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A REVIEW ON ADVANCED DRUG DELIVERY SYSTEMS

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ABSTRACT

Drug targeting to specific organs & tissues has become one of the critical endeavors of the new century. The use of conventional dosage forms generally involves difficulties in achieving the target site. New drug delivery systems include lipidic, proteic & polymer technologies to provide new sustained drug delivery with better drug distribution, drug protection from the harsh external environment & avoidance of drug clearance. This review covers advances in drug delivery.

KEYWORDS: Nanoparticles, dendrimers, nanomedicine, quantum dots.

INTRODUCTION[1-8]

Drug targeting to specific organs and tissues has become one of the critical endeavors of the new century. The search for new drug delivery approaches and new modes of action represent one of the frontier areas which involves a multidisciplinary scientific approach to provide major advances in improving therapeutic index and bioavailability at site specific delivery. The hard to target tissues such as blood-brain barrier permeation limitation can now be overcome allowing the use of therapies otherwise excluded by conventional dosage forms. These new systems can hinder solubility problems; protect the drug from the external environment such as photo degradation and pH changes, while reducing dose dumping by controlling the release profile. Moreover, controlled targeting at the site of action and reduced time of exposure at non-targeting tissues increases the efficacy of treatments and reduce toxicity and side effects thus improving patient compliance and convenience.

Biocompatibility is one of the major pre-requisites for pharmaceutical use, and designing a formulation to fit the physicochemical properties of the drug poses the challenge to new

dosage forms. Nowadays, the versatility and biodegradability of polymers such as poly (D-L-lactide-co-glycolide) (PLGA) constitute a leading approach to new dosage forms to avoid physiological and pathological hurdles encountered in developing targeting strategies. This approach can improve the pharmacokinetic profiles of numerous drugs through the delivery of a higher dose at the site-specific organs by using ligands while conferring a controlled release and degradation to non-toxic products. Meanwhile, oral administration is the most convenient route for drug delivery and the focus of recent research concerns the development of carriers that can cross biological barriers such as the gastrointestinal (GI) tract. In such a way it is necessary for the carrier to protect the drug against the hostile and degrading milieu of the GI tract while increasing the residence time (e.g. Bioadhesion) and target specific cells to enhance absorption which will most likely require less frequency regimens.

A number of drug delivery systems are currently under investigation to circumvent the limitation commonly found in conventional dosage forms and improve the potential of the respective drug. On the other hand, there has been a focus on the microenvironment of the cells and their interaction with these new dosage forms.

TYPES OF NEW DRUG CARRIER SYSTEMS

Microsponges[9]

Microsponges are biologically porous inert particles that are made of synthetic polymers. They can protect the drug from the environment and provide a controlled release.

Microsponge delivery system consisting of a polymeric bead having network of pores with an active ingredient held within was developed to provide controlled release of the active ingredients whose final target is skin itself. The system was employed for the improvement of performance of topically applied drugs. The common method of formulation remains same; the incorporation of the active substance at its maximum thermodynamic activity in an optimized vehicle and reduction of the resistance to diffusion from stratum corneum. Microsponge consists of noncollapsible structures with porous surface through which active ingredients are released in a controlled manner. Depending upon the size, the total pore length may range up to 10 ft and pore volume up to 1 ml/g. Microsponges are porous microspheres having interconnected voids of particle size range 5-300µm. Microsponges are uniform, spherical polymer particles. Their high degree of cross-linking results in particles that are insoluble, inert and of sufficient strength to stand up to the high shear commonly used in manufacturing of creams, lotions, and powders. Their characteristic feature is the

capacity to absorb or "load" a high degree of active materials into the particle and on to its surface. Its large capacity for entrapment of actives, up to three times its weight, differentiates microsponge products from other types of dermatological delivery systems. While the active payload is protected in the formulation by the Microsponge particle, it is delivered to skin via controlled diffusion.

Microsponges are microscopic spheres capable of absorbing skin secretions, therefore reducing oiliness and shine from the skin. Spherical particles composed of clusters of even tinier spheres are capable of holding four times their weight in skin secretions. Microsponge polymers possess the versatility to load a wide range of actives providing the benefits of enhanced product efficacy, mildness, tolerability, and extended wear to a wide range of skin therapies.[10] MDS technology is being used in cosmetics, over-the-counter (OTC) skin care, sunscreens and prescription products.

Market products are available such as Retin-A micro® for acne vulgaris and Carac® containing fluorouracil for actinic keratosis treatments.

***Nanotechnology*[11-14]**

The use of nanotechnology for drug delivery rapidly produced commercially available products and the term nanomedicine emerged. Nanomedicine is the application of nanometer scale materials in an innovative way to develop new approaches and therapies. At this scale, materials display different physicochemical properties due to their small size, surface structure and high surface area. These properties allow nanoparticulate systems to overcome current limitations of conventional formulation as they facilitate the intracellular uptake to specific cellular targets. Thus, nanotechnology has been adopted in several fields such as drug/gene delivery, imaging and diagnostics.

***Immunoconjugates*[15-19]**

Antibody drug-conjugates or immunoconjugates are recombinant antibodies covalently bound through a linker to a drug. The idea behind this technology is to target potent drugs to the specific site by using the specificity of monoclonal antibodies (mAb) thus avoiding nontargeted organs toxicity. These immunoconjugates can be used across a wide spectrum of diseases by selecting the appropriate molecular domains. The first approved immunoconjugate (Mylotarg, gemtuzumab ozogamicin) was used for the treatment of acute myeloid leukemia. On the other hand, new strategies have been developed to use antibodies

attached on nanoparticles and liposomes (so called immunonanoparticles and immunoliposomes, respectively). These systems can be applied to encapsulate multiple drugs while protecting from the external environment and exert a controlled release. Moreover, they can target hard-to-target tissues such as blood-brain barrier (BBB) by targeting transferrin, insulin or glutathione receptors, triggering their activation and consequent internalization.

***Virus*[20-24]**

Viruses are potential vehicles for drug and gene therapies due to their natural ability to infect specific cells and transport genomic material to the nucleus. Using recombinant virus can improve transfection efficiency while evading degradation by lysosomes thus enhancing drug delivery. The main difficulties involve creating viral vectors lacking replication machinery while maintaining the ability to infect mammalian cells. Various viruses have been tested and the most common used are lentivirus, retrovirus and adenovirus. However, the use of viruses raises concerns related to their safety due to the risk of insertional mistakes and activation of proto-oncogenes, viral replication and strong immune responses. Moreover, retroviruses have size loading limitation as they can only infect dividing cells therefore they are most used for *ex vivo* delivery. Lentivirus on the other hand can deliver gene into nondividing cells as well as adenovirus (the virus remains extrachromosomal which reduces the chances of disrupting cellular genome). These systems are most likely to be applied in cytotoxic gene therapy. In contrast to these, nonviral vectors such as liposomes (virosomes) and nanoparticles have rapidly increased due to their low immune response and ease of synthesis.

***Vesicular Systems*[25-27]**

In recent years, vesicles have become the vehicle of choice in drug delivery. Lipid vesicles were found to be of value in immunology, membrane biology, diagnostic techniques, and most recently, genetic engineering. Vesicles can play a major role in modeling biological membranes, and in the transport and targeting of active agents. Biological membranes form the ubiquitous delimiting structures that surround and compartmentalize all cells and organelles. The bilayer arrangement of lipids is perhaps the only organizational feature that is common to all biological membranes. Numerous theoretical models of membrane structure have appeared since the publication of the cell theory by Schleiden and Sehwann in 1839. Experimental models provide insight into the motional dynamics and static structures of some isolated compartments of biological membranes. Lipid vesicles are just one type of the many experimental models of biomembranes. Although developed for basic research, many

technological innovations have arisen from the applications of these models. Lipid vesicles have evolved successfully, as vehicles for controlled delivery. Conventional chemotherapy for the treatment of intracellular infections is not effective, due to limited permeation of drugs into cells. This can be overcome by use of vesicular drug delivery systems. Encapsulation of a drug in vesicular structures can be predicted to prolong the existence of the drug in systemic circulation, and perhaps, reduces the toxicity if selective uptake can be achieved. The phagocytic uptake of the systemic delivery of the drug-loaded vesicular delivery system provides an efficient method for delivery of drug directly to the site of infection, leading to reduction of drug toxicity with no adverse effects. Vesicular drug delivery reduces the cost of therapy by improved bioavailability of medication, especially in case of poorly soluble drugs. They can incorporate both hydrophilic and lipophilic drugs. Vesicular drug delivery systems delay drug elimination of rapidly metabolizable drugs, and function as sustained release systems. This system solves the problems of drug insolubility, instability, and rapid degradation. Consequently, a number of vesicular delivery systems such as liposomes, niosomes, pharmacosomes etc, were developed.

a) Liposomes, Transferosomes, Ethosomes, Niosomes, Virosomes, Cochleate, Cubosomes[3-6, 28-36]

These are phospholipid based vehicles composed of a bilayer membrane that can be divided into small unilamellar vesicles (or SUV from 20 nm to 100 nm), large unilamellar vesicles (LUV from 100 to 500 nm) and multilamellar vesicles (MVL exceeding 500 nm). These systems have the ability to encapsulate both lipophilic drugs within their membrane and hydrophilic drugs inside or outside the aqueous core and the membrane of these carriers can be altered and tuned. Liposomes which are most commonly produced with phosphatidylcholine show great compatibility, ease of preparation, wide range of drug compatibilities, increased solubility of drugs (e.g. cycloporin A), tuned pharmacokinetic profile and improved oral absorption. Commonly, they present difficulties when orally delivered due to the poor stability of the vesicles under the physiological conditions typically found in the GI tract. Liposomes can also act as a drug depot injected subcutaneously and intact vesicles were found after 96h. However, liposomes are metastable systems and their pharmaceutical use may be limited due to content leak- age with poor controlled release, low encapsulation efficiency and loading. Moreover, weak chemical and physical protection of sensitive drugs, aggregation into large particles and hydrolysis with formation of oxidation products with difficulties in industrial scale production and stability problems during storage

have been also described. As a result, ethosomes and transferosomes are liposomes with increased flexibility due to the addition of ethanol and surfactants, respectively. Niosomes are a non-ionic surfactant vesicles made up from polyoxyethylene alkyl ethers, polyoxyethylene alkyl esters or saccharose diesters. These systems are specially designed for skin delivery (ethanol is a known permeability enhancer) due to their facilitated fusion and malleability (transferosomes are ultradeformable) with membranes and have shown that they can be modulated from superficial skin (e.g. treatment of Herpes virus) to full dermal penetration (e.g. required for transdermal delivery of insulin) overcoming limitation commonly found in liposomes. The other type of liposomes is classified as virosomes which are liposomes carrying viral proteins removed from virus on their surface. This strategy has been proposed to immunization and can be administered via mucosal (nasal, vaginal, etc.), intradermal and intramuscular routes. Those systems can incorporate a variety of molecules and can be designed to improve the uptake by dendritic cells through different receptor-mediated routes. Furthermore, cochleates are stable particles (more than other lipidic structures) derived from liposomes composed mainly of charged phosphatidylserine in the presence of divalent counter ion such as Ca2+ which forms a continuous large lipid bilayer sheet with no internal aqueous space. Cochleate delivery has shown potential use for am photericin B, factor VIII delivery, proteins, peptides and DNA. Finally, there are cubosomes. Because of their multilayer structure of continuous lipid bilayer cubosomes are similar to cochleates but they are considered as novel lipid delivery systems. They have self-assembly cubic-like appearance, are biocompatible and show bioadhesive properties ideal for oral administration. More recently, the problems associated with the use of ultrasound in liposomes were overcome and a new kind of liposomes named eLiposomes were produced. The eLiposome can be used as drug carriers which can be induced to vaporize and cavitate when exposed to ultrasound being useful in several applications such as in cancer therapy. A variety of commercially available products constituted from liposomes are available such as Pevaryl® containing econazole which have been used to treat dermatomycosis, Diclac® for therapy of osteoarthritis and Daylong® containing UV filters for patients with high risk of actinic keratosis.

b) Solid Lipid Nanoparticles (SLN) and Nanostructure Lipid Carriers (NLC)[28]

Solid lipid nanoparticles (SLN) are made up from lipids, solid at room and body temperature, such as glycerol behenate, glycerol palmitostearate, lecithin, triglycerides and tristearin glyceride. SLN have shown to be stable for a long period, protect labile compounds from

chemical degradation and can be processed up to large-scale production. However, they still present problems related to their loading efficiency due to the formation of a lipid crystal matrix and possible changes of the physical state of the lipids. To overcome this limitation, a novel structure composed of a mixture of lipids solid and fluids at room temperature (semi-liquid formulations) named nanostructured lipid carriers (NLC) were produced. This system shows high encapsulation efficiency and loading capacity due to the formation of less ordered lipid matrix, and they show long term stability with a controlled release and without burst effect. These colloidal carriers have emerged as a potential alternative to other recent colloidal systems like polymeric nanoparticles.

***Microemulsions and Nanoemulsions*[3-4, 34]**

These are isotropic mixtures of oil/ water stabilized by surfactants frequently in combination with co-surfactants. They have shown high solubilization and dissolution properties, thermodynamic stability and the stabilizers prevent particle agglomeration and/or drug leakage. They have improved permeation enhancement ideal for transdermal delivery as they act in synergy. Microemulsions may work by enhanced disruption of skin-lipid structure or by improving the stability of the drug in the formulation.

***Cyclodextrins*[34, 40]**

Cyclodextrins are cyclic oligosaccharides consisting of six α-cyclodextrin, seven β-cyclodextrin, eight γ-cyclodextrin or more glucopyranose units linked by α-(1,4) bonds. They are also known as cycloamyloses, cyclomaltoses and Schardinger dextrins. They are produced as a result of intramolecular transglycosylation reaction from degradation of starch by cyclodextrin glucanotransferase (CGTase) enzyme.

β-Cyclodextrin is ideal for drug delivery due to the cavity size, efficiency drug complexation and loading, availability and relatively low cost. They can prevent the drug degradation; improve the drug stability and solubility resulting on a higher bioavailability. An example of cyclodextrins in drug delivery system is the derivate 2-hydroxylpropyl (HP*β*CD) which is a powerful solubilizer and has a hydrophilic outside and hydrophobic inside. For absorption in the GI tract, the complexes must contact with the surface thus promoting dissociation and drug permeation across the membrane. Moreover, cyclodextrins can work synergistically as permeation enhancers to improve their absorption across the skin.

***Metal Nanoparticles and Quantum Dots*[41-44]**

Inorganic nanoparticles have emerged a few years ago as drug and gene delivery systems, imaging agents and diagnostic biosensors. Magnetic drug targeting (such as the use of iron) is characterized by conjugating a magnetic material under the action of the external magnetic field, which can accumulate in target tissue areas under the action of the external magnetic field. However, magnetic particles alone are not suited for drug vehicles because of limitations in the controlled release. A mixed composition of a magnetic nucleus and a polymeric shell could take advantage of the two components. Quantum dots are colloidal cores surrounded by one or more surface coatings that reduce leaching of metals from the core. These nanoparticles are of extreme importance for diagnosis. Furthermore, titanium dioxide and zinc oxide demonstrate the potential of nanoparticles to improve therapeutic/prevention performance being particularly useful as sunscreen agents. The micronization of these compounds to nanometer range removes the opacity characteristic associated with them and increases the UV protection.

Polymers

***a) Dendrimers*[45-47]**

Dendrimers are tree-like branched synthetic polymer macromolecular nanoparticles in a dendron like structure which can be designed to target specific structures. They have a remarkable well defined control over size with narrow polydispersity. They have a large surface functionality providing a wide range of applications such as drug and gene delivery, biological adhesives, imaging agents (e.g. MRI). Thus, they can be used for oral, transdermal, ocular and intravenous deliveries. Dendrimers can easily cross cell barriers by both paracellular and transcellular pathways. Dendrimers can be structurally modified. This modification can be made to the nature of the core and the scaffold giving polyfunction capacity to the dendritic structure. Their size, molecular weight and number of surface functional groups can be modulated through the increase in generation number (1 nm per generation). Dendrimers provide a high loading capacity with controlled release which can be modulated to actively release the agent by pH-triggering cleavage. The rate of drug release from the matrix is influenced by the nature of the linking bond or spacer between the drug and scaffold and the targeted physiological domain for intended release. The surface ligands can also control the release from the dendrimers such as in creased steric hindrance of mannose and folate. A novel concept that enables simultaneous release of all functional groups by a single stimulus has been reported which has been named cascade-release

dendrimers. However, this system raises concerns about drug release at the wrong time and place which can raise toxicity profiles. Several dendrimer based diagnostic and/or in vitro technologies are already in the market such as Stratus CS which is a dendrimer-coupled antibody reagents, Superfect (activated dendrimer technology for DNA transfection into a broad range of cell lines) and PriofectTM which is a transfection reagent. Priostar™ and STARBURST® have also been designed to be used as targeted diagnostic and therapeutic delivery systems for a wide variety of drugs to cancer cells and other diseases. As well, Vivagel® is a microbicide for prevention of HIV and HSV and it is based on dendrimers.

b) Natural and Synthetic Polymeric Nanoparticles[48-51]

Drug/gene encapsulation can be achieved by embedding into the matrix or absorbed onto the surface of nanoparticles homogenously dispersed or not. Nanoparticles are solid carriers that can be either made up of natural or synthetic polymers and whether or not biodegradable. Nanoparticles have received more attention than have liposomes because of their therapeutic potential and greater stability in biological fluids as well as during storage. Nanoparticles are advantageous in many ways since they use the unique micro-anatomy of the inflamed tissue blood capillaries, which have gaps between the linings of endothelial cells causing vessel leakiness. Moreover, they show high encapsulation efficiency and protection of instable drugs against degradation of the external environment in comparison to liposomes.

Several methods have been described and nanoparticles can be obtained by polymerization of a monomer or from preformed polymers but recent methods make use of safe solvents with industrial application.

The nanoparticles properties can be tailored by using different polymers and copolymers or proteins. The new strategies use new biodegradable synthetic polymers and modified polymers from natural products such as chitosan and albumin. Chitosan has been shown to be relatively safe and is used as a food additive. Moreover, chitosan is widely used due to its biocompatibility, mucoadhesiveness and permeability enhancing properties and its derivates have shown improved characteristics. Albumin is a natural carrier of hydrophobic molecules such as fatty acids, hormones and fat-soluble vitamins. Albumin has been extensively used as it is non-toxic and non-immunogenic.

However, natural polymers raise concerns in purity and stability and thus synthetic polymers have been applied. Synthetic polymers from the ester family such as poly(lactic acid) (PLA),

poly(cyanoacrylates) (PACA), poly(acrylic acid), poly(anhydrides), poly(amides), poly (ortho esters), poly(ethylene glycol), and poly(vinyl alcohol) (PVA) and other like poly(isobutylcynoacrylate) (PIBCA), poly(ethylene oxide) (PEO), poly(ε-caprolactone) (PCL) are suitable for drug delivery due to their biodegradability. PLGA, another synthetic polymer, has been extensively used in medical applications such as suture materials and bone fixation nails and screws as well as in diverse drug delivery applications.

Recently, poly (β-amino ester) (PbAE) has emerged in the spotlight because it demonstrates a pH sensitive release in which at acid pH it rapidly releases its contents. This polymer has shown to be less toxic than other cationic polymers such as poly (ethyleneimine) and poly (L-lysine) (PLL).

CONCLUSION

The effort to produce these new drug carrier systems is clearly high. These carriers provide the hope to treat and diagnose several diseases. Several technologies have advanced into clinical studies and are nowadays market products that have been shown favorable results. It was also shown in this review that these recent drug carriers are a promising set of technologies that already penetrated the cancer area and they likely have a strong impact in this field in the future. However, there are some issues that need to be understood in order to ensure their safety and effectiveness. In the future, new entities will become available and responsive and "clever" polymers will offer new perspectives for the treatment of diseases.

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