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Targeted Drug Delivery System

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ABSTRACT
Drug targeting is a new advanced and smart method of drug delivery system that aims to deliver the drug to the target site of action or site of absorption without releasing the drug at any other non-target site. The targeted drug delivery systems have several advantages over conventional ones as improvement of pharmaceutical activity, low side effects and reduction of the administered dose. Targeting of drugs also help us to bypass first pass metabolism so a drug can be administered in a form such that it reaches the receptor sites in sufficient concentration without disturbing in extraneous tissue cells. The main purpose of the targeted drug delivery system is to obtain the pharmacological action of the therapeutic agent at diseased organs only without affecting the healthy one especially in the case of cancer treatment with chemotherapeutic agents. Drug targeting can be attained using different carriers that maintain and transport the intact drug to preselected organ or tissue. Different types of carriers can be used for drug targeting such as nanotubes and nanowires, nanoshells, quantum dots, nanopores, gold nanoparticles, dendrimers, noisome, ufasomes, virosomes, cubosomes, nanobots and transferosomes. There are different mechanisms of drug targeting such as passive targeting, inverse targeting, active targeting, ligand-mediated targeting, physical targeting, dual targeting and double targeting. The drug targeting is a useful delivery system for delivering the therapeutic agent to a specific site without causing toxicity in other organs.

KEY WORDS: Targeted drug delivery, nanoscience and nanotechnology, strategies of drug targeting, drug delivery carriers, nanomedicine.

I. INTRODUCTION

The concept of designing targeted delivery system has been originated from the Paul Ehrlich, who was a microbiologist, proposed the idea of drug delivery in the form of magic bullet. Targeted drug delivery is an advanced method of delivering drugs to the patients that increases the concentration of delivered drug to the targeted body part of interest only (organs/tissues/ cells).

The minimum distribution of the parent drug to the non target cells with higher and effective concentration at the targeted site certainly maximize the benefits of targeted drug delivery.

The targeted drug delivery system must have certain properties which include: [1]

1. It should be stable, safe (non-toxic), compatible with body fluid and biodegradable.
2. Deliver the drug only to the target site.
3. Control the drug release at a predetermined rate.
4. The rate of drug release not affecting the pharmacological effect.
5. Minimum leakage of the drug during transportation to the target site.
6. Using an inert, biodegradable, or easily eliminated carrier.
7. The preparation process of the drug delivery system should be simple, easy and costless.

Targeted drug delivery system is preferred over conventional drug delivery systems due to three main reasons. The first being pharmaceutical reason. Conventional drugs have low solubility and more drug instability in comparison to targeted drug delivery systems. Conventional drugs also have poor absorption, shorter half-life and require large volume of distribution. These constitute its pharmacokinetic properties. The third reason constitutes the pharmacodynamic properties of drugs. The conventional drugs have low specificity and low therapeutic index as compared to targeted drug delivery system. Due to these reasons targeted drug delivery system is preferred over conventional drug delivery systems.

The advantages of drug targeting:[2]

1.The protocol of drug administration becomes simpler

2. The toxicity of the drug is decreased by targeting a specific site.

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3. The desired drug response can be reached by a small dose.
4. Avoid the first-pass effect.
5. Improvement in the drug absorption from the target site.
6. Drug targeting resulted in no peak and valley plasma concentration

The disadvantages of drug targeting:[3]

1. Rapid drug elimination from the body results in high dose frequency.
2. The carrier of the targeted drug delivery system may result in the immune response.
3. The drug delivery system is not localized at the tumor tissue for sufficient time.
4. The diffusion and redistribution of released drugs.
5. The manufacturing, storage and administration of the targeted drug delivery system require high expertise in this field.
6. Toxicity may be raised from drug deposition at the target site.
7. The stability of the product will be difficult to be attained

II. COMPONENTS OF TARGETED DRUG DELIVERY

A drug delivery system primarily constitutes a target and drug carriers or markers. Target means specific organ or a cell or group of cells, which in chronic or acute condition need treatment. Route of administration involves drug carrier as a important targeting moiety and after its leakage from its carrier/markers to reach the drug to the specific or targeted site via biological metabolism with its clearance as well as not to reach at non targeted site to make this delivery system more site specific with reduced side effects of drugs and its quantity too. Carrier is one of the special molecule or system essentially required for effective transportation of loaded drug up to the pre-selected sites. These 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.[4-6].

III. STRATEGIES FOR DRUG TARGETING

Drug targeting to an area of interest within the body essentially helps to increase the therapeutic effectiveness and to reduce the toxicity of the drug. As depicted in Fig. (1), there are basically six strategies used for drug targeting to the desired organ/tissue of interest. These six strategies are Passive Targeting, Active Targeting, Inverse Targeting, Physical Targeting, Dual Targeting and Double Targeting.

Figure 1: Different Strategies of Drug Targeting.

1. Passive targeting

It refers to the accumulation of drug or drugcarrier system at a specific site such as anti-cancerous drug whose explanation may be attributed to physicochemical or pharmacological factors of the disease. Hence, in case of cancer treatment the size and surface properties of drug delivery nano-particles must be controlled specifically to avoid uptake by the reticulo-endothelial system (RES) to maximize circulation times and targeting ability.The bottom line is called passive targeting as misnomer which is simple drug delivery system via blood circulation. Drug release or drug actions are limited to selective sites within the body such as a tumour but not the liver.Other examples include targeting of antimalarial drugs

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for treatment of leishmiansis, brucellosis, candiadsis [5]

2. Active targeting

Active targeting means a specific ligand–receptor type interaction for intracellular localization which occurs only after blood circulation and extravasations. This active targeting approach can be further classified into three different levels of targeting which are

1) First order targeting refers to restricted distribution of the drug carrier systems to the capillary bed of a predetermined target site, organ or tissue e.g. compartmental targeting in lymphatics, peritoneal cavity, plural cavity, cerebral ventricles and eyes, joints.

2) Second order targeting refers to selective delivery of drugs to specific cell types such as tumour cells and not to the normal cells e.g. selective drug delivery to kupffer cells in the liver.

3) Third order targeting refers to drug delivery specifically to the intracellular site of targeted cells e.g. receptor based ligand mediated entry of a drug complex into a cell by endocytosis.[7]

3. Inverse targeting

When the passive uptake of colloidal carrier is avoided by Reticulo Endothelial Systems (RES) the process is called inverse targeting of drugs. In order to achieve this, regular function of the RES is suppressed by pre-injecting a large amount of blank colloidal carriers or macromolecules such as dextran sulphate. This approach facilitates the saturation of RES and suppression of defense mechanism. This type is commonly considered as an effective approach to target drug(s) to non-RES organs of the body.[8]

4. Physical targeting

Physical targeting utilizes some characteristics of environment conditional changes like pH, temperature of the system, light intensity, magnetic field, electric field or ionic strength and other small and even specific stimuli like glucose concentration or gaseous concentration are used to localize the drug carrier to predetermined site. [9]

This approach is the most preferred one in nanoparticulate drug targeting to tumors as well as in cytosolic delivery of entrapped drug or genetic materials. This is because these physical factors can indeed help control release of the drug at the site of the cancer

5. Dual targeting

In this 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[10]

6. Double targeting

When temporal and spatial methodologies are combined to target a 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.

IV. TYPES OF CARRIERS FOR DRUG TARGETING

The design and development of potential carriers for cell-specific delivery of therapeutics should be based on recognition sites on the surface of target cells as well as on insight into the internalization and further cellular disposition of such macromolecules. The choice of carrier system to be used in drug targeting strategies depends on which target cells should be reached and what drug needs to be delivered.

Different Type of drug carrier: drug carrier can be Liposomes, Monoclonal Antibodies and Fragments, Modified (Plasma) Proteins, Soluble Polymers, Lipoproteins, Microspheres and Nanoparticles, Polymeric Micelles, Cellular Carriers etc.

1. Liposomes

Liposomes are small artificially designed vesicles composed of phospholipid bilayers surrounding with the size ranging from 20 to 10 000 nm. Many liposome formulations are rapidly taken up by macrophages and this can be exploited either for macrophage-specific delivery of drugs or for passive drug targeting which allow slow release of the drug over time from these cells into the general circulation. Cationic liposomes and lipoplexes have been extensively researched for their application in non-viral vector mediated gene therapy [11]

Fig.2: Charged liposomes as drug delivery system10

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2. Monoclonal Antibodies and Fragments

Since the development of monoclonal antibodies by Köhler and Milstein in 1975, the monoclonal antibodies have proven its edge over the others in antibody therapy for disease. From the last 2 decates, the number of pre-clinical and clinical studies associated with monoclonal antibodies and derivatives have seen a tremendous growth. The majority of strategies based on antigen recognition by antibodies have been developed for more specifically for cancer therapy. These strategies are mostly aimed at tumor associated antigens being present or in more specific term expressed by tumor cells. Antibody drug conjugates (ADC) combine a drug with a monoclonal antibody which provides selective targeting for tumoral cell masses or lymphomas.

The drug is released by enzymatic cleavage of the linker under physiological conditions.Onesuchexample of ADC is Mylotarg (gemtuzamabozogamicin), was approved by the FDA, but later voluntarily withdrawn from the US market.

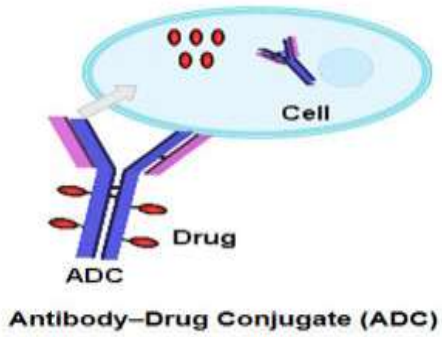

Fig. 3: Antibody- drug conjugate

3. Modified (Plasma) Proteins

Modified plasma proteins can be intelligent carriers for drug targeting as they are soluble molecules with a relatively small molecular weight. They can easily be modified by the attachment of different molecules like peptides, sugars, and other ligands, as well as drugs of interest makes them a suitable mode of drug delivery. In the case of liver cell targeting, extensive modifications of protein backbones such as albumins have been carried out effective delivery of the drug. [12]

4. Soluble Polymers

Soluble synthetic polymers have been extensively researched as versatile drug carrier systems. Polymer chemistry allows the development of tailor made conjugates in which target moieties as well as drugs can be entrapped into the carrier molecule. In such a case enhanced bioavailability is seen. As it is not desirable that the product gets adhered to cells, excessive charge or hydrophobicity should be avoided in the design of polymeric carriers. For cancer therapy, the well established (-2- hydroxypropyl) methacry lamide (HMPA) polymers have been extensively studied. Also it provide a solution for selective and targeted chemotherapy.

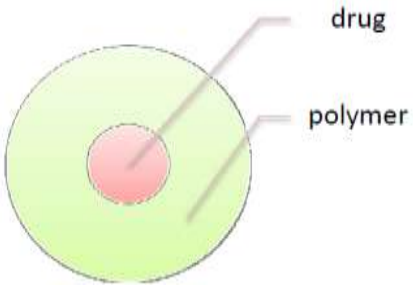

Fig. 4: Drug entrapped in a polymer

Thin films of polymers from natural resources like cellulose have also been studied and is in use forapplications in pharmaceutics, medical devices, packaging and food products. The barrier films alsoreduces gas transport through a package or control drug delivery from a tablet. Certain Cellulosederivatives show also show promising results as toextend the release of drugs. [13, 14]

5. Lipoproteins

Lipid particles such as LDL and HDL containing a lipid and an apoprotein moiety is termed as ‘natural targeted liposomes’. The lipid core can be used to incorporate lipophilic drugs or lipophilic pro-drugs, it does not require covalent bonding with the drug. The apolipoprotein moiety of these particles can be glycosylated or modified with other (receptor) targeting ligands. Modifications at the level of glycolipid incorporation can be used to introduce new targeting moieties. Same with the condition as liposomes, the size and charge of the particles determine their behaviour in vivo. Large particles will not easily pass through the blood brain barrier. The majority of the research on the use of LDL and HDL particles has been devoted to the targeting of drugs to the liver. [15]

6. Microspheres and Nanoparticles

Microspheres and nanoparticles consists of biocompatible polymers and belong either to the soluble or the particle type carriers. Besides the aforementioned HPMA polymeric backbone, carriers have also been prepared using dextrans,

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ficoll, sepharose or poly-L-lysine as the main carrier body for the drugs. Recently alginate nanoparticles have been described for the targeting of antisense oligonucleotides. As with other polymeric carrier systems, the backbone can be modified with e.g. sugar molecules or antibody fragments to introduce cellular specificity. Nanoparticles are smaller (0.2– 0.5 μm) than microspheres (30–200 μm) and may have a maller drug loading capacity than the soluble

7. Polymeric Micelles

Polymeric micelles have characterstic core-shell structure. They have a bi-block structure with a hydrophilic shell and a hydrophobic core. The hydrophobic core consists of a biodegradable polymer that serves as a reservoir for an insoluble drug. Non- or poorly biodegradable polymers can be used, as long as they are not toxic to cells and can be secreted through urine or faeces. If a water-soluble polymeric core has to be used, it should be hydrophilic and should have chemical conjugation with a hydrophobic drug. The viscosity of preparation greatly influence the physical stability of the micelles as well as drug release. The biodistribution of the micelle is mainly depends on the nature of the shell and also on micelle stabilization and interactions with plasma proteins and cell membranes. The micelles may contain functional groups at their surface for conjugation with a targeting moiety. Polymeric micelles are mostly small (10–100 nm) in size and drugs can be incorporated by chemical conjugation or physical entrapment. For efficient delivery of the desired drug, they should maintain their integrity for a sufficient amount of time after injection into the body. It has been widely utilized for targeting anticancer drugs to tumors. [16,17]

8. Cellular Carriers

Cellular carriers have an advantage for their natural biocompatibility. However, they may pass through endothelial barriers and can rather easily invoke an immunological response. Most of the research on cellular carriers has been applied to the field of cancer therapy. Antigen specific cytotoxic T lymphocytes have been studied as vehicles to deliver immunotoxins to cancer cells in vivo.

V. CONCLUSIONS

Many problems which appeared during the development of drug targeting strategies for clinical application for different types of therapies have been identified, analyzed and solved. A specific area of which belongs in the treatment of cancer therapy. Several such preparations have entered the phases of clinical testing and/or have now been marketed. However, such strategies should be subjected to continuous evaluation in the light of advances in the understanding of the numerous processes occurring in response to administration of the carriers and/or the drugs. New strategies under investigation should periodically undergo evaluation, taking advantage of the 'bench to bed-side' experience available today. Furthermore, in the coming years, combining expertise in the drug targeting field with the technological developments in molecular biology and molecular medicine will facilitate the elucidation of the cellular and molecular processes underlying disease.

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