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A Comprehensive Review on Targeted Drug Delivery Systems

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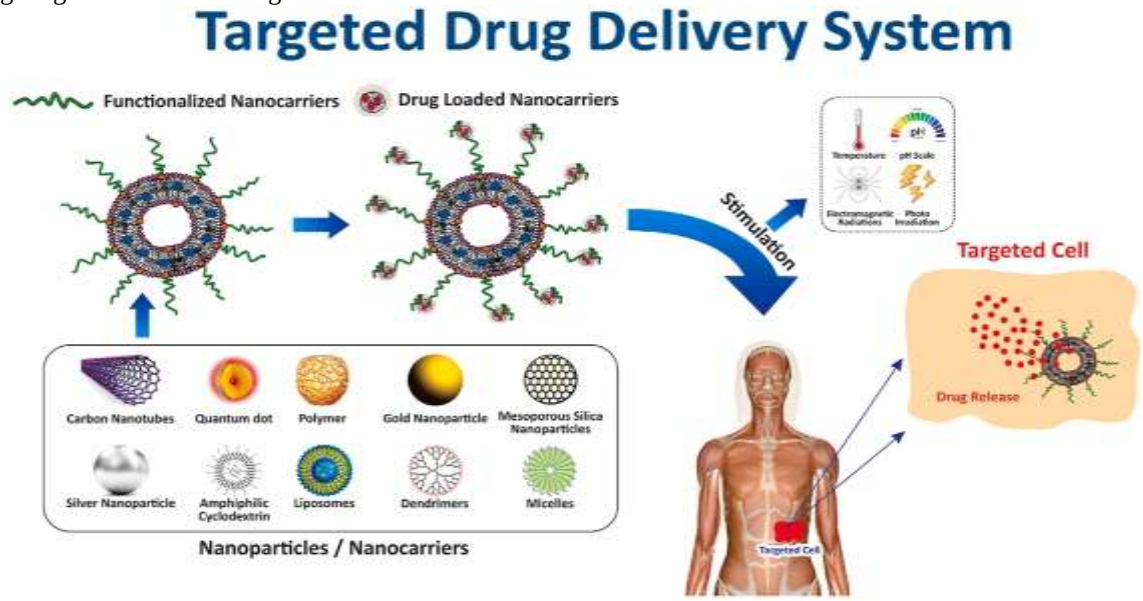
ABSTRACT;
Drug delivery systems can be described as the technologies that carry drugs to the site of action within the body. For example, tablets or pills we take or vaccines that are injected into our body. The field of drug delivery has advanced impressively in the past few decades. Targeted drug delivery system is one of the advancements of the drug delivery systems. Though the idea of drug targeting to a specific site in the body was introduced almost a century ago by Ehrlich, but in the recent years it has emerged as an important part of pharmaceutical drug delivery systems. The targeted drug delivery systems have various advantages over conventional drug delivery. The main goal of the targeted drug delivery system is to obtain the pharmacological action of the therapeutic agent at affected organs only without affecting the healthy ones. Drug targeting can be done using different carriers that maintain and transport the intact drug to pre-selected organ or tissue.

KEY WORDS; Drug targeting, Drug delivery systems, Pharmacological actions, Side effects.

I. INTRODUCTION:

Targeted drug delivery is an advanced method of delivering drugs to the patients in such a targeting sequence that increases the concentration of delivered drug to the targeted organs or tissues or cells which in turn improves efficacy of treatments by reducing side effects of drug administration.it is a special form of drug delivery system, where the pharmacologically active agent or medicament is selectively targeted or delivered only to its site of action or absorption and not to the targeted organs or tissues or cells.



The drug may be delivered [1] To the capillary bed of the active sites,[2] To the specific type of cell [or] even an intracellular region. Ex-tumor cells but not to the normal cells, [3] To a specific organ [or] tissues by complexing with the carrier that recognizes the target.

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REASONS FOR SITE SPECIFIC DELIVERY OF DRUGS;

- Drug instability in conventional dosage form
- Solubility
- Low absorption
- High membrane bounding
- Biological instability
- Short half life
- Large volume of distribution
- Low specificity

Low therapeutic index

OBJECTIVE: The main objective is to achieve a desired pharmacological response at a selected site without undesirable action or interaction at other sites, there by the drug have a specific action with minimum side effects and better therapeutic index.
Ex. In cancer chemotherapy and enzyme replacement therapy.

IDEAL CHARACTERISTICS:

- It should be nontoxic, biocompatible, biodegradable and physiochemical stable in vivo and invitro
- Restrict drug distribution to get target cells or tissues or organs and should have uniform capillary distribution.
- Controllable and predictable rate of drug release.
- Drug release does not affect the drug action.
- Therapeutic amount of drug release
- Minimal drug leakage during transit.
- Carriers used must be biodegradable 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.

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 infectious cells that compare to normal cells.

DISADVANTAGES:

- Rapid clearance of targeted systems.
- Immune reaction against intravenous administered carrier systems.
- Insufficient localization of targeted systems into tumor cells.

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- Diffusion and redistribution of released drugs.
- Require highly sophisticated technology for the formulation.
- Require skills for manufacturing, storage, administration.
- Drug deposition at the target site may produce toxicity symptoms.
- Difficulty to maintain stability of dosage form.

CARRIER OR MARKERS IN TARGETED DRUG DELIVERY:

Targeted drug delivery can be achieved by using carrier system. Carrier is one of the special molecule 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 or via spacer moiety and transport it into vicinity of target.

PROPERTIES OF AN IDEAL CARRIER:

- It must be able to cross anatomical barriers and incase of chemo therapy tumor vasculature.
- It must be recognized specifically and selectively by the target cells and must maintain the specificity of the surface ligands.
- The linkage of the drug and ligand should be stable in plasma, interstitial and other biofluids.
- Carrier should be non toxic , non-immunogenic and biodegradable particulate or macromolecule.
- After recognition the carrier system should release the drug moiety inside the target organs, tissues or cells.

Various carriers are used mainly includes polymers, microcapsules, microparticles, lipoproteins, liposomes and micelles.

STRATEGIES OF DRUG TARGETING:

[1] PASSIVE TARGETING:

Drug delivery systems which are targeted to systemic circulation are characterized as passive targeted drug delivery systems. In this technique drug targeting occurs because of the body's natural response to physiochemical characteristics of the drug or drug carrier system.

[2] INVERSE TARGETING:

In this type of targeting attempts are made to avoid passive uptake of colloidal carrier by Reticulo Endothelial System [RES] and hence the process is referred to as inverse targeting. To achieve inverse targeting, RES normal function is suppressed by pre injecting large amount of blank colloidal carriers or macromolecules like dextran sulphate. This approach leads to saturation of RES and suppression of defense mechanism. This type of targeting is a effective approach to target drugs to non-RES organs.

[3] ACTIVE TARGETING:

In this approach carrier system bearing drug reaches to specific site on the basis of modification made on its surface rather than natural uptake of RES. Surface modification technique include coating of surface with either a bio adhesive, nonionic surfactant or specific cell or

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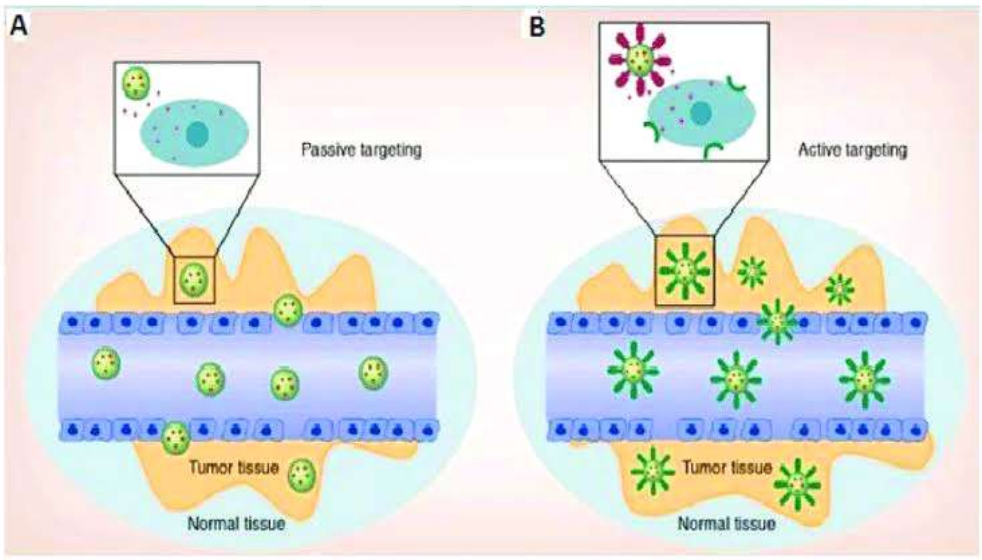
tissue antibodies [monoclonal antibodies] or by albumin protein. Active targeting is of 3 types [1] First order targeting, which target organs [2] Second order targeting, which targets cells [3] Third order targeting, which targets within the cells.



[3 [A] LIGAND MEDIATED TARGETING:

Achieved using specific mechanisms such as receptor dependent uptake of natural low-density lipoprotein or LDL particles and synthetic lipid microemulsions of partially reconstituted LDL particles coated with apo proteins.

[3 [B] PHYSICAL TARGETING:

In this type of targeting some characteristics of environment changes like pH, temperature, light Intensity, electric field, ionic strength and even specific stimuli like glucose concentration are used to localize the drug carrier to predetermined site. This approach was found exceptional for tumor targeting as well as cytosolic delivery of entrapped drug or genetic material.

[4] DUAL TARGETING:

In this type of targeting approach carrier molecule itself have their own therapeutic activity and thus increase the therapeutic effect of drug. For example, a carrier molecule having its own antiviral activity can be loaded with antiviral drug and the net synergistic effect of drug conjugate was observed.

[5] DOUBLE TARGETING;

Temporal and spatial methodologies are combined to a target carrier system, then targeting may be called double targeting. Spatial placement relates to targeting drugs to specific organs, tissues, cells or even subcellular compartment, whereas temporal delivery refers to controlling the rate of drug delivery to target site.

[6] COMBINATION TARGETING:

The combination targeting systems for site specific delivery of proteins and peptides are equipped with carriers, polymer and homing devices with molecular specificity. Modification of proteins and peptides with natural polymers, such as polysaccharides or synthetic polymers may alter their intrinsic physical characteristics, which play a crucial role on the targeting of a specific compartment, organs or their tissues within the vasculature.

BIOLOGICAL PROCESSES AND EVENTS INVOLVED IN DRUG TARGETING:

Various biological processes and events that govern drug targeting are discussed below.

CELLULAR UPTAKE AND PROCESSING:

A drug frequently passes through various cells, membranes and organs to reach its target sites. Low molecular weight drugs can enter into or pass through various cells by simple diffusion processes. Targeted drug delivery systems often comprise macromolecular assemblies and are unable to enter into cells by such simple processes, instead they are captured by a process called endocytosis.

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ENDOCYTOSIS:

Endocytosis is the process where a cell absorbs extracellular material by engulfing it with their cell membrane to form a vesicle which is then pinched off Intracellularly. These particles do not pass through the membrane. It is simply engulfed and enclosed.

EXOCYTOSIS:

The reverse process where materials are expelled or secreted from a cell. This is used to clear wastes and secreted substances[hormones] produced by the cell. It may be excretion or secretion.

PHAGOCYTOSIS:

Phagocytosis is carried by specialized cells of mononuclear phagocyte system called phagocytes by absorption of specific blood component called "opsonin". Phagocytic vacuole fuses with one or more lysosomes to form phago lysosomes. Digestion of particles occurs by lysosomal acid hydrolysis, making drug available to exert its effect.

PINOCYTOSIS:

Pinocytosis [a form of endocytosis] allows a cell to engulf large molecules and fluid that may be present in the extracellular region. The cell membrane folds inwards, encloses the fluid or particle to be transported and then fuses to form a vesicle. The vesicle detaches from the membrane and moves to the interior of the cell. It is of 2 types [1] Fluid phase pinocytosis [2] Receptor mediated pinocytosis

[1] FLUID PHASE PINOCYTOSIS:

Fluid phase pinocytosis is nonspecific and continuous process, where macromolecules adhere to general cell surface site.

[2] RECEPTOR MEDIATED PINOCYTOSIS:

Receptor mediated pinocytosis is a specific process where the macromolecules adhere to specific cell receptor site. Receptor mediated pinocytosis is a particularly efficient form of pinocytosis.

TRANSPORT ACROSS THE EPITHELIAL BARRIER:

Here, 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 layers of physiology: [1] Epithelial [2] Lamia propria [3] Basal lamina. Low molar mass drugs cross the above by passive diffusion carrier mediated systems. 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. Absorption of drugs from buccal via transcellular and paracellular later being dominant.

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 process of trans vascular exchange is called 'Extravasation ', which is governed by blood capillary walls. There are various factors that control permeability of capillaries. These are-

- Structure of the capillary wall.
- Pathological condition.
- Rate of blood and lymph supply.
- Physiochemical factors of drug

The structure of the blood capillary varies in different organs tissues. It consists of a single layer of endothelial cells joined together by intracellular junctions. Depending on the morphology and continuity of the endothelial layer and the basement membrane blood capillaries are divided into [1] Continuous, [2] Fenestrated, [3] Sinusoidal. Continuous capillaries are common and widely distributed in the body exhibit tight inter endothelial junctions and an uninterrupted basement membrane. Fenestrated capillaries show inter endothelial gaps of 20-80nm. Sinusoidal capillaries show inter endothelial gaps of 150nm. Depending on the tissue or organ the basal membrane is either absent ex- liver or present in discontinuous ex- spleen and bone marrow. Macromolecules can transverse the normal endothelium by passive process such as nonspecific fluid phase trans capillary pinocytosis and passage through inter endothelial junction's gaps or fenestrate or by receptor-mediated transport systems. Organs such as the lung with very large surface areas have a proportionately large total permeability and consequently a high extravasation, depending upon charge, shape, size, HLB & characteristics of macromolecules. The endothelium of brain is the strongest of all

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endothelia formed by continuous no fenestrated endothelial cells which show no pinocytic activity. 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 difference between the hydrostatic and osmotic forces.

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. There various factors which influence the clearance of drugs from interstitial sites. These are –

- Route of administration
- Size and surface characteristics of particles
- Formulation medium
- The composition and PH of the interstitial fluid and disease within the interstitium

The direct delivery of drugs into lymphatics has been proposed as a potential approach to kill malignant lymphoid cells located in lymph nodes.

II. CONCLUSION:

Targeted drug delivery system is a new approach intended for delivery of drug molecules to a specific site or organ within the body. The toxicity of the drug is decreased by targeting a specific site. It also results in reduction of dosing frequency. Though it has various minimal disadvantages but it will be more useful in the treatments of specific disease like cancer. Currently the scope of use and advancement of this specific targeting drug delivery is on another level of progress. Hopefully through advancement of this technique, the demerits or disadvantages will be reduced and it will be more useful in the upcoming years.

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