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Review Article

A Review on Basic Concept of Drug Targeting and Drug Carrier System

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ABSTRACT

Targeted drug delivery system as the name suggests is a science of specifying the drug moiety to targeted area. This type of delivery system is at par with the traditional drug delivery system as only a targeted area like cancer cells, kidneys, liver etc. have been targeted though this method. Despite that the researchers have faced extreme challenges to master the craft of targeted drug delivery system and also the cost of development of a single product available in the market, a vast number of positive aspects can be seen. In this review, some basic concepts of this system has been discussed, also a brief of the type of drug carrier used in formulating such a dosage form is mentioned. A list of approved and marketed formulation like Liposomal daunorubicin, Liposomal cytarabine, Liposomal amphotericin B, Liposomal amphotericin B, etc has been discussed in relevant places.

Keywords: drug targeting, drug carrier system, cancer.

INTRODUCTION

Target drug delivery system may also be referred to as smart drug delivery system[1]is the currently used form of drug delivery system where the pharmacologically active drug (or pro-drug in some cases) is targeted or is delivered specifically to the site of action. Targeted drug delivery extensively used for selective and effective localization of pharmacologically active moiety at pre-determined target in therapeutic concentration, while restricting its access to non-target normal cellular linings, thus minimizing toxic effects and maximizing therapeutic index. 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.

Products based on such a delivery system are being prepared by considering the Specific properties of target cells, Nature of markers or transport carriers or vehicles, which convey drug to specific receptors. and Ligands and physically modulated components.

Ideally targeted drug delivery system should have following characteristics:

- Should be biochemically inert (non-toxic)
- Should be non-immunogenic.
- Should be physically and chemically stable in vivo and in vitro conditions.
- Should have restricted drug distribution to target cells or tissues or organs and should have uniform capillary distribution.
- Should have Controllable and predictable rate of drug release and also Drug release should not affect the drug action.
- Should have therapeutic amount of drug release.
- Should have minimal drug leakage during transit.
- Carriers used should be bio-degradable or readily eliminated from the body without any problem.
- The preparation of the delivery system should be easy or reasonably simple, reproductive and cost effective.

Inspite of many complications and failures in the development of such a system like Rapid clearance of targeted systems, Immune reactions against intravenous administered carrier systems, Insufficient localization of targeted systems into tumour cells and Diffusion and redistribution of released drugs to name a few the advantages of drug targeting is the simplified protocols of Drug administration, reduced Drug quantity hence it affects the cost of therapy and also Drug concentration in the required sites can be sharply increased without negative effects on non-target compartments.

Different types of drug targeting

As discussed, targeting drug to a specific area not only increases the therapeutic efficacy of drugs also it aims to decreases the toxicity associated with drug to allow lower doses of the drug to be used in therapy. For the fulfillment of such conditions, two approaches are used extensively (also known as classification of drug targeting)

- passive targeting
- active targeting

1.Passive targeting: it refers to the accumulation of drug or drug-carrier system at a particular (like in case of anti-cancerous drug) site whose explaination 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 reticuloendothelial system (RES), to maximize circulation times and targeting ability. For attaining such conditions the optimal size should be less than 100 nm in diameter and the surface should be hydrophilic to circumvent clearance by macrophages (large phagocytic cells of the RES)[2] Other examples include targeting of anti-malarial drugs for treatment of leishmiansis, brucellosis, candiadsis

2.Active targeting : Active targeting includes specific modification of a drug/drug carrier nano systems with active agents having selective affinity for recognizing and interacting with a specific cell, tissue or organ in the body .in case of cancer, it is achieved by conjugating the nanoparticle to a targeting component that provides preferential accumulation of nanoparticles in the tumor-bearing organ,totumor, individual cancer cells, intracellular organelles, or specific molecules in cancer cells. Such an approach is based on specific interactions such as lectin-carbohydrate, ligand-receptor, and antibody-antigen.[3]

Fig.1: drug targeting in case of cancer

This active targeting approach can be further classified into three different levels of targeting.

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. Example includes compartmental targeting in lymphatics, peritoneal cavity, plural cavity, cerebral ventricles, eyes, joints, etc.

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

3. Third order targeting: it is defined as 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.

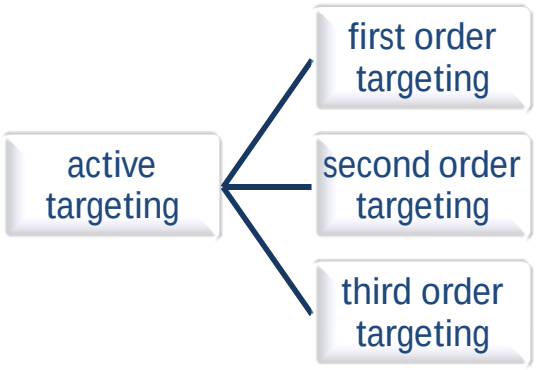

Fig. 2: Types of drug targeting

Drug carrier

Drug carrier or sometimes also referred to as drug vectors are the most important entity required for successful transportation of the loaded drug. Drug vectors transports and retains the drug and aims deliver it within or in the vicinity of target. They are made capable of performing such specific functions which can be attributed by slight structural modification.[4]

Characteristics of an ideal drug carrier[4,5]

An ideal drug carrier should be able to cross blood brain barriers and in case of tumour chemotherapy tumour vasculature. It must be recognized by the target cells specifically and selectively and must maintain the specificity of the surface ligands. The drug ligand complex should be stable in plasma, interstitial and other biofluids. The carrier used should be non-toxic, non-immunogenic and biodegradable. After recognition and internalization, the carrier system should release the drug moiety inside the target organs, tissues or cells. The biomodules used as carrier should not be ubiquitous (existing or being everywhere at the same time).

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. selection and type of drug carrier depends mainly on the type of drug, targeted area to which the drug action is desired and type of disease in which the system is being used. Targeting Moieties includes antibodies, lectins and other proteins, Lipoproteins, Hormones, Charged molecules, Polysaccharides and Low-molecular-weight ligands

Liposomes

Liposomes are small artificially designed vesicles composed of phospholipid bilayers surrounding one or several aqueous compartments[6,7]. Liposomes are of different types like

- Multilamellar vesicle (MLV)
- Small unilamellarvesicle (SUV)
- Large unilamellar vesicle (LUV)
- Cochleate vesicle[8]

Charge on the liposomes, lipid composition and size (ranging from 20 to 10 000 nm) can be varied and these variations strongly affect their behaviour in vivo. 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, allowing 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. [9]

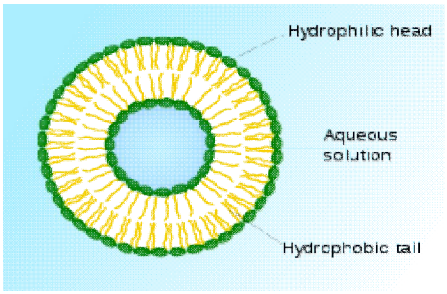

Fig. 3: Structure of liposomes

A new variety of liposomes known as 'stealth' liposomes has recently been developed by incorporating polyethylene glycol (PEG) which was considered to prevent liposomerecognition by phagocytic cells. Such liposomes have longer circulation times and increased distribution to peripheral tissues in the body.[10]

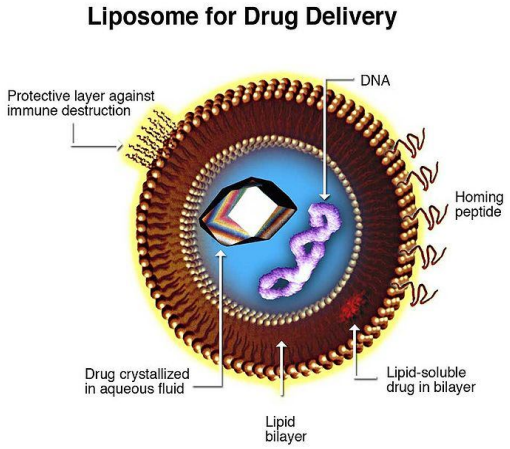

Fig.4: Charged liposomes as drug delivery system[10]

Although liposomes do not easily extravasate from the systemic circulation into the tissues, enhanced vascular permeability during an inflammatory response or pro-angiogenic conditions in tumours can favour local accumulation. Another approach is the design of target sensitive liposomes or fusogenic liposomes that become destabilized after binding and/or internalization to/into the target cells.[8]. Some of the approved liposomal drugs which are available in the market are as follows[11]

Name	Trade name	Company	Indication
Liposomal amphotericin B	Abelcet	Enzon	Fungal infections
Liposomal amphotericin B	Ambisome	Gilead Sciences	Fungal and protozoal infections
Liposomal cytarabine	Depocyt	Pacira (formerly SkyePharma)	Malignant lymphomatous meningitis
Liposomal daunorubicin	DaunoXome	Gilead Sciences	HIV-related Kaposi's sarcoma
Liposomal doxorubicin	Myocet	Zeneus	Combination therapy with cyclophosphamide in metastatic breast cancer
Liposomal IRIV vaccine	Epaxal	Berna Biotech	Hepatitis A
Liposomal IRIV vaccine	Inflexal V	Berna Biotech	Influenza
Liposomal morphine	DepoDur	SkyePharma, Endo	Postsurgical analgesia
Liposomal verteporfin	Visudyne	QLT, Novartis	Age-related macular degeneration, pathologic myopia, ocular histoplasmosis
Liposome-PEG doxorubicin	Doxil/Caelyx	Ortho Biotech, Schering-Plough	HIV-related Kaposi's sarcoma, metastatic breast cancer, metastatic ovarian cancer
Micellularestradiol	Estrasorb	Novavax	Menopausal therapy

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[12]. 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.Another ADC has been submitted for approval and at least 15 antibody conjugates are currently being investigated in clinical trials[13]. The high selectivity greatly reduces the toxic side effects of traditional chemotherapy, and also makes possible the use of newer actives with a high toxicity profile.Also antibodies against other diseases have

been developed for clinical application. Examples are anti-TNFα antibodies for treatment of chronic inflammatory diseases and anti-VEGF (vascular endothelial growth factor), such antibodies inhibits new blood vessel formation or angiogenesis. The advent of recombinant DNA technology had also led to the development of antibodies and fragments that can be synthesized and tailored for optimal behaviour in vivo. Equipping polymer-drug conjugates with target cell specific ligands like EGF and RGD peptides can provide a solution for selective and targeted chemotherapy.

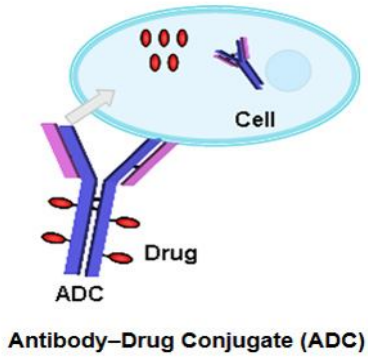

Fig. 5: Antibody- drug conjugate

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[14].

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 establishedN(-2-hydroxypropyl)methacrylamide (HMPA) polymers have been extensively studied. Also it provide a solution for selective and targeted chemotherapy.

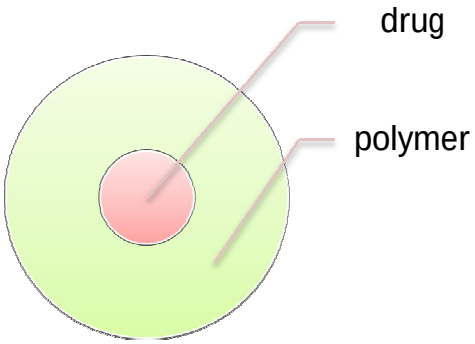

Fig. 6: Drug entrapped in a polymer

Thin films of polymers from natural resources like cellulose have also been studied and is in use for applications in pharmaceutics, medical devices, packaging and food products. The barrier films also reduces gas transport through a package or control drug delivery from a tablet. Certain Cellulose derivatives show also show promising results as to extend the release of drugs[15,16].

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[17].

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, 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

polymers. Formulation of drugs into the nanoparticles can occur at the surface of the particles and at the inner core, depending on the physicochemical characteristics of the drug. The site of drug incorporation significantly affects its release rate from the particle. After systemic administration they quickly distribute to and subsequently become internalized by the cells of the phagocytic system. Even coating of these carriers with PEG does not completely divert them from distribution to the phagocytes in liver and spleen. Consequently, intracellular infections in Kupffer cells and other macrophages are considered a useful target for these systems. Besides parenteral application of microspheres and nanoparticles for cell selective delivery of drugs, they have more recently been studied for their application in oral delivery of peptides and peptidomimetics.[18-22]

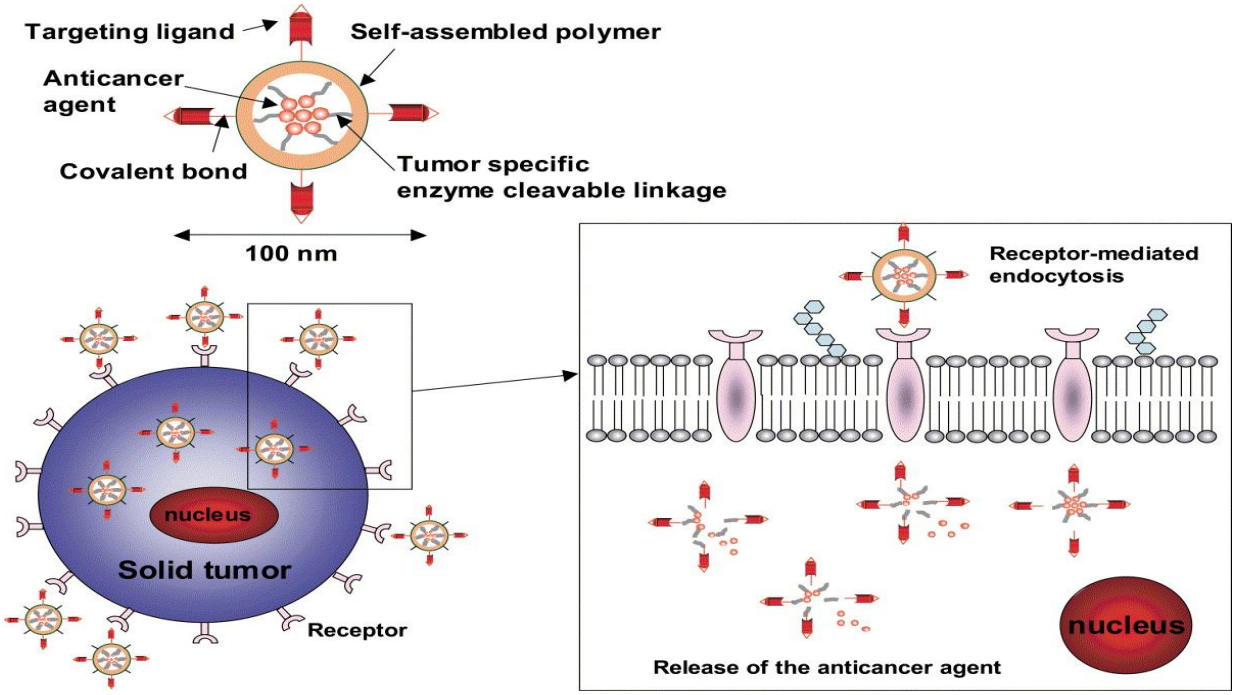

Fig. 7: Action of microspheres on tumor cells

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 bio-distribution 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[23-25]

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.

CONCLUSIONS

Manyproblems 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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