Review Article

A Review on Targeted Drug Delivery: its Entire Focus on Advanced Therapeutics and Diagnostics

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Abstract: Targeted drug delivery is anadvanced method of delivering drugs to the patients in such a targeted sequences that increases the concentration of delivered drug to the targeted body part of interest only (organs/tissues/ cells) which in turn improves efficacy of treatment by reducing side effects of drug administration. Basically, targeted drug delivery is to assist the drug molecule to reach preferably to the desired site. The inherent advantage of this technique leads to administration of required drug with its reduced dose and reducedits side effect. This inherent advantage of targeted drug delivery system is under high consideration of research and development in clinical and pharmaceutical fields as backbone of therapeutics & diagnostics too. Various drug carrierwhich can be used in this advanced delivery system are soluble polymers, biodegradable microsphere polymers (synthetic and natural), neutrophils, fibroblasts, artificial cells, lipoproteins, liposomes, micelles and immune micelle. The goal of a targeted drug delivery system is to prolong, localize, target and have a protected drug interaction with the diseased tissue.
Keywords: Drug delivery; drug carrier system; therapeutics; diagnostics; cancer

INTRODUCTION

Targeted drug delivery is a kind of smart drug delivery system which is miraculous in delivering the drug to a patient. This conventional drug delivery system is done by the absorption of the drug across a biological membrane, whereas the targeted release system is that drug is released in a dosage form [14, 19].

Targeted drug delivery 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. This helps maintain the required plasma and tissue drug levels in the body; therefore avoiding any damage to the healthy tissue via the drug. The drug delivery system is highly integrated and requires various disciplines, such as chemists, biologist and engineers, to join forces to optimize this system.When implementing a targeted release system, the following design criteria for the system need to take into account: the drug properties, side effects of the drugs, the route taken for the delivery of the drug, the targeted site, and the disease [14, 15, 20].

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 systems should be biochemically inert (non-toxic), should be non-immunogenic, should be physically and chemically stable in vivo and in vitro conditions, and should have restricted drug distribution to target cells or tissues or organs and shouldhave uniform capillary distribution. It should have controllable and predictable rate of drug release and also drug release should not affect the drug action. It should have therapeutic amount of drug release and should have minimal drug leakage during transit [13, 20, 21].

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.A 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 [14, 15, 20].

TYPES OF TARGETED DRUG DELIVERY

As discussed, targeting drug to a specific area is 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 fulfilment of such conditions, two approaches are used extensively which also known as classification of drug istargeting [8, 11, 14].

Passive targeting

It refers to the accumulation of drug or drug-carrier 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 for treatment of leishmiansis, brucellosis, candiadsis[8].

Active targeting

Active targeting means a specific ligand–receptor type interaction for intracellular localization which occurs only after bloodcirculation 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 [11].

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 [6, 8, 11].

DRUG DELIVERY VEHICLES

Drug delivery vehicles are also referred as drug vectors which are most important entity required for successful transportation of the loaded drug. Drug vectors transports and retains the drug to be delivered 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[3, 11, 20].

CHARACTERISTICS OF AN IDEAL DRUG VEHICLE

An ideal drug vehicle 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 bio-fluids. The drug vehicle used should be non-toxic, non-immunogenic and biodegradable. After recognition, the carrier system should release the drug moiety inside the target organs, tissues or cells. Targeting Moieties includes antibodies, lectins and other proteins, Lipoproteins, Hormones, Charged molecules, Polysaccharides and Lowmolecular- weight ligands[3, 12, 9, 20].

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 [18, 22].

Monoclonal antibodies and fragments

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) is complex of a drug with a monoclonal antibody which provides selective targeting for tumoral cell masses or lymphomas[23]. The drug is released by enzymatic cleavage of the linker under physiological conditions. An example of

Antibody-drug conjugates (ADC) is Mylotarg (emtuzamabozogamicin) which was approved by the U.S. Food and Drug Administration (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[16].

Modified (plasma) proteins

Modified plasma proteins can be intelligent drug vehicle for drug transportation due to their solubility and having relatively small molecular weight. They can easily be modified by the attachment of different molecules like peptides, sugars, and other ligands to transport the 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 [2].

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. Forcancer therapy, the well established N (-2- hydroxypropyl) methacrylamide (HMPA) polymershave been extensively studied. Also it provide a solution for selective and targeted chemotherapy [13].

Microspheres and nanoparticles

Microspheres and nanoparticles consist of biocompatible polymers and belong either to thesoluble or the particle type carriers. HPMA polymeric backbone carriers have also been prepared using dextrans, ficoll, sepharose or poly-L-lysine as the main carrier body for the drugs. Nanoparticles are smaller (0.2– 0.5 μm) than microspheres (30–200 μm) and may have a smaller drug loading capacity than the soluble polymers. Formulation of drugs into the nanoparticles can occur at the surface of the particles and in nucleus, depending on the physicochemical characteristics of the drug. The site of drug incorporation significantly affects its release rate from the particle. After systemic administration or transportation, they quickly distribute to the target sit and subsequently become internalized by the cells of the phagocytic system. Besides, microspheres and nanoparticles which are mostly used for cell selective delivery of drugs, they have more recently been studied for their application in oral delivery of peptides and peptidomimetics [5,7,12,17].

Lipoproteins

Lipid particles such as LDL and HDL containing a lipid and an apoprotein moiety is termed as natural targeted liposomes and its core can be used to incorporate lipophilic drugs or lipophilic pro-drugs and it does not require covalent bonding with the drug. Modifications at the level of glycolipid incorporation can be used to introduce new targeting moieties. The majority of the research on the use of LDL and HDL particles has been done and improved at the level of targeting the drugs to the liver [4].

Quantum dots

A quantum dot is a semiconductor nanostructure that confines the motion of conduction band electrons, valence band holes or bound pairs of conduction band electrons and valence band holes in all three spatial directions. The ability to tune the size of quantum dots is advantageous for many applications and it is one of the most promising candidates as vehicle for drug transportationwith its in solid-state quantum computation used for diagnosis, drug delivery, Tissue engineering, catalysis, filtration and textiles technologies too [19].

TRANSDERMAL APPROACH IN DRUG TRANSPORTATION

Transdermal drug delivery system is topically administered the drugs in the form of patches that deliver drugs for systemic effects at a predetermined and controlled rate. A transdermal drug delivery device or vehicle which may be of an active or a passive design and is a device which provides an alternative route for administering drug of interest to specific site and delivered the drug across the skin barrier too[21].

Folate Targeting

Folate targeting is a method utilized in biotechnology for drug delivery purposes. It involves the attachment of the vitamin, folate (folic acid) to drug to form folate conjugate. Based on the natural high affinity of folate for the folate receptor protein (FR) which is commonly expressed on the surface of cancer cells and folate-drug conjugates also bind tightly to thefolate receptor protein(FR)which in turn, trigger cellular uptake via endocytosis. The folate receptor protein (FR) is also a recognized tumor-antigen/biomarker. Because of this inherent property of folate receptor protein (FR), exploits its use in diagnostic and therapeutic methods especially for the treatment of cancer [10].

CONCLUSIONS

Delivery of drug molecule to reach its specific site is itself a difficult task in the complex cellular network of an organism. Finally, targeted drug delivery is coming forward as one of the brightest advanced techniquein the medical sciences in the diagnosis and treatment of couple of lethal diseases. It has crossed the infancy period and now touching height of growths in research and development in clinical and pharmaceutical fields. Overall, it may be concluded with the vast database of different studies, the science of site specific or targeted delivery of these drugs has become wiser and intelligent with tiem and the advancement of scientific technology. Manifestation of all these strategies and advanced technologies in clinical field leads to new era of therapeutic and diagnostics in future. 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 especially in the treatment of cancer. Several such preparations have entered the phases of clinical testing or trials 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 or vehicles with drugs of interest with site specificity. 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 [1, 9].

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