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NANOPARTICLES AS DRUG DELIVERY

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ABSTRACT

Controlled drug delivery systems (DDS) have several advantages compared to the traditional forms of drugs. A drug is transported to the place of action, hence, its influence on vital tissues and undesirable side effects can be minimized. Accumulation of therapeutic compounds in the target site increases and, consequently, the required doses of drugs are lower. This modern form of therapy is especially important when there is a discrepancy between the dose or the concentration of a drug and its therapeutic results or toxic effects .Cell-specific targeting can be accomplished by attaching drugs to specially designed carriers. Various nanostructures , including liposomes, polymers, dendrimers, silicon or carbon materials, and magnetic nanoparticles, have been tested as carriers in drug delivery systems. In this review, the aforementioned nano carriers and their connections with drugs are analyzed. Special attention is paid to the functionalization of magnetic nanoparticles as carriers in DDS. Then, the advantages and disadvantages of using magnetic nanoparticles as DDS are discussed.

KEY WORDS
druge delivery system ;nano cariers ; nanoparticles; magnetic nanoparticles.

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INTRODUCTION

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 [1-4]. 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 [5]. 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 [3,4]. 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 [6] 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-lac- tide-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 [7] 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 [8]. As a result, these new technologies have prompted the old concept of the magic bullet proposed by Paul Ehrich's vision [1].

Type of New Drug Carriers Systems

Microencapsulation has been important to the development of new therapeutics and has been used to produce microspheres containing both hydrophilic and hydrophobic drugs entrapped within biocompatible polymers [9]. The purpose of using these carriers is to obtain a con-trolled release thus maintaining therapeutic drug levels over a specified time period while reducing systemic absorption [9]. These systems have been used in food and cosmetic industry [4] and drug [10] and gene delivery [11]. Micro particles are a generic term to mention micro- capsules and microspheres which can be made of polymers or lipids (liposomes) with sizes ranging from 1 to 250 μm (ideally <125 μm and exceptionally 1000 μm) [12,13]. This technology is very important in drug delivery. Reduced doses due to higher absorption and pro- longed absorption time by using adhesion properties of micro particles have been envisioned [14]. On the other hand, good *in vitro/in vivo* correlations have been observed [14]. Biodegradable micro particles are easily cleared by physiological systems thus avoiding the possible cytotoxicity caused by accumulation in cells and tissues. Active substances may be either adsorbed at the surface of the polymer or encapsulated

within the particle. Furthermore, controlled release can be achieved by pH- sensitive (especially useful in intravenous delivery) and/ or thermo-sensitive micro particles. Micro particles have been used to encapsulate several peptides (e.g. calcitonin and insulin), anesthetics, anti-viral drugs, hypertension and anticancer drugs [12,14], among others. There are several methods for the preparation of micro particles including the polymerization of synthetic monomers and synthesis from preformed polymers [14]. However, sub-micron size particles have shown to offer marked advantages over micro particles [15,16]. For example PLGA micro- and nanoparticles were compared for their uptake in caco-2 cells and revealed a higher up- take from nanoparticles (41% vs. 15%) [17]. Moreover, targeting to specific tissues such as inflamed and cancerous tissues may be limited only to nanoparticles [18].

Nanotechnology

The use of nanotechnology for drug delivery rapidly produced commercially available products and the term nano medicine emerged. Nano medicine 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 [2]. These properties allow nano particulate 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 [20,21],imaging [22] and diagnostics [23].

Nano carriers used in drug delivery system

According to the definition from NNI (*National Nanotechnology Initiative*), nanoparticles are structures of sizes ranging from 1 to 100 nm in at least one dimension. However, the prefix “nano” is commonly used for particles that are up to several hundred nanometers in size.Nano carriers with optimized physicochemical and biological properties are taken up by cells more easily than larger molecules, so they can be successfully used as delivery tools for currently available bio active compounds [145]. Liposomes, solid lipids nano particles , dendrimers, polymers, silicon or carbon materials ,and magnetic nanoparticles are the examples of Nano carriers that have been tested as drug delivery systems.

Drug release from nanoparticles

The nanoparticle is coated by polymer, which releases the drug by controlled diffusion or erosion from the core across the polymeric membrane or matrix. The membrane coating acts as a barrier to release, therefore, the solubility and diffusivity of drug in polymer membrane becomes the determining factor in drug release. Furthermore release rate can also be affected by ionic interaction between the drug and addition of auxiliary ingredients. When the drug is involved in interaction with auxiliary ingredients to form a less water soluble complex, then the drug release can be very slow with almost no burst release effect (Chen et al., 1994).

To develop a successful nano particulate system, both drug release and polymer biodegradation are important consideration factors. In general, drug release rate depends on (1) solubility of drug, (2) desorption of the surface bound/ adsorbed drug, (3) drug diffusion through the nanoparticle matrix, (4) nanoparticle matrix erosion/degradation and (5) combination of erosion/diffusion process (Mohanraj and Chen, 2006). Thus solubility, diffusion and biodegradation of the matrix materials govern the release process.

Liposomal nanoparticles as drug carrier

multi lamellar vesicles (MLVs, diameter >200nm), unilamellar vesicles (large unilamellar vesicles (diameter 100–400 nm), and small unilamellar vesicles (diameter <100 nm)), based on the number of layers (lamellarity) and diameter. Both synthetic and natural lipids can be used.Phosphatidyl choline, electrically neutral phospholipids containing fatty acyl chains of varying degrees of saturation and length are most widely used in liposomal formulation. Liposomes were used as antimicrobial agents since 1995 when FDA approved Doxil (doxorubicin liposomes) as the first liposomal delivery system to treat the AIDS associated Kaposi’s sarcoma (Lian et al 2001). These are biodegradable, non-toxic and can encapsulate both hydrophobic and hydrophilic drugs in the aqueous core and the phospholipid bilayer respectively without any chemical target cell specificity, pH, reductive environmental and temperature sensitivity, which are achieved by selecting the appropriate lipid composition and surface modification for the liposomes (Lian et al.2001). Another remarkable feature of liposomes is the lipid bilayer structure that can easily fuse with the bacterial membranes, thereby releasing the drug within the cell membrane, or into the interior of the microorganism.

There are many successful examples of liposomal antimicrobial drug delivery. One such example is polymixicin B loaded liposomal formulation containing 1,2-dipalmitoyl-sn-glycero-3-phosphocholine (DPPC) and cholesterol showed dramatic improvement over free drug in terms of reduced side effect and enhanced antimicrobial activity. Liposomes are also widely used in the delivery of chemotherapeutic agents. Chan et al. (2009) synthesized core shell NPs consisting of PLGA (poly lactic-co-glycolic acid) hydrophobic core, soybean lecithin monolayer and PEG shell by modified nano-precipitation method combined with self-assembly. Docetaxal encapsulated nanoparticles showed that the amount of lipid coverage affected drug release kinetics.

SOLID LIPID NANOPARTICLES (SLN) AS DRUG DELIVERY CARRIER

SLN are a new generation of colloidal drug carriers, also called lipospheres. These submicron-sized particles in the range of 52-100 nm consist of physiologically biocompatible lipids,which remain solid at body and room temperature and remain dispersed in aqueous solution. SLN are mainly prepared from the lipids, waxes and surfactants for emulsification. Commonly used lipids in SLN formulation include fatty acids, triglycerides, steroids and surfactants. Emulsifiers for the stability of lipid dispersion are sodium cholate and sodium glycocholate. Methods employed to prepare the SLN include high pressure homogenization, emulsifier solvent diffusion, and multiple emulsion solvent injection.SLN have unique properties as potent drug carrier as they combine several advantages and avoid the disadvantages of other colloidal carriers such as lipid immersion, liposomes and polymeric NPs .that they are made up of physiologically biocompatible and tolerable lipids, hence they arenot toxic to the human body. Drug release can be controlled and targeted as immediate release or sustained release. SLN formulation also protects the sensitive drugs from any photochemical, or oxidiative degradation as the drug is immobilized by the solid lipids and drug leakage is reduced when compared to liposomes. Both lipophilic and hydrophilic drugs can be encapsulated and delivered by the SLN with slight modification in SLN formulation. Urban-Morlan et al. (2010) synthesized the solid lipid NP containing cyclosporine by emulsification diffusion method . Differential calorimetric assay revealed that cyclosporin affected the lipid structure and entrapment efficiency was higher with relatively fast release of cyclosporine .Various examples of SLN based antimicrobial drug delivery targeted against the microorganism.

Polymeric-based NPs

Polymeric NPs can be formed as nano spheres, or nano-capsules depending upon the method of preparation. Nano-capsules are vesicular systems in which drug is confined to a cavity surrounded by a polymeric membrane and nano spheres are matrix systems in which the drug is physically and uniformly dispersed. In 1976, Langer and Folkman demonstrated the first use of polymeric based delivery of macromolecules. Since then, many synthetic and semi-synthetic, biocompatible and biodegradable polymers have been used extensively in the clinic for controlled drug release. The most commonly and extensively used polymeric NPs include poly-d, l-lactide-coglycolide , polylactic acid, poly-_-caprolactone ,poly-alkyl-cyanoacrylates, chitosan and gelatin.Polymeric NPs also posses several remarkable properties making them a potential drug delivery vehicle. Firstly, they are structurally stable in the biological fluids under harsh conditions and can be synthesized with desired size distribution. Secondly, by manipulating the polymer length,

surfactants and organic solvent during synthesis, size, zeta potential and drug release profile of NP can be precisely tuned. Thirdly, the functional groups of polymers can be functionalized with desired ligands for the targeted delivery, e.g., lectin conjugated glydine NP that selectively adhered to the carbohydrate receptors on the surface of microbes were studied for treating *Helicobacter pylori* infection (Umamaheswari et al. 2003). Due to obvious advantages such as improving the therapeutic effect, prolonging the biological activity, controlling the drug release rate and decreasing the administration frequency, a great deal of work has been done on polymeric NPs. For example, polybutylvyanoacrylate NPs was loaded with rifampicin and it showed antibacterial activity against *S. aureus* and *Mycobacterium avium* due to effective delivery of the drugs to macrophages both *in vitro* and *in vivo*. Cao et al. (2010) used, xyloglucan (polymer) was grafted with doxorubicin (DOX) and galactosamine and was used totarget liver hepatocytes. This novel nano DDS showed improved transfection efficiency and hepatocyte specificity, which could be useful for tumor therapy.

Dendrimers as a drug carrier

Dendrimers are macromolecules with highly branched polymers with 3-D structures that provide a high degree of surface functionality and versatility (Nanjwadea et al. 2009). Fritz Vogtle and coworkers first introduced dendrimers in 1978(Bhuleier et al. 1978). Dendrimers consist of three components: an initiator core, an interior layer composed of repetitive units and an exterior (terminal functionality) layer attached to outermost interior layers. To develop dendrimeric systems for delivering drugs, these are prepared from two synthetic iterative approaches: one divergent and another convergent. In the divergent approach, synthesis is initiated from the core and proceed sout wards to the exterior through repetition of coupling and activation steps. In contrast, In the convergent approach synthesis starts from the periphery and proceeds towards the core (Gillies etal. 2005).Dendrimers possess several unique properties that make them efficient NP carriers for the antimicrobial drug delivery. The well defined highly branched 3D structure provides a large surface area to size ratio resulting in greater reactivity with microorganisms *in vivo*. The availability of many controlled functional surface groups, polydispersity and their ability to mimic cell membrane adds to their potency as drug carriers. Both hydrophilic and hydrophobic agents can be loaded at the same time either by encapsulating drug within the dendritic structure, or by interacting with the drugs at their terminal groups by electrostatic, or covalent bonds also due to the availability of functional groups. Dendrimers with specific and high binding affinity to a wide variety of viral and bacterial receptors can be synthesized (Sajja et al. 2009). Surfaces of dendrimers can be functionalized with PEG, which allows the delivery system to circulate in the body for prolonged time and thus maximizing the opportunity of the drug to reach the relevant site .PEGI yated dendrimers are difficult to be detected by

defense mechanism there by slowing theprocess of breakdown (Bhadra et al. 2005).PAMAMs were the first and most popularly studied dendrimers, but because of the cytotoxicity caused by the terminal amines, its clinical use as a drug carrier was limited. However, by masking theterminal amine groups by some means like terminating their carboxylic, or hydroxyl group would not only overcome its limitation but also improve the efficiency by solubility enhancement and making it more biocompatible and less toxic (Gillies et al. 2005). A study I has indicated that PAMAM dendrimers might be considered as the biocompatible carriers of quinolones (nadifloxin and prulifloxin) under suitable condition (Cheng et al. 2007). Dendrimer use resulted in increased aqueous solubility of these antibiotics. Table 5 summarizes more dendrimeric-based antibacterial drug delivery systems.

CONCLUSION

Nano carriers as drug delivery systems are designed to improve the pharmacological and therapeutic properties of conventional drugs. The incorporation of drug molecules into nano carrier can protect a drug against degradation as well as offers possibilities of targeting and controlled release. Due to small dimensions, nano carriers are able to cross the blood-brain-barrier (BBB) and operate on cellular level. In comparison with the traditional form of drugs, nano carrier-drug conjugates are more effective and selective. They can reduce the toxicity and other adverse side effects in normal tissues by accumulating drugs in target sites .In consequence, the required doses of drugs are lower.Although there are several nanoparticle-based therapeutic agents which are currently being developed and are under preclinical evaluation, only a handful of nanoparticle drugs are available on thepharmaceutical market, e.g., liposomal conjugates:Doxil® (doxorubicin) or DaunoXome® (daunorubicin).

It is due to the fact that nanoparticle based drug delivery systems do have a lot of drawbacks and limitations. Some of them arise from scaling up problems.For instance, small size and large surface area of nanoparticle-based targeting system can lead to an aggregation, making physical handling difficult. Nano carrier-drug conjugates can be phagocytosed by cells whereas their intracellular degradation may cause cytotoxic effects. Other issues include low drug loading capacity, low loading efficiency, and poor ability to control the size distribution of carriers. Furthermore, there is a lack of technological methods, which will lead to nano devices of approvable quality. Despite all the limitations and shortcomings, nano particle DDS which respond to slight changes in the local cellular environment have a potential to resolve many of the current drug delivery problems. However, before the ongoing research will bring a clinically useful drug delivery system, challenges which include developing toxicity testing protocols, improving biocompatibility, drug loading, targeting, transportand release, controlling interaction with biological barriers, detecting and monitoring exposure level and assessing the impact on the environment have to be met. Due to a number of functional groups on the surface of nanoparticles, the drug can be attached to the carrier only in a stoichiometric ratio. The oxidative stress and inflammation in different cell types have been often reported as toxic mechanisms of various types of nanoparticles. Nanoparticles of diameter10 nm can remain in cells and induct chronic inflammatory response and fibrosis of tissue. An additional problem is the lack of knowledge concerning the distribution of drug carriers and the unpredictability of the process. Thus, in our opinion, the magnetic targeted drug delivery system is one of the most attractive strategy target therapy. Magnetic nanoparticles have their unique magnetic properties and they can be attracted by magnetic fields, thus, acting as drug carriers in a target therapy. In addition, inorganic magnetic nanoparticles containing the iron and gadolinium serve as an excellent contrast enhancing agents in MRI (approved by FDA – Food and Drug Administra a real therapeutic breakthrough can be achieved solely by carrying out painstaking studies in the field of nano-therapy. Using nano systems in therapies of diseases may contribute to achieving an effective cancer treatment. Moreover, immobilization of homing devices, such as folic acid, epidermal growth factor or antibodies, to the surface of nanoparticles, improves selectivity of drug carriers. The key applications of nano particles in medicine are diagnosis and target therapy, however, their wider use is still the future).

CONFLICT OF INTEREST
There is no conflict of interest.

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