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Recent Application of Nanotechnology in Drug Delivery System

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Abstract **Review Article**

Nanoparticle drug delivery system is used for drug delivery applications in nanomedicine because of beneficial properties, such as better encapsulation, bioavailability, control release, and lower toxic effect. Nanomedicine and nano delivery systems are a relatively new but rapidly developing science where materials in the nano scale range are employed to serve as means of diagnostic tools or to deliver therapeutic agents to specific targeted sites in a controlled manner. There are a number of outstanding applications of the nanomedicine (chemotherapeutic agents, biological agents, immunotherapeutic agents etc. in the treatment of various diseases.The controlled self-assembly of organic and inorganic materials may enable their use in theranostic applications. This review presents an overview of a recent advanced nanoparticle system that can be used as a potential drug delivery carrier and focuses on the potential applications of nanoparticles in various biomedical fields for human health care.

Keywords: Nanoparticle, Encapsulation, Drug delivery, Immunotherapeutic.

INTRODUCTION

The market of nanotechnology and drug delivery systems based on this technology will be widely felt by the pharmaceutical industry. New and new moieties are coming handy for treating diseases. In the last 35 years, the growth of nanotechnology has opened New and new moieties are coming handy for treating diseases. The biotechnology has also produced several potent drugs, several new vistas in medical sciences, mostly in the field of drug delivery [1, 2]. The biotechnology has also produced several potent drugs, but many of these drugs come across problems delivering them in biological systems [3, 4]. Delivering therapeutic compound to the desirable site is a major problem in treatment of many diseases.Their therapeutic efficacy is significantly marred owing to their incompatibilities and specific chemical structure [5, 6]. Conventional utilization of drugs is characterized by poor bio distribution, limited effectiveness, undesirable side effects, and lack of selectivity [9, 10].The input of today's nanotechnology is that it allows real progress to achieve temporal and spatial site-specific delivery. In recent years, the number of patents and products in this field is increasing significantly [7, 8]. 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. 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].

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. Such approach is known as cell or tissue specific targeting. 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].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.

Nanotechnology Drug-Delivery Systems

These vehicles have the potential to eliminate or at least upgrade many problems associated with drug distribution. NPDDSs provide methods for targeting and releasing therapeutic compounds in much defined regions. 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]. NPDDSs increase their bioavailability, thereby allowing the clinicians to prescribe lower doses. Ranging from simple metal ceramic core structure to complex lipid–polymer matrices, 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. 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, 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. Below 100 nm, materials exhibit different, more desirable physical, chemical, and biological properties. 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. 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].

Nanotechnology for blood brain barrier

A number of prospects are accounted for the enhanced delivery of drugs to the brain using nanoparticles:

1. Solubilization of endothelial cell membrane lipids by surfactant action of nanoparticles leading to membrane fluidization and enhanced drug permeability to BBB.
2. Endocytosis of nanoparticles by the endothelial cells followed by the release of the drug intracellularly.
3. 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.
4. Loosening of tight junctions between endothelial cells and increased permeability of drug or drug-nanoparticle conjugates through these channels [19].

One of the possibilities suggested to overcome this barrier is drug delivery to the brain using nanoparticles. The blood-brain barrier represents one of the hurdles for drugs including antibiotics, antineoplastic agents and a variety of neuroleptic drugs.

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9. Transcyotosis of the drug bound nanoparticle through the endothelial cell layer.

Drugs that have successfully been used for brain targeting using nanoparticles include the hexapeptide dalargin, the dipeptide kyotropin, loperamide, tubocurarine and doxorubicin.

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]. Some neuropeptides are also delivered across N blood-brain barrier using nanoparticle technology. 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. 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.Kreuter and co-workers in a series of studies have advocated nanoparticles for brain delivery (Kreuter, 1994; Kreuter *et al*., 1995). 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. Leu-enkephalin dalargin and the Met-enkephalin kyotorphin are neuropeptides that normally do not cross the Blood-Brain Barrier (BBB) when given systemically.

Nanotechnology used for Lymph Targeting

A wide range of studies are carried out to date for the lymphatic targeting using nanoparticle as drug carriers. Polyalkylcyanoacrylate Nano capsules bearing marker (ASA) for lymphatic delivery [22]. The objective of lymph node targeting is involve the localization of diagnostic agent to the regional lymph node for the lymphatic vessel visualization before surgery. lactide-co-glycolide nanoparticles for the lymphatic delivery of diagnostic agents. Polyalkylcyanoacrylate nanoparticles bearing anticancer drugs for tumour of peritoneal cavity. Magnetite-dextran nanoparticles as a contrast agent in magnetic resonance imaging. Poly nanoparticles loaded with insulin for peroral peptide delivery through Peyer's patches.

Nanotechnology used for Ocular treatment

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. 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 most applications of drug-loaded ophthalmic delivery systems are for glaucoma therapy, especially: cholinergic agonists like pilocarpine. It was found that pilocarpine and betaxolol loaded polyalkylcyanoacrylate nanoparticles could prolong and maintain the reduced intraocular pressure in rabbits for more than 9h [23]. A better pilocarpine pharmacokinetics as well as pharmacodynamic response in terms of intraocular pressure (IOP) lowering effect and enhanced mitosis, was established. Various advantages are proposed for the polyalkylcyanoacrylate nanoparticles specially PHCA nanoparticles including their biodegradability, 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. Tissue adhesion and increased elimination half -life of their drainage coupled with a slow clearance. Zimmer and co-workers, 1994a, 1994b used pilocarpine loaded polybutylcyanoacrylate nanoparticles for ocular delivery. The polymers methylcellulose, polyvinylalcohol and hydroxyl propylmethylcellulose and carbopol 941 were chosen because of their bio adhesive properties (Zimmer and Kreuter, 1997).

Nanotechnology used 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 [33P] 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.

Nanotechnology used for Antibody targeting

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].

Nanotechnology used 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].

Nanotechnology used 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.

Nanotechnology used in lipid carriers

The Lipid nanoparticles have been used for many years and are still showing lots of interest in delivering drugs, and nanostructured lipid carriers for drugs. Recently conducted a study by using lipid nanoparticles for the delivery of topical psoralen delivery. This study of lipid nanoparticles with nano structured lipid carriers composed of precirol and squalene. The particle size was between 200 and 300 nm for both the carriers and used for the treatment of psoriasis. The results showed that the entrapment of 8-methoxypsoralen in Nano particulate systems 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 Anovelnanop article system to overcome in test in aldegradation 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 w`ell-known processes for the characterization of emulsions during processing. Their study of the ability to understand the impact of Nano droplets size on Self Nano Emulsified Drug delivery System of variability by different product-analyzing tools [27].

Nanotechnology used in Hydrogel drug delivery

Hamidi *et al*., Have written a good review on hydrogel nanoparticle. The applications of nanotchnology in drug delivery system and therapeutic applications in various disease conditions. Anotherpolymeric group tried by Lee *et al*., Was lactide Tocopheryl Polyethylene Glycol Succinate (PLA-TPGS) copolymers, which they used to deliver protein and peptide drugs. They used double- emulsion technique to 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. To 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].

Nanotechnology used in diagnostic medicine

The surfaces were then modified with amphiphilic triblock copolymers. Lee *et al*., Had been reported in interesting study on the subject of nanoparticles in diagnostic medicine.$MnFe_2O_4$ nano crystals employed as MRI-contrast agent. They shows clear advantage on a contrast medium to detect breast cancer tumors. Faure *et al*., Had been shown different methods for 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, 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. They used to antibody-conjugate, hydrophilic, magnetic nanocrystals as smart Nano probes for the ultrasensitive detection of breast cancer via Magnetic Resonance Imaging (MRI).

CONCLUSION

The application of nanotechnology in drug delivery system is widely used to capable of changing the landscape of pharmaceutical and biotechnology. The nanotechnology developments in industries are very promising.The nanotechnology platforms are being investigated in development or in clinical stages. The areas of interest will be effective and safer targeted therapeutics for a myriad of clinical applications.

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