REVIEW

FABRICATION OF SOLID NANOPARTICLES FOR DRUG DELIVERY

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ABSTRACT

The use of nanoparticles in biotechnology presents a growing interest for the numerous possibilities offered by combining the world of materials, with its advanced technologies and their diverse properties, and the biological world, with its elaborate molecular architectures, properties and functions. Different nanoparticles are attractive for their intrinsic properties of optical transparency, controllable porosity, chemical inertness and biocompatibility. Various synthetic methods have been developed for preparing nanoparticles with well-controlled sizes and shapes. Research in nanotechnology and biopharmaceutics or collectively nanomedicine has recently taken a new dimension, with amazing variety of methods for fabrication of nanoparticles. It is now possible to enhance or control drug delivery, this is required in case of poorly soluble drug, or drugs to cross blood brain barrier (BBB). Moreover, this technique can also be utilized for targeted delivery of drugs. There are number of methods reported in literature for the fabrication of nanoparticles. These include Sol-Gel technique, spraying the drug solution in vacuum, solvent diffusion or precipitation method. The former two techniques are mostly used to fabricate porous nanoparticles. Present paper reviews these techniques so as to give an idea to those planning to start with the fabrication of nanoparticles in a particular area of interest.

Keywords: Fabrication; solid nanoparticles.

INTRODUCTION

The application of micro- and nanotechnology to the biomedical arena has tremendous potential in terms of developing new diagnostic and therapeutic modalities. Over the last several years, micro fabrication technology has been applied to the successful development of a variety of health care-related products including diagnostic systems, techniques and apparatus for high throughput screening of new drug candidates. While the majority of research has focused on the development of miniaturized diagnostic tools, researchers have more recently concentrated on the development of micro devices for *therapeutic* applications. Micro- and nanofabrication techniques are currently being used to develop implants that can record from, sense, stimulate, and deliver to biological systems (Aitken *et al*., 2004; Sarah and Tejal 2003). Nanoscale devices are 100 to 10,000 times smaller than human cells but are similar in size to large biomolecules such as enzymes and receptors. Nanoscale devices smaller than 50 nm can easily enter most cells, and those smaller than 20 nm can move out of blood vessels as they circulate through the body. Nanodevices are suitable to serve as customized, targeted drug delivery vehicles to carry large doses of chemotherapeutic agents or therapeutic genes into malignant cells while sparing healthy cells. Nanodevices can be constructed by the molding or etching, top-down approach, or by assembling structures atom by atom or molecule by molecule, bottom-up approach.

Anatomic features such as the blood brain barrier, the branching pathways of the pulmonary system, and the tight epithelial junctions of the skin make it difficult for drugs to reach many desired physiologic targets. Nanostructured drug carriers help to penetrate or overcome these barriers to drug delivery. Courrier *et al.*, (Courrier *et al*., 2002) have shown that the greatest efficiency for delivery into the pulmonary system is achieved for particle diameters of <100 nm. Greater uptake efficiency has also been shown for gastrointestinal absorption and transcutaneous permeation (Desai 1996; Hussain *et al*., 2001; Kohli and Alpar 2004), with particles around 100 nm and 50 nm in size, respectively. However, such small particles traveling in the pulmonary tract may also have a greater chance of being exhaled. Larger, compartmental or multilayered drug carrier architectures may help with delivery to the pulmonary extremities. For instance, the outer layers of the carrier architecture may be formulated to biodegrade as the carrier travels through the pulmonary tract. As the drug carrier penetrates further into the lung, additional shedding will allow the encapsulated drug to be released. Biodegradable nanoparticles of gelatin and human serum albumin show promise as pulmonary drug carriers (Brzoska *et al*., 2004).

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The efficiency of drug delivery to various parts of the body is directly affected by particle size. Nanostructure-mediated drug delivery is a key technology for the realization of nanomedicine and has potential to enhance drug bioavailability, improve the timed release of drug molecules, and enable precision drug targeting (Dubin 2004; Dass and Su 2001).

Nanoscale drug delivery systems can be implemented within pulmonary therapies (Courrier *et al*., 2002), as gene delivery vectors (Senior 1998), and in stabilization of drug molecules that would otherwise degrade too rapidly (LaVan *et al*., 2002; LaVan *et al*., 2003). Additional benefits of using targeted nanoscale drug carriers are reduced drug toxicity and more efficient drug distribution (Ravi 2000).

History

The term *nanotechnology* was defined by Tokyo Science University Professor Norio Taniguchi in a 1974 paper (Taniguchi 1974) as follows: *Nano-technology* mainly consists of the processing of, separation, consolidation and deformation of materials by one atom or one molecule. In the 1980s the basic idea of this definition was explored in much more depth by Dr. K. Eric Drexler, who promoted the technological significance of nano-scale phenomena and devices through speeches and the book *Engines of Creation*. The Coming era of Nanotechnology and Nanosystems: Molecular Machinery, Manufacturing, and Computation (Geoffrey and Michael 2006). Nanotechnology and nanoscience got started in the early 1980s with two major developments; the birth of cluster science and the invention of the scanning tunneling microscope (STM). This development led to the discovery of fullerenes in 1986 and carbon nanotubes a few years later. In another development, the synthesis and properties of semiconductor nanocrystals was studied. This led to a fast increasing number of metal oxide nanoparticles of quantum dots (Hari 2004).

Properties

Nanoparticles are of great scientific interest as they are effectively a bridge between bulk materials and atomic or molecular structures. A bulk material should have constant physical properties regardless of its size, but at the nano-scale this is often not the case. Size-dependent properties are observed such as quantum confinement in semiconductor particles, surface plasmon resonance in some metal particles and superparamagnetism in magnetic materials (Akerman *et al*., 2002).

The properties of materials change as their size approaches the nanoscale and as the percentage of atoms at the surface of a material becomes significant. Suspensions of nanoparticles are possible because the interaction of the particle surface with the solvent is strong enough to overcome differences in density, which usually result in a material either sinking or floating in a liquid. Nanoparticles often have unexpected visible properties because they are small enough to scatter visible light rather than absorb it. For example gold nanoparticles appear deep red to black in solution. Nanoparticles have a very high surface area to volume ratio. This provides a tremendous driving force for diffusion, especially at elevated temperatures. Sintering can take place at lower temperatures, over shorter time scales than for larger particles. This theoretically does not affect the density of the final product, though flow difficulties and the tendency of nanoparticles to agglomerate complicates matters. The surface effect of nanoparticles also reduces the incipient melting temperature (Bodegal *et al*., 2003).

Classification

At the small end of the size range, nanoparticles are often referred to as clusters. Nanospheres, nanorods, and nanocups are just a few of the shapes that have been grown. Metal, dielectric, and semiconductor nanoparticles have been formed, as well as hybrid structures (e.g., core-shell nanoparticles). Nanoparticles made of semi-conducting material may also be labeled quantum dots if they are small enough (typically sub 10nm) that quantization of electronic energy level occurs. Such nanoscale particles are used in biomedical applications as drug carriers or imaging agents.

Semi-solid and soft nanoparticles have been manufactured. A prototype nanoparticle of semi-solid nature is the liposome. Various types of liposome nanoparticles are currently used clinically as delivery systems for anticancer drugs and vaccines (Bruske-Hohlfeld *et al*., 2005).

However, the scientific literature related to the nanoparticle field does not currently allow a single definition to be reached regarding the dimensions of these particles. Moreover, while ultra fine particles and nanoparticles occupy comparable granulometric domains, each author proposes a range of different dimensions (Aitken *et al*., 2004; Gorokhov and Brouwer 2004). Nonetheless, the majority of authors consider that nanoparticles are smaller than 100 nm. With such a broad definition, nanoparticles could be classified in three main categories: nanoparticles of natural origin, those already produced for decades in large quantities, and finally, those produced by new technologies. The European Commission proposed that a distinction at least be made between free nanoparticles and bonded particles, which are less likely to cause health risks due to their inability to be bioavailable.

Among the nanoparticles of natural origin, some are of biological origin, including DNA with a diameter of around 2.5 nm and some viruses (10 to 60 nm) and bacteria (30 nm to 10 μm), while others are of mineral or

environmental origin. For example, these include the fine fraction of desert sand, oil fumes, smog, fumes originating from volcanic activity or from forest fires, and certain atmospheric dusts.

Among the nanoparticles of human origin, some well-known industrial processes, such as synthesis of carbon black by flame pyrolysis, result in highly agglomerated particles, the basic components of which have nanometric dimensions. Other materials are also produced on a large scale for commercial purposes by high temperature processes. For example, silica fumes, ultra fine titanium oxide particles and ultra fine metals (Aitken *et al*., 2004; Teague 2004).

Flame hydrolysis and plasma deposition processes are already commonly used in the metal recovery industry. Paint pigments often have dimensions of 80-100 nm. Moreover, welding generates a plume of fumes, the elementary particles of which have dimensions of 10 to 50 nm before agglomeration. Combustion processes (diesel, gasoline, barbecue, coal and several industrial processes) also produce nanoparticles of 7 to 40 nm (Michael and Wolfram 2006).

Characterization

Nanoparticle characterization is necessary to establish understanding and control of nanoparticle synthesis and applications. Characterization is done by using a variety of different techniques, mainly drawn from materials science. Common techniques are electron microscopy [TEM, SEM], atomic force microscopy [AFM], dynamic light scattering [DLS], x-ray photoelectron spectroscopy [XPS], powder x-ray diffractometry [XRD], and Fourier transform infrared spectroscopy [FTIR].

Whilst the theory has been known for over a century, the technology for Nanoparticle Tracking Analysis (NTA) allows direct tracking of the Brownian motion and this method therefore allows the sizing of individual nanoparticles in solution (Scott 2006).

Fabrication of nanoparticles

The process, by which molecular subunits spatially organize into well-defined supramolecular structures in spite of non-covalent interactions, self-assembly is becoming a powerful synthetic approach for creating advanced materials out of nanoparticle building blocks (Zou *et al*., 2005; Rabani *et al*., 2003). The preparations of highly structured nanoparticle assemblies, such as wires, rings, and super-lattices are being investigated extensively.

However, controlling the particle size and shape during synthesis is still a major challenge. Nevertheless, some physical and solid state chemical methods have been developed for making semiconductors, metal nanowires, nanobelts, and nanodots (Pan *et al*., 2001; Hu *et al*.,1999; Haynes and Van Duyne 2001). Additionally, at present there are various methods for making rods with somewhat controllable aspect ratios using seeding approaches (Jana *et al*., 2001).

There are several methods for creating nanoparticles; attrition and pyrolysis are common methods. In attrition, macro or micro scale particles are ground in a ball mill, a planetary ball mill, or other size reducing mechanism. The resulting particles are air classified to recover nanoparticle. In pyrolysis, an organic precursor (liquid or gas) is forced through an orifice at high pressure and burned. The resulting ash is air classified to recover oxide nanoparticle.

A thermal plasma can also deliver the energy necessary to cause evaporation of small micron-size particles. The thermal plasma temperatures are in the order of 10000 K, so that solid powder easily evaporates. Nanoparticles are formed upon cooling while exiting the plasma region.

The main types of the thermal plasmas torches used to produce nanoparticles are DC plasma jet, DC arc plasma and Radio Frequency (RF) induction plasmas. In the arc plasma reactors, the energy necessary for evaporation and reaction is provided by an electric arc which forms between the anode and the cathode. For example, silica sand can be vaporized with an arc plasma at atmospheric pressure.

The resulting mixture of plasma gas and silica vapour can be rapidly cooled by quenching with oxygen, thus ensuring the quality of the fumed silica produced. In RF induction plasma torches, energy coupling to the plasma is accomplished through the electromagnetic field generated by the induction coil. The plasma gas does not come in contact with electrodes, thus eliminating possible sources of contamination and allowing the operation of such plasma torches with a wide range of gases including inert, reducing, oxidizing and other corrosive atmospheres.

The working frequency is typically between 200 kHz and 40 MHz. Laboratory units run at power levels in the order of 30-50 kW while the large scale industrial units have been tested at power levels up to 1 MW. As the residence time of the injected feed droplets in the plasma is very short it is important that the droplet sizes are small enough in order to obtain complete evaporation.

The RF plasma method has been used to synthesize different nanoparticle materials, for example synthesis of various ceramic nanoparticles such as oxides, carbours/carbides and nitrides of Ti and Si (Aprahamian *et al*., 1987).

Gas phase synthesis and sol-gel processing

Major efforts in nanoparticle synthesis can be grouped into two broad areas: gas phase synthesis and sol-gel processing. Nanoparticles with diameters ranging from 1 to 10 nm with consistent crystal structure, surface derivatization, and a high degree of monodispersity have been processed by both gas-phase and sol-gel techniques. Typical size variances are about 20%; however, for measurable enhancement of the quantum effect, this must be reduced to less than 5% (Murray *et al*., 1993).

Initial development of new crystalline materials was based on nanoparticles generated by evaporation and condensation (nucleation and growth) in a sub-atmospheric inert gas environment (Siegel 1991; Siegel 1994). Various aerosol processing techniques have been reported to improve the production yield of nanoparticles, these include synthesis by combustion flame (Zachariah 1994; Calcote and Keil 1997; Axelbaum 1997; Pratsinis 1997), plasma (Rao *et al*., 1997), laser ablation (Becker *et al*., 1997), chemical vapor condensation (Jana *et al*., 2001; Kear *et al*., 1997), spray pyrolysis (Messing *et al*., 1994), electrospray (Mora *et al*., 1994) and plasma spray (Berndt *et al*., 1997).

Sol-gel processing is a wet chemical synthesis approach that can be used to generate nanoparticles by gelation, precipitation, and hydrothermal treatment (Kung and Ko 1996).

Size distribution of semiconductor, metal and metal oxide nanoparticles can be manipulated by either dopant introduction (Kyprianidou *et al*., 1994) or heat treatment (Wang *et al*., 1997). Better size and stability control of quantum-confined semiconductor nanoparticles can be achieved through the use of inverted micelles (Gacoin *et al*., 1997), polymer matrix architecture based on block copolymers (Sankaran *et al*., 1993) or polymer blends (Yuan *et al*.,1992), porous glasses (Justus *et al*., 1992) and ex-situ particle-capping techniques (Majetich, and Canter 1993; Olshavsky and Allcock 1997).

Additional nanoparticle synthesis techniques include sonochemical processing, cavitation processing, micro-emulsion processing, and high-energy ball milling. In sonochemistry, an acoustic cavitation process can generate a transient localized hot zone with extremely high temperature gradient and pressure such sudden changes in temperature and pressure assist the destruction of the sonochemical precursor (e.g. organometallic solution) and the formation of nanoparticles. The technique can be used to produce a large volume of material for industrial applications (Kannan *et al*., 2004).

Synthesis of gold nanoparticles

Synthesis of gold nanoparticle dimers is done by a solid phase approach using a simple coupling reaction of asymmetrically functionalized particles (Rajesh *et al*. 2007). The method may be used to generate dimers with a wide size range and containing two nanoparticles with different sizes. The dimers demonstrate remarkable stability in ethanol. The process could be generalized to obtain metal-semiconductor conjugates. In addition, the distance between nanoparticles could be controlled, generating a molecular ruler, by simply varying the chain length of the linker molecules.

Metal nanoparticles have received great attention due to their unique optical properties and wide range of applicability. In this context, controlling the particle-particle interaction is a major challenge to generate programmable assembly of nanoparticles, which shows potential usefulness in device fabrication and detection systems. Several methods have been developed to prepare gold nanoparticle assemblies. For example, polymer single crystals, organic bridged ligands, DNA and solid phase approaches have been used to fabricate gold nanoparticle dimer, trimer, or tetramer assemblies. Considering all of these architectures, dimers are of special interest because of their application as substrates in surface-enhanced Raman spectroscopy (SERS). Theoretical calculations have shown that nanoparticle dimers produce strong electromagnetic field enhancements which contribute efficiently to the signal enhancement in SERS.

Various techniques such as electrostatic assembly, colloidal epitaxy, convective self-assembly and physisorption mediated by surface tension and application of an external electric field have been employed to direct the assembly of nanoparticles on surface. However, there existed weak adsorption between these nanoparticles and the substrate. Recently, covalent interactions have been utilized to bind the nanoparticles to a substrate, and it is considered necessary for nanoparticles and the substrate to have active groups, amine and carboxyl groups have brought attention due to their better activity (Yanqing *et al*., 2006).

In nanoparticle dispersions, each particle is stabilized against aggregation with a layer of organic/inorganic coating. Such nanoparticles can be used as building blocks to fabricate functional nanostructures via self-assembly. This nanoparticle-based self-assembly is governed by particle-particle and particle-substrate interactions. Controlled self-assembly of magnetic nanoparticles has stimulated great interest recently as it may offer a convenient tool for magnetic nano device fabrication. A tightly packed assembly of exchange-decoupled magnetic nanoparticles may serve as future ultrahigh-density data storage media. Magnetic nanoparticles buried in a dielectric or nonmagnetic metal matrix may exhibit novel giant magneto-resistive properties. Controlled assembly of small magnetic

nanoparticles on the end of a sharp tip, such as an AFM probe, is expected to yield high sensitivity for magnetic force sensing at high spatial resolution. Selective combination of biomolecules with magnetic nanoparticles may enhance the ability for biomolecule recognition and magnetic field-assisted drug delivery.

Solution-phase synthesis has been proved to be an efficient way of making mono disperse magnetic nanoparticles, including elemental Co, Fe and binary FePt and CoPt nanoparticles. Self-assembly of these mono disperse nanoparticles via solvent evaporation yields magnetic nanoparticle arrays that exhibit high local ordering. Such regular arrays are difficult to form over an extended area with controlled assembly structure and thickness, and generally, various gaps among groups of regular arrays exist. For the application in ultrahigh density magnetic recording, the magnetic nanoparticles need to be assembled uniformly over a large area in only two to three nanoparticle layers. Unfortunately, current self-assembly approaches fail to gain such precise control. The reported polymer-mediated nanoparticle assembly has the advantage of highly controlled assembly thickness and dimension and shows great potential for magnetic recording applications (Shouheng *et al*., 2001).

Polyketals forming nanoparticles

Polyketals are hydrophobic polymers with biodegradable ketal linkages in their backbone. They are synthesized by a polymerization strategy based on the acetal exchange reaction.

Polyketals form nanoparticles that can encapsulate either hydrophobic drugs or proteins. The polymers undergo acid-catalyzed hydrolysis into low molecular weight hydrophilic compounds, Murthy planed to use this feature to build a capsule that releases its therapeutic cargo directly in the low pH conditions inside target cells. Polyketals have a particular advantage over current biodegradable polymers for drug delivery, such as polyesters, these materials release acidic byproducts as they degrade in the body, which can cause inflammation; polyketals do not release inflammatory byproducts, this is where the driving force for the polyketals comes in. The synthesis of polyketals is also relatively simple (Suslick *et al*., 2006).

University of Michigan researchers have developed a faster, more efficient way to produce a wide variety of nanoparticle drug delivery systems, using DNA molecules to bind the particles together. Nanometer-scaled dendrimers can be assembled in many configurations by using attached lengths of single-stranded DNA molecules, which naturally bind to other DNA strands in a highly specific fashion. With this approach, one can target a wide variety of molecules drugs, contrast agents to almost any cell. A series of experiments using cell sorters, 3-D microscopes and other tools verified that these dendrimers hit their targets, were admitted into the cells and gave off their signaling light. The self-assembled dendrimers clusters were shown to be well formed and functional (James 2005).

Drug delivery through nanoparticles

Nanoparticles are widely used in several areas of drug delivery and cosmetics (Adam and Chris 2001; Manja *et al*., 2000; Manja and Eija 2001; Bhattacharjee *et al*., 2002). Nanoparticles have unusual properties that can be exploited to improve drug delivery, because of their fine size, they are often taken up by cells where larger particles will be excluded or cleared from body. Recent strategies include the use of polymers to increase circulation time as well as the use of polymers in competition with binding groups to reduce non-specific attachments or uptakes (Valter and Cinzia 2004).

Nano sized particles have physical and chemical properties of neither the atoms nor the bulk counterpart. Based on their unique mesoscopic physical, chemical, thermal and mechanical properties nanoparticles offer a high potential for several biomedical applications (Ajay and Mona 2005; Michael *et al*., 2003; Bhattacharjee *et al*., 2002a).

Biodegradable polymers find widespread use in drug delivery, as they can be degraded to non-toxic monomers inside the body. Polymeric delivery systems are mainly intended to achieve either a temporal or spatial control of drug delivery (Omathanu and Ramesh 2001; Glen and Teruo 1996; Dennis and Adi 2002).

The efficiency of drug delivery to various parts of the body is directly affected by particle size. Nanostructure-mediated drug delivery, a key technology for the realization of nanomedicine, has the potential to enhance drug bioavailability, improve the timed release of drug molecules, and enable precision drug targeting (Dass and Su 2001). Nanoscale drug delivery systems can be implemented within pulmonary therapies (Courrier *et al*., 2002; Desai 1996) and in stabilization of drug molecules that would otherwise degrade too rapidly (LaVan *et al*., 2002; LaVan *et al*., 2003). Additional benefits of using targeted nanoscale drug carriers are reduced drug toxicity and more efficient drug distribution (Ravi 2000).

Anatomic features such as the blood brain barrier, the branching pathways of the pulmonary system, and the tight epithelial junctions of the skin make it difficult for drugs to reach many desired physiologic targets. Nanostructured drug carriers help to penetrate or overcome these barriers to drug delivery (Dass and Su 2001). Greatest efficiency for delivery into the pulmonary system is achieved for particle diameters of <100 nm. Greater uptake efficiency has also been shown for

gastrointestinal absorption (Hussain *et al*., 2001; Desai 1996) and transcutaneous permeation (Omathanu and Ramesh 2001; Gorka *et al*., 2004), with particles around 100 nm and 50 nm in size, respectively. However, such small particles traveling in the pulmonary tract may also have a greater chance of being exhaled. Larger, compartmental or multilayered drug carrier architectures may help with delivery to the pulmonary extremities. For instance, the outer layers of the carrier architecture may be formulated to biodegrade as the carrier travels through the pulmonary tract. As the drug carrier penetrates further into the lung, additional shedding will allow the encapsulated drug to be released. Biodegradable nanoparticles of gelatin and human serum albumin show promise as pulmonary drug carriers (Brzoska *et al*., 2004).

One of the ultimate goals of nanotechnology is to create medically useful nanodevices that can function inside the body. It is envisioned that nanodevices will be hybrids of biologic molecules and synthetic polymers that can enter cells and the organelles to interact directly with DNA and proteins (Xie and Gao 2005).

Additionally, nanomedicine will have an impact on the key challenges in cancer therapy: localized drug delivery and specific targeting. Among the newly developed nanomedicine and nanodevices such as quantum dots, nanowires, nanotubes, nanocantilevers, and nanopores, nanoshells and nanoparticles are the most promising applications for various cancer treatments. We reviewed use of nanoparticles in drug delivery for the treatment of cancer in which many methods for the use of gold and other metal nanopticles including gold coated silica nanoparticles were discussed (Arayne and Sultana 2006). The gold nanoshell-antibody complex can be used to ablate breast cancer cells (Shi *et al*., 2005).

Behaviour of nanoparticles like viruses

The layers of mucus that protect sensitive tissue throughout the body have an undesirable side effect they can also keep helpful medications away. To overcome this hurdle, researchers have found a way to coat nanoparticles with a chemical that helps them slip through this sticky barrier.

During experiments with these coated particles, the researchers also discovered that mucus layers have much larger pores than previously thought, providing a doorway that should allow larger and longer-acting doses of medicine to reach the protected tissue. Mucus layers, which trap and help remove pathogens and other foreign materials, can block the localized delivery of drugs to many parts of the body, including the lungs, eyes, digestive tract and female reproductive system. Because of these barriers, doctors often must prescribe pills or injections that send drugs through the entire body, an approach that can lead to unwanted side effects or doses that are too weak to provide effective treatment.

Mucus barriers evolved to serve a helpful purpose: to keep things out. But if you want to deliver medicine in a microscopic particle, they can also keep the drugs from getting through. There has been found a way to keep helpful nanoparticles from sticking to mucus and learned that the openings in the mucus 'mesh' are much larger than most people expected.

These findings set the stage for a new generation of nanomedicines that can be delivered directly to the affected areas. To get its particles past the mucus, an unlikely model is studied. Earlier research had established that some viruses are able to make their way through the human mucus barrier. A chemical coating that might mimic the characteristics of a virus is found, it was also observed that the viruses that got through hard surfaces were attracted to water, and they had a net neutral electrical charge. It was thought that if a drug-delivery nanoparticle is coated with a chemical that had these characteristics, it might not get stuck in the mucus barrier.

To make nanoparticles behave like viruses, the researchers coated them with polyethylene glycol, PEG, a non-toxic material commonly used in pharmaceuticals. PEG dissolves in water and is excreted harmlessly by the kidneys.

The researchers also considered the size of their nanoparticles. Previous studies indicated that even if nanoparticles did not stick to the mucus, they might have to be smaller than 55 nanometers wide to pass through the tiny openings in the human mucus mesh. (A human hair is roughly 80,000 nanometers wide.) Using high-resolution video microscopy and computer software, the researchers discovered that their PEG-coated 200-nanometer particles could slip through a barrier of human mucus. Larger nanoparticles are more desirable because they can release greater amounts of medicine over a longer period of time. They wanted to make the particles as large as possible. The shocking thing was how fast the particles that were 500 nanometers wide moved through the mucus mesh.

The openings in the mucus barrier are much larger than originally expected by most and it was also surprising to find that the larger nanoparticles (200 and 500 nanometers wide) actually moved through the mucus layer more quickly than the smaller ones (100 nanometers wide). This has important implications, because a 500-nanometer particle can be used to deliver medicine to a targeted area, released over periods of days to weeks.

Larger particles also allow a wider array of drug molecules to be efficiently encapsulated. This system is believed to have great potential in the delivery of

chemotherapy, antibiotics, nucleic acids and other treatment directly to the lungs, gastrointestinal tract and cervicovaginal tract (Kannan *et al*., 2004).

Drug loading into nanoparticles

Drug loading in nanoparticulate system can be done by two methods, incorporation and incubation, which differs in a way that earlier is employed during the preparation of particles and later after the formation of particles. In these systems, the drug is embedded into the matrix or adsorbed onto the surface. Efficiency of loading is largely dependent upon method of preparation and physicochemical properties of drug. Maximum drug loading can be achieved by incorporation but it may get affected by process parameters, such as method of preparation or presence of additives etc (Lexis and Santosh 2004; Samuel 1995; Gorka *et al*., 2004; Sunil and Nadagouda 2005; Janet and Pablo 2002).

Toxicology due to nanoparticles

The first feature of nanoparticles is their pulmonary deposition mode, whereby the particles, even though they are very small, will be deposited throughout the pulmonary system and not only in the alveolar region clearly shows that mucociliary clearance and phagocytosis are well-documented pulmonary clearance mechanisms for micrometric particles. Because of their size, nanometric particles can enter the extra pulmonary organs.

This involves migration of solid particles through the epithelial layers and through the nerve endings, along the neuronal axons to the central nervous system. Thus, insoluble nanoparticles pass through the respiratory or gastrointestinal protective mechanisms and are distributed to various organs throughout the body, including brain. They are stored in the cells and end up in the bloodstream.

These properties are currently being studied extensively in pharmacology, because nanoparticles could be used as vectors to transport drugs to targeted sites in the body. Moreover, nanoparticles can also be distributed throughout the body when workers inhale them. Some of these nanoparticles have exhibited highly toxic effects (Oberdörster 2005; Oberdörster et. al., 2005). Despite it is recognized that the toxicity of nanoparticles is often linked to their small size, this factor does not always check out (Peters *et al*., 2004).

CONCLUSION

In conclusion, this study provides several interesting findings about drug loaded nanoparticles prepared by solvent diffusion or precipitation method. Extension to other living and controlled polymerization systems will open up a wider route to functionalize surfaces for promoting the fabrication of new types of nanoparticles that can be used in many targeted drug actions. With regard to the targeting issues, the importance of physiological barriers, on the fate and activity of these nanoparticles with respect to their biodegradability/ bioerodibility is also stated. These nanomaterials form the building blocks for new bottom-up approaches to materials assembly for a range of uses. Such materials also receive attention because of their intrinsic size-dependent properties and resulting applications. Different methodology provides a simple and convenient route to a variety of building blocks for assembling materials with novel structure and function in nanotechnology.

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