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# Engineered Nanoparticles as Precise Drug Delivery Systems

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**Abstract** With the remarkable development of nanotechnology in recent years, new drug delivery approaches based on the state-of-the-art nanotechnology have been receiving significant attention. Nanoparticles, an evolvement of nanotechnology, are increasingly considered as a potential candidate to carry therapeutic agents safely into a targeted compartment in an organ, particular tissue or cell. These particles are colloidal structures with a diameter smaller than 1,000 nm, and therefore can penetrate through diminutive capillaries into the cell's internal machinery. This innovative delivery technique might be a promising technology to meet the current challenges in drug delivery. When loaded with a gene or drug agent, nanoparticles can become nanopills, which can effectively treat problematical diseases such as cancer. This article summarizes different types of nanoparticles drug delivery systems under investigation and their prospective therapeutic applications. Also, this article presents a closer look at the advances, current challenges, and future direction of nanoparticles drug delivery systems. J. Cell. Biochem. 97: 1184–1190, 2006. 

**Key words:** nanoparticles; architecture; material; nanotechnology; drug delivery; therapeutic agent; therapeutic application

Precise drug release into highly specified targets involves miniaturizing the delivery systems to become much smaller than their targets. It is highly expected that these minute drug delivery systems can be realized through the advances in nano-biotechnology. The integration of nanotechnology products, such asnanoparticles with therapeutic agents, has recently created a new therapeutic trend that would not otherwise be possible. Nanoparticles can be defined as colloidal systems with a diameter smaller than 1,000 nm [Brigger et al., 2002]. Recently, many therapeutic agents including small molecules, proteins, DNA, and peptides have been developed into potent and complex agents. Using traditional drug delivery approaches, including the oral and injection methods, to treat diseases with these agents could be useless and toxic [Davis and Illum, 1998]. In the common oral doses, these agents are often destroyed during intestinal transit or inadequately absorbed and therefore become ineffective. Moreover, the uncontrolled level of these agents could cause concentration spikes, thereby harming the body. However, attaching these small therapeutic agents to nanoparticles may circumvent most of these delivery challenges and produce smart pills. Nanoparticles drug delivery systems, due to their diminutive size, can penetrate across barriers through small capillaries into individual cells to allow efficient drug accumulation at the targeted locations in the body [Unezaki et al., 1996; Hobbs et al., 1998]. By doing so, the therapeutic agent toxicity is reduced, the drug side effects are decreased and the treatment efficacy is enhanced. Also, therapeutic agents can be loaded into nanoparticles that are not identified by the immune system. This stealth mode makes them potential candidates to carry antiviral drugs to selectively target

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human immunodeficiency virus (HIV)-infected cells [Schafer et al., 1992].

Nanoparticles have been realized using a number of materials including polymers, metals, and ceramics. Based on their manufacturing method and material, these particles can take various shapes and sizes with distinct properties. In this paper, nanoparticles are classified based on their materials and briefly presented with some of their potential applications as drug delivery vehicles. The paper also highlights the recent progress and the challenges that these novel nanoscale delivery systems undergo.

## NANOPARTICLES DRUG DELIVERY SYSTEMS

Many types of nanoparticles drug delivery systems are in various stages of investigation. These particles have been fabricated from various materials with unique architectures to serve as a possible drug vehicle to treat a particular disease. Most of the current research is mainly focusing on using nanoparticles as drug delivery carriers for challenging, in most cases, lifelong diseases such as cancer, HIV, and diabetes (Table I). The current therapy for these diseases can be ineffective and most of the cases suffer death. Using nanoparticles to carry drugs securely to the infected locations could be a useful tool to fight these diseases. For example, to deliver anticancer therapeutic agents to cancer cells, anticancer drugs must conquer the resistance to the drug at the organ, tissue, and/or cellular level [Brigger et al., 2002]. Also, because anticancer drugs tend to disperse to the entire body destroying both the cancer and the normal cells, traditional chemotherapy in some cases might not be successful. Targeting cancer cells using nanoparticles loaded with anticancer agents is a promising tactic that could meet these challenges.

Vaccination against problematic diseases is yet another area of investigation that is being optimistically affected by the development of nanoparticles. A recent study by Cui et al. [2005] has reported a novel cancer vaccine delivery system using nanoparticles. Liposome polycation pDNA (LPD) nanoparticles were utilized to carry a strong peptide antigen to immunize mice. This immunization method seems to be more effective than using traditional vaccines, which exploit either live attenuated or killed bacteria or viruses. The potency of the new vaccines including peptides, proteins, and DNA is attractive. However, to maintain the in vivo potency of these vaccines, a delivery system and/or adjuvant is frequently essential [Plotkin, 2003]. The nanoparticles vaccine delivery system offers a platform to enhance the in vivo potency of the next generation vaccines.

The real thrust of the current therapy for the puzzling diseases is in the direction of developing new powerful drugs. The next generation of drugs will involve more complex biological or chemical entities and gene therapy. The solubility, in vivo stability, intestinal absorption, route of administration and targeting, effectiveness, and/or the side effects of these new drugs are among the challenges that push researchers toward exploring a new drug delivery strategy. Engineered hybrid nanoparticles systems have been proposed as an alternative approach to tackle these challenges (Table I). Yet, the hybridization of these nanoparticles to a fully functioning therapy is still in the early stages. Drugs can be loaded into nanoparticles via encapsulation, surface attachment, or entrapping. The nanoparticles architecture and material, drug type, and targeted location can determine the attachment technique.

## RECENT DEVELOPMENT IN NANOPARTICLES ENGINEERING

Sahoo and Labhasetwar [2003] and Hughes [2005] dedicated their reviews to the details of nanoparticles architecture, fabrication, and drug attachment methods. Generally, nanoparticles have been realized in polymers, ceramics, metals, and biological materials with various forms. Nanoparticles might take spherical, branched, or shell structures. Each structure offers unique characteristics that make it a suitable drug delivery candidate for a particular therapy.

### Polymeric Nanoparticles

Significant research has been devoted to investigating a number of polymeric types of nanoparticles, particularly biodegradable polymers [Raghuvanshi et al., 2001; Kreuter et al., 2003]. These particles can be fabricated in a wide range of sizes and varieties. In addition to the steady drug release for weeks, biodegradable nanoparticles do not accumulate in the body; as a result, they have drawn considerable

**TABLE I. Nanoparticles as Drug Delivery Carriers**

| Nanoparticle | Size (nm) | Carried therapeutic agent | Examples of potential targeted therapeutic application | Advantage |
|---|---|---|---|---|
| Polymeric biodegradable nanoparticles | 10–1,000 | Plasmid DNA, proteins, peptides, low molecular weight compounds | Brain tumor therapy [Olivier et al., 1999; Kreuter et al., 2003], bone healing [Labhasetwar et al., 1999], vaccine adjuvant [Raghuvanshi et al., 2001], coating gut suture [Cohen et al., 2000], restenosis [Guzman et al., 1996; Panyam et al., 2002], inflamed colonic mucosa [Lamprecht et al., 2001], diabetes therapy [Al Khouri et al., 1986; Watnasirichailkul et al., 2000] | Sustain localized drug therapeutic agent for weeks |
| Ceramic nanoparticles | <100 | Proteins, DNA, anticancer therapeutic agents, high molecular weight compounds | Photodynamic therapy [Roy et al., 2003b], liver therapy [Roy et al., 2003a; Dey, 2005], diabetes therapy [Cherian et al., 2000] | Can be easily prepared, water-soluble, and stable in biological environment |
| Metallic nanoparticles | <50 | Anticancer therapeutic agents, proteins, DNA | Cancer therapy [Wang et al., 2004; Priyabrata et al., 2005] | Extremely small size with vast surface area to carry large dose |
| Polymeric micelles | <100 | DNA, anticancer therapeutic agents, proteins | Solid tumors therapy [Yokoyama et al., 1990; Kataoka et al., 2001; Rapoport et al., 2003], antifungal treatment [Yu et al., 1998] | Have hydrophobic core, and so they are suitable carriers for water-insoluble drug |
| Liposomes | 50–100 | Proteins, DNA, anticancer therapeutic agents | Tumors therapy [Goren et al., 1996; Versluis et al., 1998; Lasic et al., 1999], HIV therapy [Slepushkin et al., 1996], vaccine delivery [Rao and Alving, 2000] | Effective in reducing system toxicity and can stay longer in targeted tissue |
| Dendrimers | <10 | DNA, anticancer therapeutic agents, antibacterial therapeutic agents, antiviral therapeutic agents, high molecular weight compounds | Tumors therapy [Kobayashi et al., 2001; Quintana et al., 2002; Latallo et al., 2005], bacterial infection treatment [Chen and Cooper, 2002; Boas and Heegaard, 2004], HIV therapy [Witvrouw et al., 2000; Rojo and Delgado, 2004] | Can be modified to carry hydrophobic or hydrophilic drug |

attention. Earlier reviews [Soppimath et al., 2001; Panyam and Labhasetwar, 2003] were dedicated to biodegradable nanoparticles preparation methods, drug loading, and their potential use in drug delivery systems. Biodegradable nanoparticles have the ability to carry various therapeutic agents including DNA, proteins, peptides, and low molecular weight compounds. Furthermore, these particles recently have been synthesized to be sensitive to the level of acidity in their environment [Herffernan and Murthy, 2005]. Consequently, polymeric nanoparticles can be possible drug carriers for a diverse number of pharmacological therapies for various types of tumors, diabetes, bone healing, and vaccination.

Polymeric micelles are another form of nonbiodegradable nanoscale polymeric structures. These nanostructures are physiologically stable in biological environment, and thus can deliver drugs securely to the targeted location. Furthermore, the ability to engineer their hydrophobic segments makes them an appealing system to deliver water-insoluble drugs. A review complied by Panyam and Labhasetwar [2003] reveals that polymeric micelles can be an effective candidate to deliver drugs for fighting solid tumors. Because of their small size ($<$100 nm) and the flexibility to engineer their drug/nanoparticle attachment, polymeric micelles can effectively target solid tumors and destroy only the cancer cells.

### Ceramics Nanoparticles

Ceramic nanoparticles are inorganic systems with porous characteristics. Because these particles can be easily engineered with the desired size and porosity, growing interest has recently emerged to utilize ceramic nanoparticles as drug vehicles. Most of this research has been exploring typical biocompatible ceramic nanoparticles such as silica, titania, alumina, etc. in cancer therapy. A study by Roy et al. [2003a,b] reveals that silica-based doped nanoparticles can be an achievable drug delivery tactic in the photodynamic therapy to fight cancer. A recent study by Dey [2005] suggests that, because of their physiological stability, hybridizing ceramic nanoparticles with DNA offers a potential therapy to target liver cancer cells. In a different investigation of ceramic nanoparticles, insulin has been entrapped in hydroxyapatite nanoparticles [Paul and Sharma, 2001]. The insulin release profile shows promising results for orally administered insulin instead of repeatable injections.

### Metal Nanoparticles

Metal nanoparticles can be synthesized in extremely small sizes ($<$50 nm), therefore their large surface area has the ability to carry a relatively high drug dose. Functionalizing the surface of conventional nanoparticles metals like gold or silver to carry drugs is under investigation. Recent research by Priyabrata et al. [2005] reveals that gold nanoparticles can be functionalized into a composite system to carry both an anti-angiogenic (angiogenesis is the growth of blood vessels needed to support the growth of tumor cells) and anticancer agent in one gold nanoparticle. By doing so, the tumor's cells can be destroyed at the same time the survival of other possible tumors can be prevented. In a different study, the use of metal nanoshells to encapsulate drugs inside their hollow core is being explored [Sun et al., 2002]. In this method, metal nanoparticles release their drug into the targeted location using an external exciting source like an infrared light or a magnetic field.

### Liposomes

Liposomes are small spherical systems that are synthesized from cholesterol and non-toxic phospholipids. Liposomes can be engineered to possess different characteristics depending upon the lipid of choice in the production process. Because they are natural materials, liposomes are considered attractive, harmless drug delivery carriers that can circulate in the blood stream for a long time. A recent review indicates that liposomes are being investigated to carry anticancer drugs using various encapsulating technologies [Hofheinz et al., 2005]. Liposomes that carry anticancer drugs can sustain a long releasing process targeting the cancer cells without harming the normal cells.

### Other Nanostructures

*Dendrimers* are emerging as a rather new class of polymeric nanosystems with applications in drug delivery. These systems are built from a series of branches around an inner core, providing products of different generations, and offer intriguing possibilities in this regard. They can be synthesized from almost any core molecule and the branches similarly

constructed from any bi-functional molecule. The distinctive architecture (star-shaped) of dendrimers has attracted interest in loading drug molecules in either the interior of the dendrimers or attached to the surface groups. In a recent in vivo study, dendrimic polymers (<5 nm) have been loaded with an anticancer drug to selectively target tumor cells [Latallo et al., 2005]. This promising in vivo study was performed on mice using anticancer conjugated polyamidoamine (PAMAM) dendrimers.

*Carbon nanotubes* are extremely small tubes with either a single or multi wall carbon structure. The exclusive structures of these tiny tubes make them an appealing candidate to encapsulate drugs inside their cavities. At the present, these nanotubes are still under widespread investigation in laboratories. However, the toxicity of these carbon-based tubes is of concern, particularly if they circulate in the blood stream or accumulate in the targeted tissue.

## OVERALL SUMMARY

Although significant effort has been devoted to develop a nanoparticles drug delivery system, to the knowledge of the authors a fully functioning therapy based on a nanoparticles delivery system is not yet in use. Nanoparticles drug delivery systems are mainly proposed as an alternative to sustain the effectiveness of newly developed drugs, which are potent and complex. To accomplish the desired goals of this innovative system, further clinical trials need to be done. These trials are the key to the realization and success of the next generation of therapy.

New nanoparticles structures and materials are continuously being reported and new methods of encapsulation are being developed. With these dedicated efforts, it seems that the synergic future of a nanoparticles delivery system holds substantial promise. Engineering drug/nanoparticle loading, controlling the drug release profile, and guiding nanoparticles systems to the desired target are among other challenges that are currently being evaluated. An important concern regarding the use of non-biodegradable nanoparticles is their accumulation in the body. Their high level of accumulation might reach a harmful boundary, and thus cause undesirable side effects. Therefore, in vivo toxicological studies are needed at this stage.

The future vision of nanoparticles drug delivery systems is to develop a self-actuated therapy through localized medical implants. Yih et al. [2002, 2005a,b,c] have been developing bio-micro electro mechanical (BioMEMS) micropumps for controlled localized drug delivery systems such as hydrogel nanoparticles. These systems, when implanted, will be able to determine the necessary dose via sensory systems. The implants are normally designed to operate for a long period of time, possibly months. The stability and usefulness of nanoparticles delivery systems might be influenced by time. Thus, further studies are essential to evaluate their efficacy over time when encapsulated and stored.

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