



AMERICAN JOURNAL OF PHARMTECH RESEARCH

Journal home page: <http://www.ajptr.com/>

A Review On Targeted Drug Delivery

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ABSTRACT

The main aim of this review article is to introduce the basic concepts of drug targeting as they have evolved over previous decades. The most important chemical features and biological behavioral characteristics of the carrier molecules exploited for drug targeting purposes will be addressed. Targeted drug delivery is also known as smart drug delivery. This is self-contained, discrete dosage form which is applied to intact skin, at a controlled rate to the systemic circulation. In this system medicament given to a patient in a manner that increases the concentration of the medication in some parts of the body relative to others. System involves nanoparticles-mediated drug delivery in order to reduce drawback of conventional drug delivery. Active and passive targeting are two types of methods used for targeted drug delivery. Targeted drug delivery has some side advantages like reduces side effects, avoid hepatic first pass metabolism, enhance drug absorption, dose is less as compare to conventional drug delivery, reduced fluctuation in circulating drug levels etc. Brain targeted drug delivery system and tumor targeted drug delivery system are most widely used. Many drug carriers are used in this advanced drug delivery system are lipoprotein, liposome, micelles and immune micelles. The goal of targeted drug delivery system is to prolong, localize, target and have a protected drug interaction with disease tissues.

Keywords: - Nanoparticles, Brain targeted drug delivery system, Normal cell and cancerous cell.

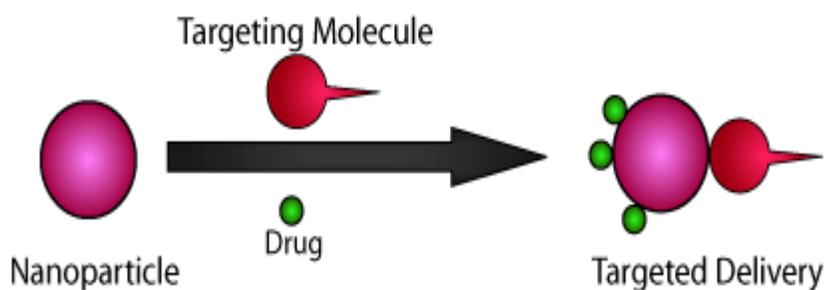
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Received 01 June 2018, Accepted 26 June 2018

Please cite this article as: Nagoba SN *et al.*, A Review On Targeted Drug Delivery. American Journal of PharmTech Research 2018.

INTRODUCTION

The conventional drug delivery system involves the absorption of the drug across a biological membrane, whereas the targeted release system releases the drug in a dosage form. Targeted drug delivery is a special form of drug delivery system where the medicament is selectively targeted or delivered only to the site of action and not to the non-targeted organs or tissues or cells. The system is based on a method that delivers a certain amount of a therapeutic agent for a prolonged period of time to a targeted diseased area within the body and improves the efficacy and reduces the side effect. This helps maintain the required plasma and tissue drug levels in the body, thereby preventing any damage to the healthy tissue via the drug. Carriers used should be biodegradable or readily eliminated from the body without any problem. The preparation of the targeted drug delivery system should be simple, reproducible and cost effective. Targeted drug delivery has high solubility and more drug stability as compared to conventional drug delivery. Conventional drug delivery has poor absorption, shorter half-life and requires a large volume of distribution, these problems are reduced in targeted drug delivery.

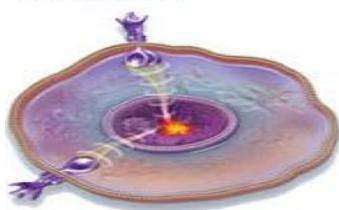


Difference between normal cell and cancer cell

Sr. no	Normal cell	Cancer cell
1	Normal cells are small uniformly shaped nuclei.	Cancer cells are variable shaped nuclei.
2	It contains large cytoplasmic volume.	It contains small cytoplasmic volume.
3	It has low level of dividing cells.	It has high level of dividing cells.
4	Normal cells have definite size and shape.	Cancer cells have variation in their size and shape.
5	Normal cells are arranged in discrete tissues.	Cancer cells show disorganized arrangement of cells.
6	It contains single nuclei.	It contains multi nuclei.
7	It contains normal chromosomes.	It contains abnormal chromosomes.
8	Normal pH	Low intracellular pH
9	Lymphatic drainage developed in normal cells.	Impaired lymphatic drainage developed in cancer cells.

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Normal cell



Example of one type of abnormal or cancerous cell

**Ideal characteristics of Targeted drug delivery system are**

- It should be non-toxic and Non-immunogenic.
- It should be physically and chemically stable in vivo and in vitro.
- They control the drug distribution to target cells or tissues or organs.
- Must have uniform capillary distribution.
- Convenient and predicate rate of drug release.
- Drug release does not influence the drug action.
- Curative amount of drug release.
- Minimal drug leakage during transfer.
- 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.

Advantages of Targeted drug delivery system

- Drugs deliver / releases over extended period of time.
- Intermittent dosing can be avoided.
- Improve patient compliance.
- Reduce inter and intra-patient variability.
- Drug can be administered in a smaller dose to produce the desired side effect.
- No peak and valley plasma concentration.
- Toxicity is reduced by delivering drug at the targeted site.
- Self administration is possible.
- Enhance absorption of drug.

Disadvantages of targeted drug delivery system

- Requires a skill in manufacturing storage, administration.
- Diffusion and redistribution of drug release.

- Rapid clearance of targeted systems.
- Maintaining stability of dosage form is difficult.
- Highly sophisticated technology requires for formulation.
- Expensive.
- Yields comparatively very less.

Biological processes and events involved in drug targeting^{7,8,9}

- Cellular uptake and processing
- Transport across the epithelial barrier.
- Extravasation.
- Lymphatic uptake.

Cellular uptake and processing

Macromolecular assemblies hence cannot enter by such simple process hence take up by a process called endocytosis. Cellular uptake and processing involve two Steps are

- Internalization of the plasma membrane,
- Concomitant with engulfment of extracellular material.

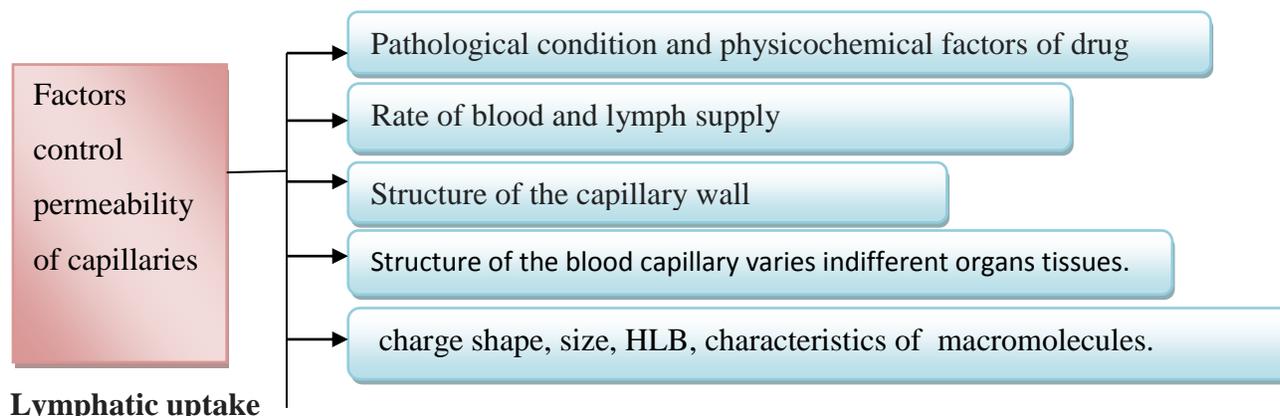
Pinocytosis is universal phenomenon as compared to phagocytosis. Fluid phase pinocytosis capture's molecule is comparatively slower as compare to phagocytosis and it is directly proportional to the concentration as well as size.

Transport across the epithelial barrier.

One or more layers of epithelial cells lined internally in the oral, buccal, nasal, vaginal and rectal cavities. Low molar mass drug cross epithelial barrier by passive diffusion and selective and non selective endocytosis. Polar material diffuse through tight junction of epithelial cells. Passive transport is usually higher in injured mucosa where as active transport depends on structural integrity of epithelial cells.

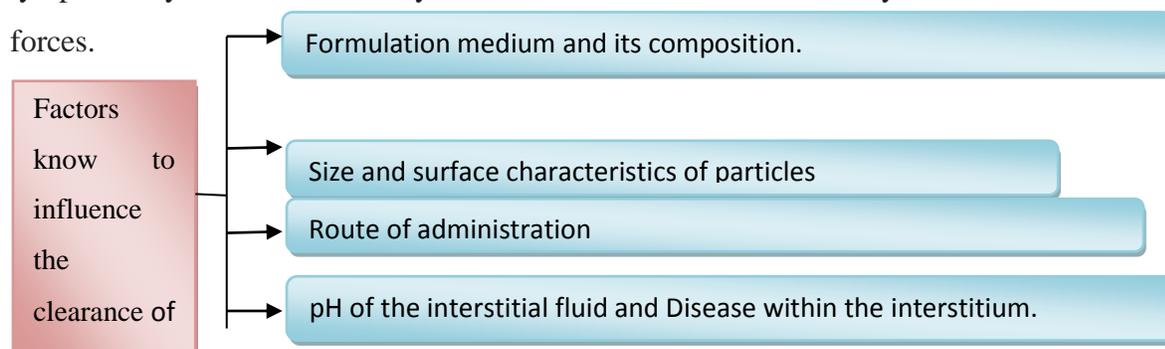
Extravasation:-

Dysfunction of cells located outside the cardiovascular system leads to many diseases therefore a drug to exert its therapeutic effects it must depart from the central circulation this process of trans vascular exchange is called Extravasation which is governed by blood capillary walls.



Lymphatic uptake

After extravasation drug molecules can either reabsorb into the blood stream directly or enter into the lymphatic system and arrival with the lymph to the blood circulation. Also drugs administered by subcutaneous intracellular transdermal peritoneal routes can reach the systemic circulation by lymphatic system. It is directly related difference between the hydrostatic as well as osmotic forces.



Brain targeted drug delivery system^{10,11,12}

The brain is the most versatile and sophisticated organ in the body and is protected by a very effective barrier as Blood Brain Barrier (BBB) and Blood Cerebrospinal Fluid Barrier (BCSFB). More than 98% of small molecular weight drugs and practically 100% of large molecular weight drugs like peptides and proteins developed for CNS pathologies do not readily cross the BBB. In the treatment of diseases or situation that results from the lack of simple hormones and peptides administration of drugs in a controlled manner provides effective managing of disease and therapy. In case of treating fatal CNS disease, such as brain tumors, HIV encephalopathy, epilepsy, cerebrovascular disease and neurodegenerative disorders is particularly challenging because a variety of difficult obstacles often delay drug delivery to brain and spinal cord. So drug targeting to brain is essential to increase treatment efficacy and it also reduces toxicity due to localizing drug at the desired site of action.

Barriers to CNS Drug Delivery

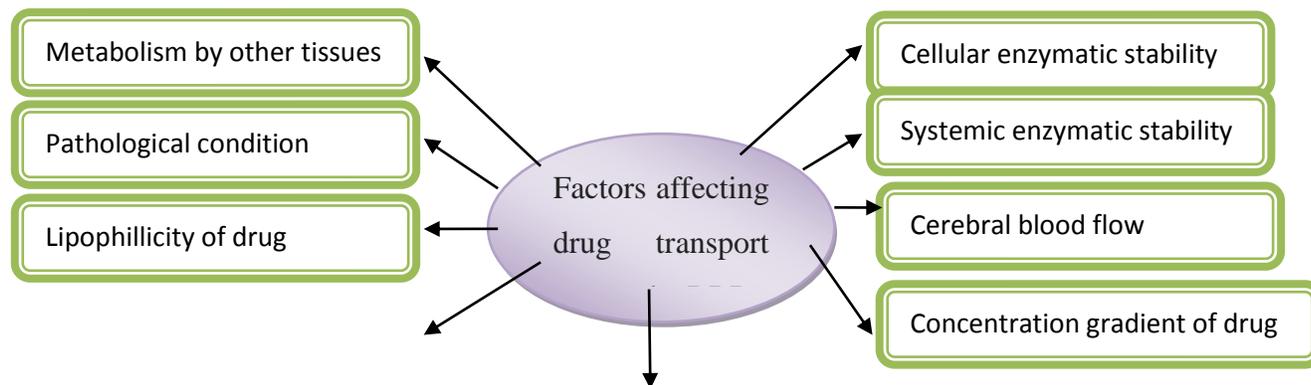
The failure of drugs in the effective treatment of many CNS diseases can be rationalized by considering a number of barriers that inhibits drug delivery to the CNS are Blood Brain Barrier (BBB)

BBB consist of Basal membrane and brain cells, such as pericytes and astrocytes, surrounding the endothelial cells which maintain enzymatic and physical barrier of brain. Capillaries of the vertebrate brain and spinal cord lack pore and are lined with a layer of special endothelial cells that lack fenestrations and are sealed with the tight junctions.

Blood-Cerebrospinal Fluid Barrier (BCSFB)

The epithelial cells have an arrangement in such a manner that it prevents the entry of molecules. The CSF freely exchange molecules with the extracellular fluid of brain, parenchyma, delivering drugs into the CSF could theoretically result in therapeutic CNS drug concentrations.

Factors affecting drug transport across the BBB.



Approaches to CNS drug delivery

A. Invasive approaches or neurosurgical approaches

- Intra cerebro ventricular (ICV) infusion
- Convection-enhanced delivery (CED)
- Intra-cerebral injection or implants
- Disruption of the BBB.

B. Non-invasive

- Chemical techniques
 - a. Prodrug
 - b. drug conjugate
- Colloidal Techniques
 - a. Nano particles
 - b. Liposome

C. Miscellaneous techniques a. Intranasal delivers

A. Invasive approaches or neurosurgical approaches

It involves placement of a biodegradable chemotherapeutic impregnated pellets into tumor restriction area. Drug added to polymer and compressed to form pellets. These are implanted intracranially through which drug bypass the BBB and release drug molecule locally to the brain in the sustained fashion.

Intra-cerebroventricular (ICV) infusion

Intra cerebro ventricular infusion one strategy for bypassing BBB intra-ventricular infusion of drug directly into the CSF. Drug solution can be subcutaneously injected into the implanted reservoir and delivered to the ventricles manual compression of the reservoir through the scalp.

BBB Disruption: - disruption makes tight junction between the endothelial cells of the brain capillaries leaky. The BBB can be transiently disrupted by a variety of techniques such as osmotic disruption technique. MRI guided focused ultrasound BBB.

Convention enhanced delivery: - it involves insertion of a small caliber catheter into the brain parenchyma. Through this catheter, infusate is actively pumped into the brain parenchyma and penetrates in the interstitial space.

B. Non-invasive techniques:-

This technique usually interrelated to drug manipulation which may include alternation as prodrugs, lipophilic analogues, chemical drug delivery, carrier mediated drug delivery, receptor mediated drug delivery etc.

• **Chemical techniques:** - it improves some deficient physiological property such as membrane permeability. Chemical methods involve the chemical transformation of drugs by changing the various functionalities.

Prodrug¹³: - Prodrug which is lipid soluble and can cross the BBB. Prodrug is pharmacologically inactive compounds that results from transient chemical modification of biologically active species. It is metabolized within the brain and converted to the parent drug. Prodrug is used to improve gastrointestinal tolerance, increase in systemic availability, and improve solubility, taste and shelf life.

Examples levodopa, GABA, Niflumic acid, valproate.

Drug conjugates: - it involves caging of compounds within glycosyl, maltosyl, diglucosyl and dimaltosyl derivatives of cyclodextrin. The therapeutic complexes comprise of an omega 3-fatty acid such as alpha linolenic acid, eicosapentaeoic acid and their derivatives.

Colloidal Techniques

Nano particles¹⁴: - Nano particles are micronized solid colloidal particles prepared of polymeric materials ranging in size from 1-1000 nm. It is used as carrier systems in which the drug is dissolved, entrapped, encapsulated, adsorbed or chemically linked to the surface. Systems in CNS targeted drug therapy supply better penetration of therapeutic and diagnostic agents, and a reduced risk in comparison to conventional treatments. Nano particles are used to deliver drugs through oral, nasal, parenteral, intra- ocular etc. Through Nano particles particle size can be easily altered resulting in attaining both active and passive drug targeting after parenteral administration became the most advantageous in the treatment of many chronic diseases.

Liposome¹⁵: - liposomes are colloidal, vesicular structures composed of one or more lipid bilayer surrounding an equal number of aqueous compartments. A free drug injected in blood stream typically achieves therapeutic level for short duration due to metabolism and excretion. Drug encapsulated liposome achieves therapeutic level for long duration. Liposomes are biodegradable and essentially non toxic vesicles can encapsulate both hydrophilic and hydrophobic materials and are utilized as drug carrier in drug delivery system. Many liposome- based DNA delivery systems have been described, including molecular components for targeting given cell surface receptors or for escaping from lysosomal compartment.

Tumor targeting drug delivery

A specific interaction between drug and its receptor at the molecular level. A rapidly growing tumor requires various nutrients and vitamins. Tumor cells express many tumor specific receptors which can be used as target to deliver cytotoxic agent into tumors. Tumor targeting improve the drug chemotherapeutic index by

- a. preferentially localizing its pharmacological activities at the site of action cellular concentration.
- b. recognition and interaction with target cell.
- c. achieving cellular concentration so as to exhibit therapeutic response.

Tumor targeting is classified in different ways by pioneers of the area. It is classified as active and passive targeting.

Active targeting: -

Active targeting is also known as receptor mediated targeting. It is widely used for cancer treatment. Cancer sequence is characterized by a vast variation at tissue and cellular level which include abnormal growth, change in the cells extracellular matrix and blood vessels. Some conditions like over expression of receptor at tumor acidity, hypoxic tumor environment are

utilized to target chemotherapeutic agent to tumor cells. The main mechanism behind active targeting is to recognition of ligand by its target substrate. Representative ligand includes antibodies, protein peptide, nucleic acids sugars and small molecules such as vitamins. Receptor includes epidermal growth factors; vascular epithelial growth factors and transferrin are used in targeted drug delivery in cancer cells.

Active targeting moieties

Monoclonal antibodies recognize the protein or antigen on the surface of the cancer cell and lock into it. Some most exploited targets for antibody targeting are; Transferrin receptors: - high level of transferring receptor on glioma cells. Fibronectin: - expressed in the around neoplastic blood vessels during angiogenesis. Epidermal growth factors receptor: - over expressed in the portion of breast cancers and other solid tumors.

Vascular endothelial growth factor: - expressed in neoplastic blood vessels.

Passive targeting: -

Passive targeting involves therapeutic exploitation of the natural distribution pattern of a drug-carrier construct in vivo. Passive targeting is based on drug accumulation in the areas around the tumors with leaky vasculature; commonly referred to Enhanced Permeation and Retention (EPR) effect. Enhanced permeability and retention effect provide accumulation of nanoparticles at the tumor site at high concentration due to pathological difference between normal tissues and tumor tissues this phenomenon is called as passive targeting. Pathophysiological environment of tumor tissues differ from normal tissues, leading to EPR effect, which is utilized for the targeted delivery systems. Irregular tumor vasculature structure and lack of lymphatic recovery system in the solid tumor provide high drug concentration at the tumor site. Optimum EPR efficiency could be obtained with Nano particles with sizes around 400 nm. Role of lymphatic system in passive tumor targeting are

- Inside of tumor tissues no functional lymphatic system.
- Pressing force from the growing tumor cells and lacks of internal balancing pressure cause the collapse of tumor lymphatic system.
- Retention of high molecular weight molecules in tumor.

Application of targeted drug delivery system

- Targeted drug delivery is utilized to treat many diseases, such cardiovascular diseases and diabetes. Regenerative technique is developed to cure various diseases. The development of a number of regenerative techniques in recent year for curing heart diseases.

- Targeted drug delivery is also used in the stem cell therapy. This therapy helps to regenerate myocardium tissue and return the contractile function of heart by creating a microenvironment before myocardial infarction.
- Liposome is used in the treatment of tuberculosis. Chemotherapy is used for treatment of tuberculosis but it is not effective. Liposome shows better microphages penetration and optimum concentration at the targeted site.
- It is also used in 3 D printing to investigate how to target cancerous tumor. By printing a plastic a plastic 3 D shape of tumor and filling it with drug and show therapeutic effect at a targeting location of the drug.
- Detection of proteins
- Bio detection of pathogens.
- Tissue engineering.
- MRI contrast enhancement.
- Drug and gene therapy.
- Probing of DNA structure.
- Drug discovery

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