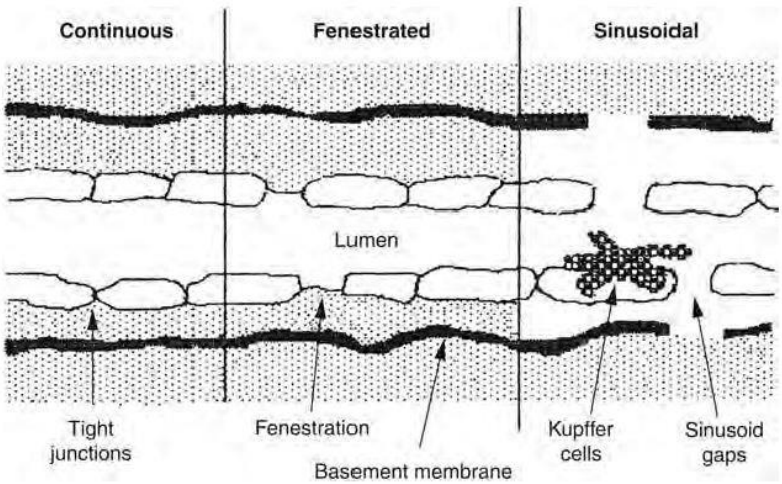

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[redacted]

Continuous capillaries are common and widely distributed in the body exhibit tight inter endothelial junctions and an uninterrupted basement membrane

Fenestrated capillaries shows inter-endothelial gaps of 20-80 nm

Sinusoidal capillaries show inter endothelial gaps of 150 nm

Depending on the tissue or organ the basal membrane is either absent eg. liver or present discontinuously eg. spleen and bone marrow

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[redacted]

Macromolecules can transverse the normal endothelium by passive processes such as:

- Nonspecific fluid phase trans capillary pinocytosis
- Passage through inter endothelial junctions gaps or fenestrate
- Receptor-mediated transport systems

Soluble macromolecules permeate the endothelial barrier more readily than particulate macromolecules. The rate of movement of fluid across the endothelium appears to be directly related to the differences between the hydrostatic and osmotic forces

Depends on charge shape, size, HLB, characteristics of macromolecules

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The endothelium of brain is the strongest of all endothelia formed by continuous non-fenestrated endothelial cells which show no pinocytic activity

Organs such as the lung with very large surface areas have a proportionately large total permeability and consequently a high extravasation

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Lymphatic uptake

Following extravasation drug molecules can either reabsorb into the blood stream directly or enter into the lymphatic system and return with the lymph to the blood circulation

Also drugs administered by subcutaneous intracellular transdermal peritoneal routes can reach the systemic circulation by lymphatic system

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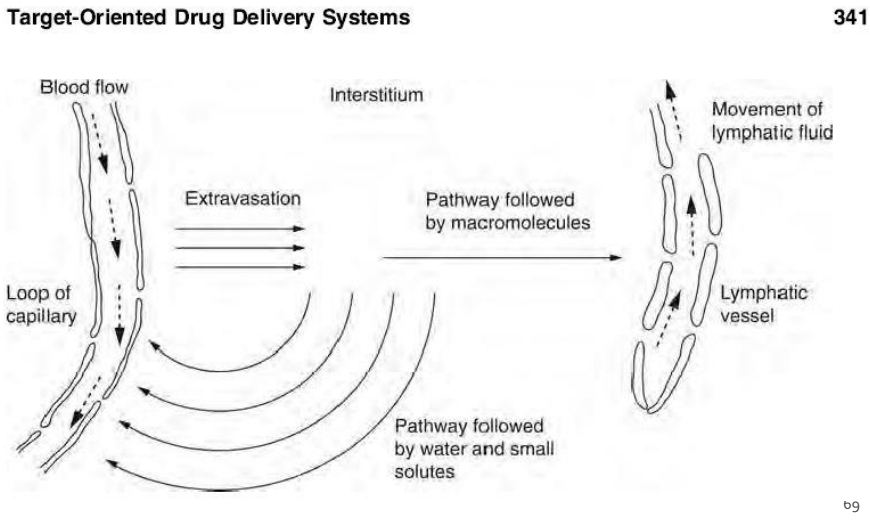

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Problems associated with targeting

1. Rapid clearance of targeted systems eg. Antibody targeted carriers
2. Immune reactions against iv administered carriers
3. Target tissue heterogeneity
4. Insufficient localisation of targeted systems into tumor cells
5. Diffusion and re-distribution of released drug leads to non-specific accumulation

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