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Review Article

Applications of Nanoparticles in Drug Delivery System: A Review

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Abstract

Nanotechnological application is significantly important in the field of drug delivery because of its high specificity towards the target site, so it is able to reduce toxic side effects of drugs to normal cells. The Nanoparticles (NP) plays a vital role and it can conjugate with various drugs by different methods to deliver drugs to the target site. The NP surface is designed with ligands to get affinity towards specific cells and co-polymers to get protection from immune cells. The nanoparticles conjugated drug can ultimately recognize the site and join to the target and enter to the cell by receptor mediated endocytosis. Then NPs are able to release drugs controllably to cure diseases. This review paper gives an overview of various applications of nanoparticles in drug delivery system.

Keywords: Applications; Drug Delivery; Nano Particulate Drug Delivery System (NPDDS); Nanoparticles

Introduction

In the last 35 years, the growth of nanotechnology has opened several new vistas in medical sciences, mostly in the field of drug delivery [1,2]. New and new moieties are coming handy for treating diseases. The biotechnology has also produced several potent drugs, but many of these drugs come across problems delivering them in biological systems [3,4]. Their therapeutic efficacy is significantly marred owing to their incompatibilities and specific chemical structure [5,6]. The input of today's nanotechnology is that it allows real progress to achieve temporal and spatial site-specific delivery. The market of nanotechnology and drug delivery systems based on this technology will be widely felt by the pharmaceutical industry. In recent years, the number of patents and products in this field is increasing significantly [7,8]. The most straightforward application is in cancer treatment, with several in market such as Caelyx®, Doxil®, Trans drug®, Abraxane®, etc.

Delivering therapeutic compound to the desirable site is a major problem in treatment of many diseases. Conventional utilization of drugs is characterized by poor bio distribution, limited effectiveness, undesirable side effects, and lack of selectivity [9,10]. Strategies like controlling drug delivery can potentially overcome these limitations by transporting drug to the place of action. Moreover, drug delivery system provides protection against rapid degradation or clearance. It also enhances drug concentration in target tissues; therefore, lower doses of drug are required. Such type of therapy is required when there is a discrepancy between a dose or concentration of a drug and its therapeutic results or toxic effects. Targeting cell or specific tissue by the means individually designed carriers that are attached to drugs is a more reliable approach in drug delivery system. Such approach is known as cell or tissue specific targeting. Size reduction of targeted formulation and designing its pathways for suitable drug delivery system is a more fundamental and successful approach that forms the basis of nanotechnology [11,12].

Recent advancement in nanotechnology has proven that nanoparticles acquire a great potential as drug carriers. Size reduction methods and technologies yields different types of nanostructures that exhibit unique physicochemical and biological properties [13,14].

Nano particulate Drug-Delivery Systems:

Nano Particulate Drug-Delivery Systems (NPDDSs) are being explored for the intention of solving the challenges of drug delivery. Coming in many shapes and sizes, most carriers are less than 100 nm in diameter. NPDDSs provide methods for targeting and releasing therapeutic compounds in much defined regions.

These vehicles have the potential to eliminate or at least upgrade many problems associated with drug distribution. As many drugs have a hydrophobic component, they often suffer from problems of precipitation in high concentration, and there are many examples of toxicity issues with excipients designed to prevent drug aggregation [15,16].

To battle these issues, many NPDDSs provide both hydrophobic and hydrophilic environments, which facilitate drug solubility. On the other hand, many drugs suffer from rapid breakdown and/or clearance in vivo. Encapsulating the drugs in a protective environment, NPDDSs increase their bioavailability, thereby allowing the clinicians to prescribe lower doses. With recent advances in polymer and surface conjugation techniques as well as micro fabrication methods, perhaps the greatest focus in drug-delivery technology is in the design and applications of NPDDSs. Ranging from simple metal ceramic core structure to complex lipid–polymer matrices, these submicron formulations are being functionalized in numerous ways to act as therapeutic vehicles for a variety of conditions PDDSs can be defined as the DDSs where nanotechnology is used to deliver the drug at nanoscale. Below 100 nm, materials exhibit different, more desirable physical, chemical, and biological properties. Given the enormity and immediacy of the unmet needs of therapeutic areas such as CNS disorders, this can lead to drugs that can extend life and save untimely deaths [17,18].

Nanoparticles for Brain Delivery

The blood-brain barrier represents one of the hurdles for drugs including antibiotics, antineoplastic agents and a variety of neuroleptic drugs. One of the possibilities suggested to overcome this barrier is drug delivery to the brain using nanoparticles. Drugs that have successfully been used for brain targeting using nanoparticles include the hexapeptide dalargin, the dipeptide kyotropin, loperamide, tubocurarine and doxorubicin. A number of prospects are accounted for the enhanced delivery of drugs to the brain using nanoparticles:

1. Higher concentration gradient at the blood brain barrier that may enhance the transport across the endothelial cell layer and hence increased retention in the brain.
2. Solubilization of endothelial cell membrane lipids by surfactant action of nanoparticles leading to membrane fluidization and enhanced drug permeability to BBB.
3. Loosening of tight junctions between endothelial cells and increased permeability of drug or drug-nanoparticle conjugates through these channels [19].
4. Endocytosis of nanoparticles by the endothelial cells followed by the release of the drug intracellularly.
5. Transcyotosis of the drug bound nanoparticle through the endothelial cell layer.

Kreuter and co-workers in a series of studies have advocated nanoparticles for brain delivery (Kreuter, 1994; Kreuter et al., 1995). Kreuter and co-workers, 1995 reported transport of the hexapeptide dalargin across the blood-brain barrier using poly (butyl cyanoacrylate) nanoparticles, which were coated with polysorbate 80. Intravenous injection of polysorbate 80 coated nanoparticles with sorbed drug resulted in n significant analgesic effect in mice model as s compared against all controls, including a simple that mixture of the three components (drugs, nanoparticles, and surfactant) mixed directly before i.v. injection. Fluorescent and electron microscopic studies indicated that the passage of the particle bound drug occurred by phagocytic uptake of the d polysorbate 80-coated nanoparticles by the brain blood vessel endothelial cells. Some neuropeptides are also delivered across N blood-brain barrier using nanoparticle technology. Leu-enkephalin dalargin and the Met-enkephalin kyotorphin are neuropeptides that normally do not cross the Blood-Brain Barrier (BBB) when given systemically. To transport these neuropeptides across the BBB they were adsorbed onto the surface of poly (butyl cyanoacrylate) nanoparticles, which were coated with polysorbate 80 [20].

Nanoparticles for Lymph Targeting

The major purpose of lymph targeting is to provide an effective anticancer chemotherapy to prevent the metastasis of tumour cells by accumulating the drug in the regional lymph node via subcutaneous administration. The objective of lymph node targeting also involve the localization of diagnostic agent to the regional lymph node for the lymphatic vessel visualization before surgery and also the improvement of peroral bioavailability of macromolecular drugs like polypeptides and proteins, which are absorbed via Peyer's patches in the intestine [21]. A wide range of studies are carried out to date for the lymphatic targeting using nanoparticle as drug carriers:

1. Polyalkylcyanoacrylate nanoparticles bearing anticancer drugs (Couvreur et al., 1990) for tumour of peritoneal cavity
2. Polyisobutylcyanoacrylate nanoparticles loaded with insulin for peroral peptide delivery through Peyer's patches (Damge et al., 1990)
3. Poly (lactide-co-glycolide) nanoparticles for the lymphatic delivery of diagnostic agents (Hawley et al., 1997)
4. Magnetite-dextran nanoparticles as a contrast agent in magnetic resonance imaging (Chouly et al., 1996)
5. Polyalkylcyanoacrylate Nano capsules bearing marker (ASA) for lymphatic delivery [22].

Nanoparticles for Ocular Delivery

The most applications of drug-loaded ophthalmic delivery systems are for glaucoma therapy, especially: cholinergic agonists

like pilocarpine. The short elimination half-life of aqueous eye drops (due probably to lachrymal drainage) can be extended from a very short time (1-3 min) to prolonged time (15, min) using nanoparticles, which have biodegradable properties. These include polyalkylcyanoacrylate nanoparticles (Li et al., 1986: Losa et al. 1991), polyester nanoparticles (Marchal-Heussler et al 1992), and Albumin nanoparticles (Zimmer et al., 1995). In addition, it has been demonstrated that nanoparticles adhere to the inflammed tissue in a more quantitative manner as compared to the healthy tissue, thus these could also be used for targeting of anti-inflammatory drugs to inflammed eyes. Various advantages are proposed for the polyalkylcyanoacrylate nanoparticles specially PHCA nanoparticles including their biodegradability, tissue adhesion and increased elimination half -life of their drainage coupled with a slow clearance. It was found that pilocarpine and betaxolol loaded polyalkylcyanoacrylate nanoparticles could prolong and maintain the reduced intraocular pressure in rabbits for more than 9 h [23]. Zimmer and co-workers, 1994a, 1994b used pilocarpine loaded polybutylcyanoacrylate nanoparticles for ocular delivery. A better pilocarpine pharmacokinetics as well as pharmacodynamic response in terms of intraocular pressure (IOP) lowering effect and enhanced mitosis, was established. A possibility to increase the efficacy of pilocarpine-loaded nanoparticles is the classic approach of coating them with bioadhesive or viscous polymers (Zimmer et al., 1995). The polymers methylcellulose, polyvinylalcohol and hydroxyl propylmethylcellulose and carbopol 941 were chosen because of their bio adhesive properties (Zimmer and Kreuter, 1997).

Nanoparticle for Oligonucleotide Delivery

Antisense therapeutic agents bind to DNA or RNA sequences, blocking the synthesis of cellular proteins with unparalleled specificity. Transcription and translation are the two processes with which the agents interfere. There are three major classes of antisense agents: antisense sequences, commonly called antisense oligonucleotides; antigene sequences; and ribozymes (Putnam, 1996). Antisense sequences are derivatives of nucleic acids that hybridize cytosolic messenger RNA (mRNA) sense strands through hydrogen bonding to complementary nucleic acid bases. Antigene sequences hybridize double-stranded DNA in the nucleus, forming triple helixes. Ribozymes, rather than inhibiting protein synthesis simply by binding to a single targeted mRNA, combine enzymatic processes with the specificity of antisense base pairing, creating a molecule that can incapacitate multiple targeted mRNAs. Antisense Oligonucleotides (ODNs) are being investigated in vitro and in vivo for evaluating their possible use in treating human immunodeficiency virus infection, hepatitis B virus infection, Herpes Simplex Virus infection, papillomavirus infection, cancer, restenosis, rheumatoid arthritis, and allergic disorders. A major goal in developing methods of or delivering antisense agents is to reduce their susceptibility to nucleases while retaining their ability to bind to targeted sites. Carrier systems designed to protect the antisense structure and improve passage through the cell membrane include liposomes, water-soluble polymers, and nanoparticles. Due to their hydrophilic and polyanionic character, ODNs poorly combine with polymeric systems, however, three main strategies have been put forward recently for binding of ODN and nanoparticles [24].

1. ODNs may covalently link to hydrophobic anchor allowing insertion with polymer surface (A) 2. Cationic polymers coated particles will interact with the negatively charged ODN molecules (B)

3. Loading of ODN can be achieved using a specialized Nano-particulate system, Nano sponge, which uses diffusion/reputation process for the loading of ODNs (C)

Oligonucleotides adsorbed onto polyalkylcyano-acrylate nanoparticles have been demonstrated to enhance stability against nucleases and more ideal cellular disposition. Positively charged nanoparticles prepared from Diethylaminoethyl (DEAF)-dextran and Polyhexylcyanoacrylate (PHCA) were evaluated as carriers for ODNs (Zobel et al., 1997). Oligonucleotides adsorbed to the surface of the nanoparticles remained protected against degradation by the endonuclease DNase I and under in vitro cell culture conditions whereas unprotected ODNs were totally digested under these conditions. Fattal and co-workers, 1998 studied oligonucleotides associated biodegradable polyalkylcyanoacrylate nanoparticles through the formation of ion pairs between the negatively charged oligonucleotides and hydrophobic cations. Oligonucleotides bound to these nanoparticles were protected from nuclease attack in cell culture media and their cellular uptake was increased as a result of the capture of Nano-particles by an endocytotic/phagocytotic pathway. Berton and co-workers, 1999 investigated Nano-particles (NP) of poly (D, L) lactic acid for the intracellular delivery of oligonucleotides and reported their intracellular compartmentalization. Aynie and co-workers, 1999 designed a new antisense Oligonucleotide (ON) carrier system based on "sponge-like" alginate nanoparticles and investigated its ability to protect ON from degradation in the presence of serum. This new alginate-based system was found to be able to protect [^{33}P] radiolabeled ON from degradation in bovine serum medium and exhibited modified biodistnbution in the lungs, liver and spleen after intravenous admimstration into mice. Such Nano sponges are promising carriers for specific delivery of ON to lungs, liver, and spleen. Recent studies suggested that lipophilic Polymethyl-Methacrylate (PMMA) homo polymer nanoparticles show a negative surface charge and, therefore, are not suitable for the adsorption of anionic oligonucleotides. However, if the surface charge is changed to positive values by the incorporation of basic monomer, the resultant cationic copolymer (amino methylaminoethyl-methacrylate) nanoparticles containing 30%

(w/w) methylaminoethyl-methacrylate were found to be optimal in regard to biocompatibility and carrier properties for hydrophilic anionic antisense oligonucleotide entrapment (Zobel et al., 1999; 2000). A significant portion of adsorbed oligonucleotides was protected from enzymatic degradation. The cellular uptake of oligonucleotides into Vero cells was significantly enhanced by this methylaminoethyl-methacrylate derivative.

Antibody targeting of nanoparticles

Many studies have reported the antibody mediation of the nanoparticles to develop targeted drug delivery systems, especially in the application of cancer treatment. Antibody targeting of drug substances can improve the therapeutic efficacy of the drug substance, as well as improve the distribution and concentration of the drug at the targeted site of drug action. McCarron et al. studied two novel approaches to create immunonanoparticles with improved therapeutic effect against colorectal tumor cells. They used poly (lactide) polymers and CD95/ APO-1 antibody to target nanoparticles. Pan et al. used dendrimer-magnetic nanoparticles for efficient delivery of gene-targeted systems for cancer treatment. Olton et al. have described the use of nanostructured calcium nanophosphates for non-viral gene delivery and studied the influence of synthesis parameters on transfection efficiency [25].

Nanoparticles for DNA Delivery

Nanoparticles have been recently used as a delivery vehicle for the transfection of plasmid DNA and to prove their stability in the bio-environment. Truong-Le and co-workers, 1998 developed a novel system for gene delivery based on the use of DNA-gelatin nanoparticles (Nano spheres) formed by salt-induced complex concertation of gelatin and plasmid A. Nano sphere-DNA incubated in bovine serum was more resistant to nuclease digestion compared naked DNA. Various bioactive agents could be encapsulated in the Nano spheres through is interaction with the matrix components, physical entrapment, or covalent conjugation.

Troung-Le and associates, 1999 further developed DNA-gelatin nanoparticles system containing chloroquine and calcium. The targeting ligand, transferring, was covalently bound to the gelatin, as a gene delivery vehicle. Optimum cell transfection by Nano sphere-DNA required the presence of calcium and Nano spheres containing transferring. James and co-workers, 2001 reported chitosan-DNA hybrid colloidal systems either as chitosan-DNA complex or as chitosan-DNA Nano spheres and reported comparatively better gene expression [26].

Nanoparticles for vaccine delivery

Nanosomic systems incorporating therapeutic agents with molecular-targeting and diagnostic imaging capabilities are emerging as the next generation of functional Nano medicines to improve the outcome of therapeutics. Yoshikawa et al. developed a technique to prepare uniform nanoparticles based on poly-y-glutamic acid nanoparticles and used them successfully as carriers for vaccines in the treatment of cancer. The development of compounds that enhance immune responses to recombinant or synthetic epitopes is of considerable importance in vaccine research. An interesting approach for formulating aquasomesis described by Goyal et al. These were prepared by self-assembling hydroxyapatite by co precipitation, and then they were coated with polyhydroxyl oligomers (cellobiose and trehalose) and adsorbed on Bovine Serum Albumin (BSA) as a model antigen. BSA-immobilized aquasomes were approximately 200 nm in diameter, and it was observed that these formulations elicit combined T-helper Thl and Th2 immune responses.

Lipid nanoparticles and nanostructured lipid carriers

Lipid nanoparticles have been used for many years and are still showing lots of interest in delivering drugs, as well as nanostructured lipid carriers for drugs. Fang et al. recently conducted a study by using lipid nanoparticles for the delivery of topical psoralen delivery. This study compared lipid nanoparticles with nanostructured lipid carriers composed of precirol and squalene, a liquid lipid. They showed that the particle size was between 200 and 300 nm for both the carriers. It was used for the treatment of psoriasis. Their results showed that the entrapment of 8-methoxypsoralen in Nano particulate systems could minimize the permeation differentiation between normal and hyper proliferative skin compared with that of free drug in aqueous control.

Mucoadhesive Nano particulate drug delivery systems and improving the gastrointestinal tract absorption

A novel nanoparticle system to overcome intestinal degradation and drug transport-limited absorption of P-glycoprotein substrate drugs is reported by Nassar et al. Dr. Juliano has written a very good article about the challenges in macromolecular drug delivery and the use of various techniques including polymeric carriers for the macromolecular drugs. Zidan et al. had an interesting report on quality by design for understanding the product variability of a Mucoadhesive, Self-Nano Emulsified Drug Delivery System (SNEDDS) of cyclosporine A. This is probably one of the first of its kind of research report on quality by designing the field of pharmaceutical nanotechnology. They used near infrared and chemo-metric analysis and several other well-known processes for the characterization of emulsions during processing. Their study demonstrated the ability to understand the impact of Nano droplets size on the SNEDDS variability by different product-analyzing tools [27].

Hydrogel nanoparticles in drug delivery

Hamidi et al. have written a very good review on hydrogel nanoparticles and their applications in drug delivery as well as therapeutic applications in various disease conditions. Another

polymeric group tried by Lee et al. was poly (lactide) –Tocopheryl Polyethylene Glycol Succinate (PLA-TPGS) copolymers, which they used to deliver protein and peptide drugs. They used double-emulsion technique for protein drug formulation, with BSA as the model protein drug. They used confocal laser scanning microscopy observations to demonstrate the intracellular uptake of the PLA-TPGS nanoparticles by fibroblast cells and Caco-2 cells, showing great potential of these polymeric carriers for protein and peptide drugs. Cheng et al. showed that the size of the nanoparticles affects the bio distribution of targeted and non-targeted nanoparticles in an organ-specific manner. Nair et al. described the enhanced intratumoral uptake of quantum dots concealed within hydrogel nanoparticles. To develop a functional device for tumor imaging, they embedded quantum dots within hydrogel nanoparticles. Their results suggest that the derivatized quantum dots enhance tumor monitoring through quantum dot imaging and that they are useful in cancer monitoring and chemotherapy. An interesting work was reported by Vihola et al. (They have discussed the effect of cross-linking on the formation and properties of thermosensitive Polymer Particles of Poly (N-Vinyl Caprolactum) (PVCL) and PVCL grafted with poly (ethylene oxide) macro monomer. They showed different levels of drug release profiles based on varying polymer cross-linking. Baroli wrote a review on hydro-gels for tissue engineering, and it has lots of information on the formulation and characterization of hydrogels for various applications including NPDDS [28].

Nanoparticles in diagnostic medicine

Lee et al. have reported very interesting study on the subject of nanoparticles in diagnostic medicine. They used to antibody-conjugate, hydrophilic, magnetic nanocrystals as smart Nano probes for the ultrasensitive detection of breast cancer via Magnetic Resonance Imaging (MRI). $MnFe_2O_4$nanocrystals employed as MRI-contrast agents for MRI were synthesized by thermal decomposition. The surfaces were then modified with amphiphilic triblock copolymers. They showed clear advantage as a contrast medium to detect breast cancer tumors. Faure et al. have shown different methods to detect streptavidin by attaching a molecule to dielectric particles made of a rare earth oxide core and a polysiloxane shell containing fluoreschein for bio detection. A new, interesting class of magnetic nanoparticles, gadolinium hydroxide and dysprosium oxide, are characterized by different methods by using X-ray diffraction, NMR relaxometry, and magnetometry at multiple fields. These have very good applications in diagnostic purposes. Shao et al. have used nanotube antibody biosensor arrays for the detection of circulating breast cancer cells. This is the first report giving information on the new technique by using the nanotube and the antibody cancer cell detection system.

Conclusion

The industrial scene of nanotechnology developments is very promising. The application of nanotechnology to drug delivery is widely expected to create novel therapeutics, capable of changing the landscape of pharmaceutical and biotechnology industries. Various nanotechnology platforms are being investigated, either in development or in clinical stages, and many areas of interest where there will be effective and safer targeted therapeutics for a myriad of clinical applications. It will be evolving out very soon for the benefit of humanity at large.

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