Recent Developments in Drug Delivery System via Nanotechnology

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Abstract: Present article deals the detail applications of drug delivery based on nanotechnology and also report the investigations on drug delivery based systems. The synthesis of particles using nanotechnology is used for reduction of toxicity of drugs. This review emphasize mainly the role of nanomaterials in drug delivery, kind of hazards that produced for delivery of drugs and highlights the future opportunity of several areas related to drugs.

Keywords: Nanomaterial, Drug Delivery, Pharmaceutical Agents, Nanotechnology.

1. Introduction

Nanotechnology is a revolutionary field of micro manufacturing involving physical and chemical changes to produce nanosized materials. A nanometer is equal to one thousand millionth of a meter [1]. It involves the study of monitoring the matter on an atomic and molecular scale. The molecular level investigation occurs at the range usually below 100 nm. In simple terms, a nanometer is one billionth of a meter and the properties of materials at this atomic or subatomic level are different significantly from properties of the same materials having larger sizes [2]. The primary properties of nanomaterials were applied for its physical, mechanical, electrical, magnetic, chemical and biological applications. Recently, attention has been focus towards its nanotechnology application, especially in the area of drug delivery. The reason is the challenges with use of bulky materials in drug delivery which include poor bioavailability, solubility, and intestinal absorption, sustained and targeted delivery to site of action, healing effectiveness and plasma fluctuations of drugs [3–7]. Several researches in nanodrug delivery have been designed to overcome these challenges through the improvement and manufacture of nanostructures. It has been reported that, the technology can allow target delivery of drugs to various areas of the body. Due to this technology, delivery of drugs is badly water soluble. Nanotechnology increases oral bioavailability of drugs due to their specific mechanisms. Nanostructures are able to penetrate tissues and are easily taken up by cells, allowing efficient delivery of drugs to target sites of action [8, 9, 10].

2. Significance of Nanomaterials in drug delivery

The nano sized drug delivery systems are attractive to formulation scientists. The most important reason is that number of surface atoms or molecules to the total number of atoms or molecules increases in drug delivery systems [1]. Due to which surface area increases and size of the nanomaterial decreases. This helps to bind, adsorb and carry with other compounds such as drug, probes and proteins. The nanoparticles itself can be engineered to form nanoscale size materials too [9, 10]. The nanosized device systems having sizes smaller than eukaryotic or prokaryotic cells [11], can eventually much more in amount reach in generally inaccessible areas such as cancer cells, swollen tissues etc. Due to their enhanced permeability and retention effect (EPR) [12] and can damage lymphatic drainage thus that can be used for administration of genes, proteins through the route. The nanomaterials used for this purpose, must be soluble, safe and biocompatible as well as bioavailable. They must not include blood vessel and less invasive and the toxicity associated with the nanomaterials for drug delivery should be very low so that they can be used to target the specific diseased tissue or all in a safe concentration [13]. They need protecting drug from enzymatic and hydrolytic degradation in the gastrointestinal tract and help in bypassing the “first-pass” metabolism in the liver. They generally remaining the circulation for longer time especially those coated with hydrophilic polymers [14] and hence suitable for enhancing the efficiency of drugs which can be used to monitor drug as sustained release formulation as well as for delivering DNA. When dissolution rate of drug enhanced, onset of therapeutic action increased, and the dose reduced. The premature loss of drug through rapid clearance
and metabolism can also be prevented. They also increase retention due to bio-adhesion. Nano-scale drug delivery systems such as fullerene, nanoparticles, nanotubes, nanoshells, quantum dots, nanocapsule, nanosphere, nanovaccines, nanocrystals etc. are believed to have potentials to revolutionize for drug delivery systems[8]. Further the nonmaterial on chips, nano robotics, and magnetic nanoparticles are useful to attachement for specific antibody.. The nanosized empty virus capsids and magnetic immunoassay are new dimensions of their use in drug delivery[10]. Thus nanomaterials can be used for strategic development of new drug delivery systems. These are reformulating existing drugs to enhance the effectiveness, safety of drugs and decreasing the cost of health care[9].

3. Nano-scale drug delivery systems

3.1 Nanoparticles

Nanoparticles are submicron-sized polymeric colloidal particles with beneficial agents of interest encapsulated or dispersed within their polymeric matrix or conjugated onto the surface. Synthetic polymers are used to prepare nanoparticles for drug delivery is generally recyclable. Nanoparticles may also be composed or transport a variety of substances such as silica, gold and other heavy metals, quantum dots, nanocrystals, quantum rods and various contrast agents[9].

![Figure 1: Targeted drug delivery via nanoparticle](image1.png)

A gold nanoparticle (NPs) consists of a center of gold atoms that can be functionalized by addition of a monolayer of moieties containing a thiol (SH) group. Gold NPs can be synthesized using NaBH₄ to reduce AuCl₄-salts[7] in the presence of thiolcontaining moieties that subsequently form a monolayer around the core gold atom, which depend on the stoichiometric gold/thiol ratio. Drug delivery using gold NPs has been made in DNA delivery for gene therapy and imaging [16]. PEG coated micelles containing drugs are also used to deliver drug as new delivery system. Many other nano-sized synthetic, semisynthetic, natural and metals are under investigation to know their potentials as drug delivery materials [1]. Polymeric nanoparticles may adhere to the cell surface and release drug molecules by diffusion which may enter inside the cell to work. However the entire polymeric nanoparticles can also enter the cell by endocytosis. They bind with the cell surface receptor and formation of endosome takes place. Endosome may be lysed with the help of lysosomes enzymes and the nanoparticles release in the cytoplasm[15,16] as shown in figure 3.

![Figure 2: Polymeric Nanoparticle with targeting ligands](image2.png)

![Figure 3: Polymeric nanoparticles with targeting ligands](image3.png)
material. They are particles with physical dimensions smaller than the excited Bohr radii [5]. QD have a future in imaging because their size range (2 to 8 nm) reveals unique optical and electronic properties such as tunable fluorescent emission by varying particle size or compositions. [11]. Optical imaging equipment costs are cheaper than competing technologies such as Magnetic Resonance Imagining. By using QD-labeled tumor cells, it was possible to follow their paths after intravenous administration as they extravagated into the lungs [6]. This can potentially help to study metastatic tumor cell extravasations.

The biomolecule conjugation of the QD can be modulated to target various biomarkers. They can be tagged with biomolecules and used as highly sensitive probes. QD can also be used for imaging of guard node in cancer patients for tumor staging and planning of therapy. This technology also introduces some early success in the detection and treatment of breast cancer. QD may provide new insights into understanding the pathophysiology of cancer and real time imaging and screening of tumors [1]. Bioconjugated QD is collections of variable sizes of nanoparticles surrounded in small beads made of polymer material. In a process called “multiplexing,” they can be finely tuned to many luminescent colors. Another benefit is that quantum dot probes emitting at different wavelengths can be used together for imaging and tracking multiple cancer rmarkers simultaneously, increasing the specificity and sensitivity of cancer detection. Recent progress in the chemistry of QD has extended their use in biological applications, reduced their cytotoxicity and rendered quantum dots a powerful tool for the exploration of distinct cellular processes, like uptake and intracellular delivery. Another application of QD is for viral diagnosis. Rapid and sensitive diagnosis of Respiratory Syncytial Virus (RSV) is important for infection control and development of antiviral drugs. Antibody-conjugated nanoparticles rapidly and sensitively detect RSV and estimate relative levels of surface protein phrase[17]. A major development is the use of dual-color QD or fluorescence energy shiftnanobeads that can be simultaneously excited with a single light source. QD linked to biological molecules, such as antibodies, have shown promise as a new means for detecting and quantifying a wide variety of cancer-associated molecules. In the field of nanomedicine, QD can make a worthy contribution to the development of new diagnostic and delivery systems as they offer single optical properties for highly sensitive detection and they are well defined in size and shape and can be customized with various targeting principles.

![Figure 3: Endocytosis Mediated Cellular internalization of drug Nanocarriers. (9)](image)

3.2 Fullerenes and Nanotubes

Fullerenes consist of carbon in the form of a hollow sphere or ellipsoidal tube. These are also known as ‘Bucky balls’ because of their similarity to the dome, design of Buckminster Fuller. Fullerenes are being investigated for drug delivery of antiviral, antibiotics and anticancer agents. Fullerenes have the potential to stimulate host immune response and production of fullerene specific antibodies. Soluble derivatives of fullerenes such as C_{60} have shown great utility as pharmaceutical agents [7]. Carbon nanotubes can be made more soluble by absorption of carboxylic or ammonium groups to their structures and can be used for the transport of peptides, nucleic acids and other drug molecules. The capability of nanotubes to transport DNA across cell membrane is used for studies of gene therapy. DNA can be attached to the tips of nanotubes or can be incorporated within the tubes [8].

3.3 Nanopores

Nano-pores having diameter of 20nm consist of wafers with high density of pores which allow entry of oxygen, glucose and other chemicals such as insulin to go through. Nanopores can be used as devices to protect transplanted tissues from the mass immune system, at the same time, utilizing the advantage of immunosuppressive agents [8]. Cells of pancreas can be enclosed within the nanopore device and implanted in the recipient’s body. Nanopores can also be employed in DNA sequencing. Nanopores are also being developed with an ability to differentiate purines from pyrimidines [9].

3.4. Quantum dots

Quantum dots (QD) are crystalline aggregate of a few hundred atoms of elements from group II-VI or III-V of the periodic table, layered with an insulating outer shell of a different
3.5 Nanoshells

Nanoshell particles are special class of nanocomposite materials. They consist of concentric particles, in which particles of one material are coated with a thin layer of another material using specialized procedure [14-15]. Nanoshell particles are highly functional materials show modified and improved properties than their single constituent counterparts or nanoparticles of the same size. Their properties can be modified by changing either the constituting materials or core-to-shell ratio. Nanoshell materials can be synthesized from semiconductors (dielectric materials such as silica and polystyrene), metals and insulators. Generally dielectric materials such as silica and polystyrene are generally used as core because they are highly stable [16]. Metal nanoshells are a new type of composite spherical nanoparticles consisting of a dielectric core enclosed by a thin hard shell which is typically gold. Nanoshells offer other advantages over conventional organic dyes including better optical properties and economical susceptibility to chemical/thermal denaturation. Furthermore, the same conjugation protocols used to join biomolecules to gold colloid are easily modified for nanoshells. Nanoshells possess highly favorable optical and chemical properties for biomedical imaging and therapeutic applications [17]. By carefully choosing the core to shell ratio, it is possible to design novel nanoshell structures, which absorb light or scatter [18]. When a nanoshell and polymer matrix is illuminated with rich wavelength, nanoshells absorb heat and transfer to the local environment. This causes collapse of the network and discharge of the drug. In core shell particles-based drug delivery systems either the drug can be encapsulated or adsorbed onto the shell surface. The shell interacts with the drug via a specific functional group or by electrostatic stabilization method. When it gets in touch with the biological system, it directs the drug. In imaging applications, nanoshells can be tagged with specific antibodies for ill tissues or tumors. Nanoshell materials have considerable awareness in recent years because of potential applications associated with them [19,20]. The nanoshells for drug delivery and imaging systems are shown in figure 4.

4. Applications of nanoscale drug delivery systems

4.1 Nanotechnology for brain drug delivery

The blood brain barrier (BBB) is a structure created by a complex system of endothelial cells, astroglia, pericytes, and perivascular mast cells, preventing the way of most circulating cells and molecules. The tightness of the BBB is recognized mostly to the vascular layer of brain capillary endothelial cells which are interconnected side-by-side by tight and adherents’ junctions. Amongst the unlikennanodevices, nanosize drug delivery systems between 1 and 100 nm work as a whole unit in terms of transport to cross BBB. Nanosize brain drug delivery systems may promote the targeting ability of drug in brain and at the similar time increase the permeability of molecules through BBB. However crossing of BBB by the nano drug carriers will depend completely on the physicochemical and biomimetic features and does not depend on the chemical construction of drug, within the nanoparticles. Nanosized drug carriers which do not cross BBB generally can be made “stealth” covered with some polymeric materials or other chemicals to avoid the reticuloendothelial system, to display long circulation time and stability in blood, and may be functionalized to successfully cross the BBB and target brain [21].

4.2 Nanosized drug carriers in ocular drug delivery

Drug loaded nanoparticles with favorable organic properties include prolonging the residence time, decreasing toxicity and high capability of drug penetration into the deeper layers of the ocular structure and minimizing precorneal drug loss by the rapid tear fluid turnover.
Nanocarriers could target the cornea, retina and choroid by surficial applications. Nanocarrier-based drug delivery is suitable in the case of the retina, as it has no lymph system, hence retinal neovascularisation and choroid neovascularization contain similar environments to that of solid tumors, and the EPR effect as offered for solid nanoparticles in case of solid tumor may also be available for drug delivery targeted to eyes by nanoparticles. Nanoparticles can deliver ocular drugs to the target sites for the treatment of various diseases such as glaucoma, corneal diseases, diabetic retinopathy etc. The uses of nanotechnology based drug delivery systems like nanosuspensions, SLNPs and nanoliposomes have better effect for ocular therapeutic efficiency. Nanotechnology-based drug delivery is also very capable in crossing membrane barriers, such as the blood retinal barrier in the eye[1].

4.3. Nanoparticle loaded contact lenses

Contact lenses loaded with nanoparticles can be effective for current administration of ophthalmic drugs. Drug loaded contact lenses can also supply continuous drug release because of slow diffusion of the drug molecules through the lens matrix. The saturated contact lenses also delivered drugs only for a period of few hours for some typical drugs. The period of drug delivery from contact lenses can be significantly increased if the drug is first entrapped in nanoformulations, such as nanoliposomes, nanoparticles, or micro emulsions. Such drug nanocarriers can then be dispersed during the contact lens material. The setup of drug in nanocarriers also prevents the interaction of drug with the polymerization mixture. This provides extra resistance to drug release, as the drug must first diffuse through the nanocarriers and go through the drug carrier surface to reach the contact lens matrix[17].

4.4. Biodistribution of Nanoparticles in the retina

The ocular bio distribution of nanoparticles can give insights into the bioavailability, cellular uptake, duration of drug achievement and toxicity. Factors such as particle size, composition, surface charge and mode of administration influence the bio distribution in the retinal structures and also their drainage from the ocular tissues. Larger particles (2μm) were found to stay in vitreous cavity near the trabecular meshwork from which they are discharged out from the ocular Tissue inside 6 days, whereas the particles 200 nm were found evenly distributed in the vitreous cavity, and the inner limiting membranes. The lesser particles ~50 nm crossed the retinal barriers, and was detected in the retina even after 2 months post injection. The surface chemistry can also affect nanoparticle distribution. Positively charged nanoparticles can hold to the anionic vitreous network components and aggregate within the vitreous network. The chemistry can also involve nanoparticle distribution. Positively charged nanoparticles can adhere to the anionic vitreous network components and combined within the vitreous humor. Anionic nanoparticles were found to spread through the vitreous humor and can even penetrate the retinal layers to be taken up by Muller Cells. Vitreous humor is regarded as the obstacle for non-viral ocular gene therapy because of the strong interaction of conventional cationic nature of non-viral gene vectors with the anionic vitreous humor. The cationic PEI nanoparticles aggregated inside vitreous humor and were prevented from distributing to the retina by the vitreal barrier. In contrast, cationic glycol chitosan (GC) nanoparticles and GC/PEI blended nanoparticles can penetrate the vitreal barrier and even reach at the inner limiting membrane because of the existence of glycol groups on nanoparticles[17,18,19].

4.5. Nanoparticles in cancer

Cancer cells are weaker than usual cells to the effect of chemotherapeutic agents and the most of the anticancer drugs can cause injury to the normal cells. Optimum dose and frequency are both important factors in the persistence of cancer cells during cancer chemotherapy. Now attempts are focused on efforts to kill cancer cells by more precise targeting while sparing the usual cells. Nanoparticulate delivery systems in cancer therapies offer better penetration of therapeutic and diagnostic substances inside the cancerous tissue in comparison to conventional cancer therapies. Nanoparticles are constructed to take recompense of fundamental cancer morphology. Nanoparticulate drug delivery systems are being developed to transport lesser doses of chemotherapeutic agents in an effective form and control drug distribution inside the body. Nanocarriers can offer many advantages over free drugs in cancer chemotherapy such as they protect the drug from early degradation, prevent drugs from prematurely interacting with the biological environment, enhance absorption of the drugs into a chosen tissue (solid tumor), control the pharmacokinetic and drug tissue distribution profile and improve intracellular penetration[16,17,18].

Nano-particulate delivery systems utilize specific targeting agents for cancer cells minimizing the uptake of the anticancer agent by usual cells and enhance the entry and retention of the agent in tumor cells. Nanocarriers may actively bind to the specific cancer cells by attaching targeting agents with the help of ligand molecules to the plane of the nanocarriers that bind to specific
receptorantigens on the cell surface. Nanocarriers will recognize and attach to target cells through ligand receptor interactions. It is even possible to increase the drug targeting efficiency with the help of antibodies by conjugating a therapeutic agent directly to it for targeted delivery.

Like receptor targeting, targeting of angiogenic factors also takes advantage of properties unique to cancer cells. Anti-angiogenic treatment is the use of drugs or other substances to stop tumors from developing new blood vessels. In a study nanoparticles were formulated comprising a water-based nucleus of Vickers microhardness sodium alginate, cellulose sulphate, and anti-angiogenic factors likethrombospondin (TSP)-1 or TSP-517, crosslinked with dextran polyaldehyde with calcium chloride or conjugated to heparin sulphate with sodium chloride. In addition bioluminescent agent, luciferase, or dissimilarity agent, polymeric gadolinium was located within the polyanionic core for drug targeting and detection. Similarly, many pains are on for cancer cell targeting specifically with drug nanocarriers. Thus the drug nanocarriers are of great hope for future cancer therapy [11, 12].

Figure 5 shows the systematic diagram of nanoparticle permeation and retention effect in normal and tumors tissues.

**Figure 5:** Schematic diagram of nanoparticle permeation and retention effect in normal and tumor tissues [11].

Usual tissue vasculatures are lined by rigid endothelial cells, hereby preventing nanoparticulate drug delivery system from escaping, whereas tumor tissue vasculatures are permeable and hyper permeable allowing preferential accumulation of nanoparticles or nanoliposomes in the growthinterstitial space bypassivetargeting [7].

### 4.6 Gene delivery

Transfer of genetic material in nanocarriers may be moved toward for the treatment of various genetic disorders such as diabetes mellitus, cystic fibrosis and may more. A number of systemic diseases are caused by lack of enzymes factors that are due to missing or faulty genes. Previously gene therapy which was used to treat genetic disorders today being contemplated as carrier systems which could be implanted for combating diseases other than genetic disorder like malignant form of tumor, heart diseases and nervous diseases. Nanoliposomes can be used to deliver genetic materials into cells. Nanoliposomess include with PEG (polyethylenglycol) and galactose target liver cells effectively due to their rapid uptake by liver Kupffer cells. Gene therapy can be tried with liposomal nanocarriers for liver disorders such as Wilson’s and hereditary hemochromatosis. Cationic nanoliposomes have been considered as potential non-viral human gene delivery system. Another effective method for administering nanoliposomes is by using ligand receptor complex using EGF-EGFR system for targeting principle by nanoliposomes where EGF is a small protein which binds through receptor EGFR. Also mixing cationic lipids with plasmid DNA leads to the creation of lipoplexes where the process is driven by electrostatic interactions. The negatively charged genetic material (e.g. plasmid) is not encapsulated in nanoliposomes but complexed with cationic lipids by electrostatic interactions. Plasmid liposome complexes can come in the disease cells by infusion with the plasma or endosome membrane. Allovector-7 (gene transfer product) is composed of a plasmid containing the gene for the main histocompatibility complex antigen HLA-B7 with B2 microglobulin formulated with the cytofectin. The life of a composed lipid decides the unloading of the gene from nanoliposomes which enables control over the mode of release, doping of nanoliposomes with unbiased lipids such as 1,2-Dioleoyl-sn-glycero-3-phosphoethanolamine (DOPE) which helps in endosomal membrane fusion by recognizing and destabilizing the phospholipids in a flip flop manner which paves method for the liposomes to incorporate the membrane with the dissociation of nucleic acid into the cytoplasm. Viral system based gene carrier have the ability to conquer the biological barriers within the body and then access to the host nucleus replicative machinery which resulted in the exploitations of the system for drug delivery using nanotechnology. The development of a non-viral method for in vivo gene transfer was designed where the vector was packed into compact nanoparticles by successive add-ons of oppositely charged polyelectrolytes including an incorporation of ligands into the DNA-polyelectrolyte shells which be mixed with Plutonic F127 gel serving as a biodegradable adhesive to keep shells in contact with the targeted vessel. A novel method of gene delivery is with viruses like adenovirus associated viruses (AAV) which have their virulent genes
detected with lent viruses, clearly showing their efficiency.

5. Conclusion

Nanotechnology has revolutionized the drug delivery system. Advancements in this area have allowed some Nano medicines in the market to achieve desirable properties like to reduce toxicity and improve the patient compliance, as well as clinical outcomes. The combination of nanoparticles in drug delivery technologies in preformulation work, not only accelerates the increase of new therapeutic moieties, but also helped in the reduction of attrition of new molecular entities caused by unwanted biopharmaceutical and pharmacokinetic properties. The applications of nanotechnology in drug delivery are widely expected to change the scene of pharmaceutical and biotechnology industries for the predictable future. Target-specific drug therapy and methods for early diagnosis of pathologies are the precedence research areas where nanotechnology would play a prominent role.

6. REFERENCES