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ABSTRACT

There has been huge interest in applications of nanomaterials in biomedical science, including diagnosis, drug delivery, and development of human organs. Number of these nanomaterials has been already studied in human or at pre-clinical trial. There is a growing concern on potential toxicity and adverse effects of nanomaterials on human health, including lack of standard method of assessment of toxicology of these materials. Our investigation indicated that the bare and small nanoparticle have higher toxicity than modified and bulk materials, respectively. In addition, spherical nanoparticles have less toxicity than rod nanoparticles due to immune response of body.

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Introduction

Nanotechnology is an emerging field involving manipulation of the matter at nanometer scale, which results in a novel class of materials with improved properties for a wide range of applications. Nanomaterials are defined as substances with one or more dimensions in the size range of 1–100 nanometers (Bleeker et al. 2012). Their use in diverse areas has been vastly explored in recent years, offering great advantages over conventional materials. In particular, the engineered nanomaterials have been widely investigated for the biomedical applications, including development of new diagnostic tools such as nanobiosensors and precise imaging modalities, novel therapeutics based on targeted drug delivery systems, and scaffolds for tissue engineering (Chang 2014, Karimi et al. 2015, Ketabchi et al. 2016, Naghibzadeh and Adabi 2014). Due to the increasing usage of nanomaterials in various fields of science and technology, the concerns have been emerged about their safety, biocompatibility, and toxicity.

Nanotoxicology as a branch of toxicology has been attracted researchers attention to specifically investigate potential toxic effects of nanomaterials. Nanotoxicology is an interdisciplinary field dealing with different aspects of the potential toxicity of nanomaterials. While there is a growing interest in the use of nanomaterials in different fields, the safety concerns about their use is also on the rise. Hence, there is an urgent need to address these concerns and expand our knowledge on the safety, biocompatibility, and toxicity of nanomaterials. In biomedical applications, in particular, there are serious concerns on the safety and biocompatibility of nanomaterials, considering the possibility of greater interactions between nanomaterials and biological system.

According to a consensus conference of the European Society for biomaterials in 1986, the biocompatibility is defined as the ability of a substance to present an appropriate host response in a particular application (Duncan and Izzo 2005, Williams 1989). It is worth noting that the interactions between a material and a host are influenced by several factors including the host factors and the properties of the material and the site and duration of the exposure. To understand the type and scale of these interactions, nanomaterials should be tested for potential toxicity in a variety of *in vitro* and *in vivo* settings. However, there is no harmonized standards for evaluating toxicity and biocompatibility of nanomaterials in biological systems and the rules are still being investigated (Dobrovolskaia and McNeil 2007). The aim of this research was to critically review the biocompatibility and toxicology of nanomaterials.

Several nanostructured materials have been explored for the biomedical applications. The most commonly studied materials are based on carbon, silica, and metals in different shapes (i.e., spheres, tubes, and rods) (Adabi et al. 2011, Ketabchi et al. 2016, Shakoori et al. 2015, Tavakol et al. 2014). The toxicity and biocompatibility of these materials depends on several factors such as the size, surface area, functional

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groups, concentration, and dosage (Foldvari and Bagonluri 2008). In general, the toxicity responses induced by ultrafine particles is higher in comparison with larger sizes of similar composition (Donaldson et al. 2001, Kang et al. 2008, Oberdürster 2000). Not only the size but also the surface plays an important role in the toxicity of nanomaterials. Each parameter could affect the toxicity and biocompatibility of a nanomaterial independently or in association with other parameters.

Clinical applications of nanostructures

Nanomaterials with its large surface area and nano size has huge applications for drug delivery (Kamali et al. 2015). As nanomaterials can cross the blood brain barrier, they have become the top research theme in delivery of drugs to brain. Nanomaterials with capability to be used in medical field, e.g., tissue engineering, drug delivery, and diagnosis, have potential toxicity and harmful effects on human health. To more clarify about importance of nanoparticles safety, clinical applications of nanomaterials with a focus in regenerative medicine and tissue engineering and blood brain barrier are mentioned in the following.

Regenerative medicine and tissue engineering

Nanotechnology provides the basic scientific foundation for the development of regenerative medicine along with tissue engineering. Applications of nanomaterials in biomedical sciences include molecules delivery (drugs, growth factors, and DNA), imaging and tracking iPSC, surface modifications of implantable materials or nanodevices (biosensor), and nanofibers for tissue scaffolds (Engel et al. 2008, Ramalingam and Rana 2015).

Nanoparticles research within regenerative medicine has been addressed mainly towards the development of entrapment and delivery systems. Delivery systems can enhance the success of therapeutic agents in nanoparticles for continuous release in a controlled manner which will boost the success rate of regeneration (Martin et al. 2004, Reddy et al. 2006). Nanoparticles are also useful for the delivery of molecules to stem cells, since stem cells undergoing lineage commitment require a specific spatio-temporal presentation of factors. Efforts have been made to incorporate these nanoparticles into biomaterials for controlled release rates (La Francesca 2012). Solid surface-modified nanoparticles might also be used for regenerative purposes. Although polymers are the most used nanoparticles in the delivery area, the use of ceramics has also been investigated. Hydroxyapatite nanoparticles conjugated with biomolecules could enhance osteoblast adhesion and bone regeneration (Liu and Webster 2007).

In addition, nanofibers are used for preparing tissue scaffolds and for modifying the surface of implantable materials and nanodevices such as biosensors (Adabi et al. 2015a, 2015b, Yang and Leong 2010). Depending upon the cells that need to be targeted, functionalization of scaffold is done accordingly with a variety of biological molecules. Ceramic nanoparticles and nanofibers have been reported by Sarvestani et al. (2007) to be suitable in the elaboration of bio-inspired nanocomposites for bone tissue engineering applications, acting as the reinforcing phase of a polymer matrix, and improving scaffold bioactivity. The tantalum blocks were also found to provide even better bone fusion rates than structural bone grafts in several different clinical applications (Levine et al. 2006, Wigfield et al. 2003), indicating the importance of nanoparticles in tissue and surface engineering. Despite the fact that nanoparticles utilization in tissue engineering and regenerative medicine is increasing, their toxicity has not been fully addressed. Therefore, comprehensive studies are required about their toxicity before the use.

Blood brain barrier

Blood brain barrier is composed of different cell types including endothelial cells, astrocytes, pericytes, and microglial cells (Begley 2004). The transfer of almost all drugs is limited by the highly restrictive tight junctions and only small lipophilic molecules with molecular weight less than 500 Da could cross blood brain barrier (Pardridge 1998, Reese and Karnovsky 1967, Wolburg and Lippoldt 2002, Wu and Pardridge 1998). Likewise, these molecules may be transported out of blood brain barrier by active efflux mechanisms specially P-glycoprotein even after successful endothelial cell absorption (Begley 1996, Cordon-Cardo et al. 1989).

The size of particles can influence entrance of the particles into the cells. For example, particles less than 12 nm are able to cross the blood brain barrier (Sarin et al.2008). Besides, the size may affect the mechanism of endocytotic uptake. Totally, clathrin-mediated endocytosis was proposed as the predominant pathway for the uptake of particles less 200 nm, whereas the uptake of particles 200–500 nm seems to be caveolae-mediated (Hillaireau and Couvreur 2009).

Other properties such as surface charge and hydrophobicity also affect transcytosis rate due to the effect on proteins adsorbed from plasma (Gessner et al. 2002). After intravenous injection, bare nanoparticles are immediately adsorbed via plasma and cleared from the blood stream by the macrophages of RES within 5 min (Pardridge 1992). However, by modifying nanoparticle surface, their blood circulation time can enhanced and their distribution in the body may alter and increase their uptake in the brain (Tiwari and Amiji 2006, Tröster et al. 1990). For example, 30 min, 2 h, and 4 h after intravenous injection of doxorubicin solution containing 1% of polysorbate 80, doxorubicin-loaded poly(butyl cyanoacrylate) nanoparticles with and without polysorbate 80-coating into the rats, their brains were removed. Considerable concentrations of doxorubicin in the were only observed after injection of the polysorbate 80-coated nanoparticles, proving the successful crossing of the blood brain barrier (Triguero et al. 1990). After administration of drug solution alone, doxorubicin was not taken up into the brain. Moreover, toxicological investigation of doxorubicin bound to poly(butyl cyanoacrylate) demonstrated that the doxorubicin toxicity significantly decrease after intravenous injection of the polysorbate 80-coated nanoparticles in comparison with the doxorubicin solutions. A considerably reduced cardio- and hepatotoxicity occur

in comparison with free drug. The lower toxicity of the nanoparticulate formulations of doxorubicin can be attributed to the altered biodistribution of the doxorubicin loaded nanoparticles. As the tumor therapy with doxorubicin is limited due to cardiotoxicity, the reduced cardiotoxicity with doxorubicin loaded nanoparticles can play great importance. Likewise, the binding doxorubicin to nanoparticles alter distribution of the drug, resulting in lower accessible to hepatocytes and consequently less toxicity (Gelperina et al. 2002, Gulyaev et al. 1999, Pereverzeva et al. 2007).

The effects of nanomaterials properties on toxicity in clinical applications

Many factors could potentially influence material's biocompatibility and toxicity including their surface chemistry (Chou et al. 1999, Tsai et al. 2001), roughness (Campoccia et al. 2003), surface energy (hyrophobicity/hydrophilicity) (Cai et al. 2002), the level of degradation products and release of by-products (Sun et al. 2007), concentration (Sun et al. 2011), particle size (Singh et al. 2007), oxidative stress functions (Reddy et al. 2010, Yang et al. 2009), crystallinity (Braydich-Stolle et al. 2009), coating (Harris et al. 2010, Lin et al. 2012), and the longevity of particles (Ai et al. 2011). Although, it is difficult to determine the specific role of any individual factor in toxicity and biocompatibility of nanomaterials, but some of the most important characteristics were summarized in the following.

The size

For the application of nanomaterials in biomedicine, all of effective characteristics on toxicity and biocompatibility should be considered. One of the most effective parameters on toxicity of nanomaterials is the size of the materials. Nanoparticles could pass through cell membranes and go into the blood and organs (Gatti and Rivasi 2002). Hence, the areas of biological systems which are normally inaccessible for larger particles may be accessible for nanoparticles (Dhawan and Sharma 2010). Besides, when the size of a bulk material decreases below a specific critical threshold, it results in an increase in surface area (Ai et al. 2011). Thus, the number of chemical molecules bounded to the surface increases and consequently the reactivity enhances. This can be a reason behind the potential toxic effects of nanoparticles which could be more significant compared to the larger particles (Ai et al. 2011, Linkov et al. 2008, Suh et al. 2009). For instance, studies demonstrated that the size-dependent cytotoxicity of gold nanoparticle (with diameter 1.4 nm) capped with triphenyl phosphine monosulfonate (TPPMS) resulted in cell death via induction of oxidative stress and mitochondrial damage (Kunzmann et al. 2011, Pan et al. 2009) whereas gold nanoparticles (with size 3.7 nm) modified with poly(ethylene glycol) (PEG) had no toxic effects despite their entrance into the nucleus of cells (Gu et al. 2009, Kunzmann et al. 2011). Likewise, titanium dioxide (TiO_2) with the size of 20 nm induced 43-fold more inflammation than Tio_2 with the size of 250 nm in short-term experiments of pulmonary toxicity in rats (Hallock et al. 2009). Park et al. (2011) demonstrated that silver nanoparticles with the size of 20 nm are more toxic than the larger ones and Shi et al. (2013) in a study revealed that there was negative correlation between the particle size and the toxicity effects; it means, small silver nanoparticles (5–10 nm) had higher toxicity effects than large ones (15–25 nm) in a model organism of Tetrahymena pyriformis. Other investigations also indicated that smaller particles had more pathological effects on the lungs in comparison with the larger particles of the same material (Oberdörster et al. 1994, Singh et al. 2007).

In general, nanomaterials in comparison with the bulk materials have higher surface energy and catalytic activities. For example, a number of nanoparticles such as metal oxide nanoparticles, fullerenes and silica particles can cause reactive oxygen species (ROS) generation in cell-free systems (Cristina Yeber et al. 2000, Fubini and Hubbard 2003, Isakovic et al. 2006, Kim et al. 2004). ROS production via nanoparticles with the size of 2–4 nm was 100–1000 times faster in comparison with 100 nm nanoparticles (Hoffman et al. 1994). Therefore, the enhanced catalytic activity might be a size-dependent phenomenon. However, the effect of other parameters on potential toxicity of nanoparticles in correlation with the size such as shape and charges could be considered.

The shape

Studies have demonstrated that the shape could influence the biocompatibility and toxicity of a nanoparticle. It has been illustrated with altering material's shape from an equiaxed to acicular one, the toxic response was enhanced. Wang et al. reported that gold nanorods are highly toxic to the presence of hexadecyl cetyl trimethyl ammonium bromide (CTAB) as coating material for human skin cells whereas spherical gold nanoparticles are not inherently toxic. They explained that it is difficult to understand the cytotoxicity of gold nanomaterials individually, because CTAB was used for synthesis of gold nanorods and this surfactant alone show cytotoxicity whereas CTAB is not in gold nanoparticles (Wang et al. 2008). Likewise, Hsiao et al. reported that the nanorod zinc oxide (ZnO) particles are more toxic than the spherical ones on human lung epithelial cell (A549) at a fixed size (Hsiao and Huang 2011). It could be due to the interaction forces of lengthwise-oriented nanomaterials which enhance proportionally with their lengths (Brown et al. 2007). Therefore, the van der Waals forces of rod-shaped nanomaterials are greater in comparison with spherical ones.

The shape of nanomaterials could also influence the cellular internalization rate. Spherical particles are more easily internalized into the cell membrane in comparison with the large length-to-radius ratio (elongated) particles laying parallel to the cell membrane (Decuzzi et al. 2009). For example, the uptake of spherical-shaped gold nanoparticles is more than rod-shaped counterparts (Chithrani et al. 2006). Therefore, nanomaterials can be designed in an appropriate shape in order to enter the cells more easily for therapeutic purposes such as cancer therapy.

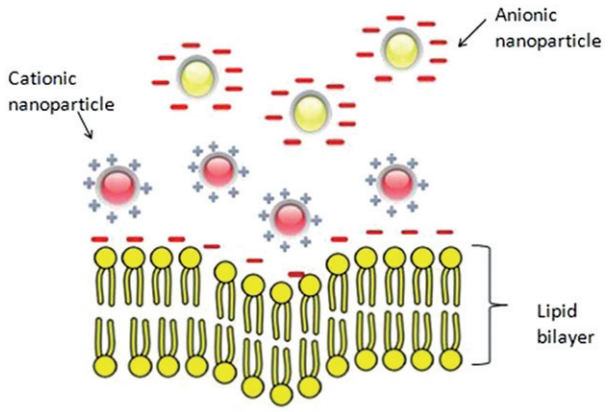

Figure 1. The effect of surface charge on nanoparticle–cell interactions. Cationic nanoparticles are more prone to enter the cells by electrostatic attraction of negatively charged cell membrane.

Surface charge

Surface charge of the nanoparticles is another important factor which can affect biocompatibility. The zeta potential is commonly used for characterizing the surface charge of nanoparticles. Zeta potential of nanoparticles in solutions in the ranges above (±) 30 mV leads to stability and prevents aggregation of the particles (Mohanraj and Chen 2007). However, surface charge affects the behavior of particles with biological moieties like cell–membrane interactions, penetration, protein adsorption, and stability in biological fluid (Maffre et al. 2011). Neutral particles show slower opsonization rates than the charged particles (Owens Iii and Peppas 2006, Roser et al. 1998) and nanoparticles with slight negative charges tend to accumulate in tumor tissues more efficiently (He et al. 2010, Patil et al. 2007). Positive charged particles could be more easily uptaken by the cells than the other nanoparticles due to the attractive interaction between positively charged nanoparticles and the negative cell membranes (Chen et al. 2011, Zhu et al. 2010) as seen in schematic Figure 1. On the other hand, cationic nanoparticles are much more potent in activation of immune response than neutral or anionic nanoparticles (Kedmi et al. 2010, Zolnik et al. 2010).

Other factors

The aforementioned properties of nanoparticles as well as hydrophilicity, hydrophobicity, and surface topography, roughness, and tension may affect the protein adsorption, platelet activation, cellular growth, and consequently biocompatibility (Hsu and Lin 2004). Toxicity of nanoparticles can be decreased or eliminated using various surface modification techniques. For instance, it has been shown that coating of superparamagnetic iron oxide nanoparticles with pullulan significantly reduced toxicity of these nanoparticles (Ai et al. 2011). Uncoated magnetic nanoparticles (MNP) were associated with increased acidity of cell media to a cytotoxic level, leading to greater cytotoxicity in comparison with MNP coated with polyethyleneglycol-co-fumarate or polyvinyl-alcohol (Arsianti et al. 2010, 2011, Cedervall et al. 2007b, Nel et al. 2009). The hydrophobicity of nanoparticles determines the type and the amount of adsorbed biological components, mainly proteins (opsonins). Hydrophobicity influences both the amount of opsonization and the features of nanomaterial-binding proteins (Cedervall et al. 2007a, Goppert and Muller 2005). Opsonin proteins bound to hydrophobic nanoparticles facilitate macrophage-mediated phagocytosis of nanoparticles. In general, it seems that hydrophilic nanoparticles are safer and less toxic than the hydrophobic ones in biological systems (Sadaf et al. 2012, Yan et al. 2006, Zhu et al. 2010). In order to increase the blood circulation half-life of nanoparticles, one solution is to increase hydrophilicity of the surface. The most preferred method is modification of the surface by physical adsorption or chemical grafting of the poly(ethylene glycol) (PEG) to the surface of nanoparticles (Aggarwal et al. 2009, Jokerst et al. 2011, Moghimi and Szebeni 2003, Owens Iii and Peppas 2006). This could increase the circulation half-life of the nanoparticle by avoiding phagocytosis and rapid clearance from the blood. Likewise, it has been shown that the presence of poly-(vinyl pyrrolidone (PVP), a hydrophilic block polymer, on the surface of polyethersulfone (PES) membranes, which is used as hemodialysis membranes, could improve the biocompatibility (Ran et al. 2011). For some applications, however, hydrophobic surface could be preferred. For instance, surface modification of nanoparticles by hydrophobic polymers showed more adsorption in intestinal mucus (Ai et al. 2011). Surface modification of the polymeric membrane with amphiphilic triblock co-polymer, poly(vinyl pyrrolidone)–b-poly(methyl methacrylate)–b-poly(vinyl pyrrolidone), revealed a superior biocompatibility (Ran et al. 2011). The blood-compatibility of these modified membranes enhanced in comparison with PES membrane without modification (Ran et al. 2011). Different surface modification methods have been explored to enhance biocompatibility of various nanomaterials. However, the optimum modification technique with the best effect on biocompatibility for a particular nanomaterial is yet to be found.

Nanomaterials and immune system

The immune system protects the body from foreign invasions. Antigen-presenting dendritic cells, macrophages and the other phagocytic cells recognize foreign bodies and trigger an appropriate immunological response to the foreign materials. The recognition of nano-scaled particles as foreign stimuli may promote different levels of immune responses. Therefore, minimized or diminished immunogenicity of nanomaterials is favored in biomedical application of nanomaterials and nanoparticles as novel diagnostic or therapeutic modalities.

Most materials are coated by a layer of proteins, as exposed to the biological system after entrance to the body (Cedervall et al. 2007b, Lynch and Dawson 2008, Sahoo et al. 2007). The proteins corona on nanoparticles, depending on the amounts and the type of the adsorbed proteins, determines the subsequent interactions between nanoparticles and the immune cells and plays an effective role on biodistribution and uptake of nanomaterials by the reticuloendothelial system (RES) (Aggarwal et al. 2009, Chonn et al. 1992, Kiwada et al. 1987, Patel 1992, Tyrrell et al. 1977). It is now widely known that nanoparticles remarkable properties (e.g.,

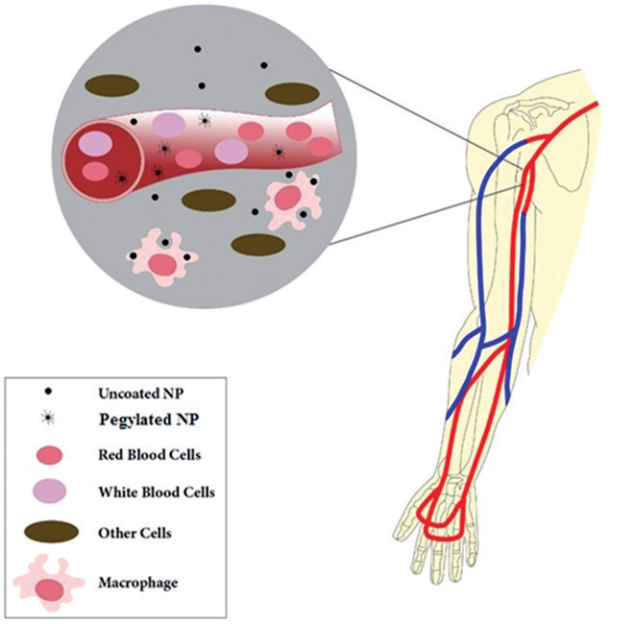

Figure 2. PEGylation of nanoparticles. Uncoated nanoparticles are mainly picked up by macrophages whereas coating of nanoparticles with PEG leads to an enhanced circulation time due to prevention of nanoparticles internalization by macrophages.

size, surface charge and coating, hydrophobicity and hydrophilicity, etc) could be effective on their biocompatibility (Aggarwal et al. 2009, Dobrovolskaia and McNeil 2007, Dobrovolskaia et al. 2008). According to the reports, unmodified nanoparticles are taken up from the bloodstream within seconds by phagocytic cells, i.e., macrophages via opsonization (a process conducted by opsonins, a constituent of plasma proteins that makes nanomaterials more susceptible to ingestion) (Gref et al. 1994). Modifying the nanoparticles surface may considerably reduce their immunotoxicity and enhance their biocompatibility (Aggarwal et al. 2009, Dobrovolskaia and McNeil 2007, Dobrovolskaia et al. 2008, Gref et al. 1994). For example, the surface characteristics of nanoparticles such as hydrophobicity and hydrophilicity affect opsonization potential, as hydrophilic materials are opsonized slower than the hydrophobic ones, most likely due to reduced absorbability of hydrophilic surfaces (Carrstensen et al.1992, Müller et al. 1992, Norman et al. 1992, Owens Iii and Peppas 2006). Therefore, surface modification of hydrophobic nanoparticles by coating with poly(ethylene glycol) (PEG), called "PEGylation", or other kinds of hydrophilic polymers leads to a hydrophilic surface and act as an effective strategy for shielding of nanoparticles from plasma proteins, thereby hindering them from immune recognition and resulting in a prolong blood circulation half-life (Figure 2) (Gref et al. 1994, 2000, Kim et al. 2007, Lemarchand et al. 2006, Moghimi 2002, Owens Iii and Peppas 2006, Paciotti et al. 2004, Peracchia et al. 1999a, 1999b). It has been also reported that opsonization rate of neutrally charged particles is slower in comparison with the charged particles, representing a direct relationship between protein binding and the surface charge of particles (Owens Iii and Peppas 2006, Roser et al. 1998). Gessner et al. (2002) reported that adsorption of plasma proteins enhanced as the surface charge density increased no significant differences in the type of adsorbed proteins.

Toxicity and biocompatibility studies: *in vivo*

Pre-clinical evaluation of nanoparticles in appropriate animal models is a crucial step of characterization to prove their safety and efficacy. The type of the nanomaterial and its particular application mainly determines the choice of animal model, route of administration, dosage, study end points, and other parameters. The interactions between nanomaterial as a foreign body and the animal as a host are mainly influenced by physicochemical properties of the nanomaterial. Totally, in most of the cases, there is no enough evidence to prove the safety or toxicity of nanomaterials. Besides, there is no a unique protocol for *in vivo* biocompatibility studies and several different procedures can be adapted to investigate the safety and efficacy of a specific nanomaterial *in vivo*.

However, before this can become a clinical reality, toxicity, and biocompatibility of the nanoparticles has to be carefully evaluated, with emphasis on an understanding of the physiochemical properties that account for the adverse biological responses (Fadeel and Garcia-Bennett 2010).

One of the most widely accepted defining characteristic of nanoparticle-based medicine is particle size and distribution, because size can significantly impact pharmaco-kinetics, biodistribution, and safety (Moghimi et al. 2001). The pharmacokinetics and distribution of nanoparticles in the body depends on their surface physicochemical characteristics, shape as well as size (Hoet et al. 2004). Distribution can be either monodisperse or polydisperse, whereas the former with narrow distribution are desirable for consistency. It has been proposed that nanoparticles population of mixed sizes (polydisperse) is intentionally introduced for different rates of drug release to sustain delivery over time. To show that adsorption and distribution of nanoparticles are size dependent, Hillyer and Albrecht administered metallic colloidal gold nanoparticles with different sizes orally to mice. They noticed that distribution of nanoparticles increases with a decrease in size of nanoparticles to several organs (Hillyer and Albrecht 2001), and concluded that bigger particles reside in the gastrointestinal tract. In addition, nanoparticles with 10 nm in size were found in blood, liver, spleen, kidney, testis, thymus, heart, lung, and brain but larger particles were only in spleen, liver, and blood (De Jong et al. 2008). Chen et al. investigated the effect of colloidal gold nanoparticles in different sizes (3–100 nm) on physical and behavioral status of mice model. Intraperitoneal administration of 3–5 nm gold nanoparticles did not induce sickness but larger gold nanoparticles induced loss of appetite, fatigue, change of fur's color, and weight loss and most of them died within 21 days (Chen et al. 2009).

Route of administration of nanoparticles include oral, pulmonary and dermal delivery. After the absorption process of nanoparticles by the various ports of entrance, the systemic circulation can distribute them towards all organs and tissues in the body. Several studies have shown distribution of particles to several organs including liver, spleen, heart, and brain (Hillyer and Albrecht 2001, Ji et al. 2006, Nemmar et al. 2002,

Oberdörster 2002). Nanoparticles distribution to these organs is often mediated by their combination with human serum albumin (HSA), coagulant factors, RBC, WBC, and platelets available in systemic circulation. Therefore, their interaction with serum component (like Apo-A1) *in vitro* result in cytotoxic effect reduction (Barrett et al. 1999). Cartiera et al. (2009) reported that the intracellular distribution of particles within cells is also time and dose-dependent. PLGA nanoparticles within renal tubule cells appeared to co-localize with early endosomes 2 h after exposure whereas they were also found in other compartments after 4–24 h. This is in agreement with finding of Panyam and Labhasetwar (2003) who reported endo-lysosomal escape of nanoparticles. Cellular uptake of nanoparticles did not involve endocytosis (Geiser et al. 2005) since erythrocytes have no phagocytotic receptors (Rothen-Rutishauser et al. 2006). This finally suggests that nanoparticles are able to cross the cell membrane using processes other than phagocytosis and endocytosis.

The clearance of nanoparticles is also size and surface characteristics dependent. Small nanoparticles with size smaller than 20–30 nm are rapidly cleared by renal excretion, while 200 nm particles or those greater in size are more efficiently taken up by the Kupffer cells and mononuclear phagocytic system (reticuloendothelial system) located in the liver, spleen, and bone marrow (Moghimi et al. 2001). Previous reports have shown that nanoparticles of 150–300 nm are localize mainly in the liver and spleen (Gaumet et al. 2008), and colloids of sizes 200 to 400 nm undergo rapid hepatic clearance. The nanoparticle clearance is facilitated by the opsonization of blood components and complement proteins on the particle surface (Moghimi 2003). The inhibition of opsonization and evasion of detection by macrophages with approaches such as pegylation prolong the circulation of nanoparticles in the case of liposomal doxorubicin (Doxil) (Cattel et al. 2002).

In addition to cellular uptake of nanomaterials via different pathways of body, biodegradation, size- and dose-dependent cytotoxicities of nanomaterials, and the interaction between organs cells and nanoparticles are important issues that should be considered. The studies have been shown that various nanoparticles, e.g., micelles, liposomes, polymeric, and inorganic nanoparticles, interact with plasma proteins via different mechanisms (Karmali and Simberg 2011).

Dose is other determinant factor in the toxicity of nanomaterials *in vivo*. In a study in mice model, the toxicity of 13.5 nm citrate coated gold nanoparticles proved adverse effects of higher concentration of the nanoparticles such as weight loss, decreased red blood cells count (Zhang et al. 2010). In another study, different groups of rats received 4, 10, 20, and 40 mg/kg silver nanoparticles, intravenously. Results indicated that low doses (4 and 10 mg/kg) did not affect the hematological parameters of the animals, while in higher concentrations, 20 and 40 mg/kg, there was a significant change in the level of ROS, liver function enzymes such as ALT, AST, ALP, and bilirubin. DNA damage was also observed in the high dose groups, showing genotoxicity of these nanoparticles in high concentrations (Tiwari et al. 2011).

Properties related to the surface of nanoparticles determine the type and extent of interactions between nanoparticles and different plasma proteins such as immunoglobulin, lipoproteins, coagulation, and complement factors. These proteins can be adsorbed to the surface of nanoparticles and affect the metabolism, clearance, and long-term fate of nanoparticles. Manipulating the surface of nanoparticles via altering the surface charge and coating with different materials is an effective strategy to make the particles more soluble and biocompatible. Different coating material has been used to modulate surface properties of nanoparticles and control the biological response to those particles in living organisms. Surface modification can also affect the biodistribution of nanomaterials in different organs. Thi Ha Lien et al. (2012) showed that PEG and BSA coated gold nanoparticles are accumulated in liver Kupfer cells and no gold nanoparticles were found in other cell types and other organs like kidney. PEG is one of the most widely used polymers for *in vivo* application of nanoparticles owing to its good solubility and biocompatibility. Nanoparticles with PEG coating have shown more blood circulation time due to the ability to escape from RES system (Gref et al. 1994, Peracchia et al. 1999a).

Conclusion

There are still several hindrances in the use of nanomaterials in various fields in general, and in biomedical field in particular, which should be resolved. One of the main restricting factors in the application of the nanomaterials is their safety, which remains a real concern. The concern is more serious when these materials are supposed to enter into human body, either intentionally or accidentally. One might be very optimistic about the potential benefits that nanomaterials offer, underscoring the risks associated with their use. However, studies conducted on testing toxicity and biocompatibility of nanomaterials reveals various ranges of toxicity and biocompatibility, which reflects the distinct response of biological system toward different nanostructures and nanomaterials. To date, our knowledge on the interactions of nanomaterials with biological systems is limited and harmonized standards do not exist for evaluating toxicity of nanomaterials on biological systems. There is also a huge controversy on the influence of different parameters related to nanomaterials properties on their toxicity and safety. Therefore, despite rapid development in the field of nanotechnology, there are still important challenges that necessitate further studies to provide more accurate data on the potential risks and hazards of biomedical applications of nanomaterials.

Disclosure statement

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