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Review Article

Biocompatibility and Toxicity of Nanoparticles and Nanotubes

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In recent years, nanoparticles (NPs) have increasingly found practical applications in technology, research, and medicine. The small particle size coupled with their unique chemical and physical properties is thought to underline their exploitable biomedical activities. Its form may be latex body, polymer, ceramic particle, metal particles, and the carbon particles. Due to their small size and physical resemblance to physiological molecules such as proteins, NPs possess the capacity to revolutionise medical imaging, diagnostics, therapeutics, as well as carry out functional biological processes. But these features may also underline their toxicity. Indeed, a detailed assessment of the factors that influence the biocompatibility and toxicity of NPs is crucial for the safe and sustainable development of the emerging NPs. Due to the unique structure, size, and shape, much effort has been dedicated to analyzing biomedical applications of nanotubes.This paper focuses on the current understanding of the biocompatibility and toxicity of NPs with an emphasis on nanotubes.

1. Introduction

First of all, we would better have a clear understanding of the definition of biocompatibility and toxicity. In 2008, Williams redefined biocompatibility as follows [1]: biocompatibility refers to the ability of a biomaterial to perform its desired function with respect to a medical therapy, without eliciting any undesirable local or systemic effects in the recipient or beneficiary of that therapy, but generating the most appropriate beneficial cellular or tissue response in that specific situation, and optimising the clinically relevant performance of that therapy. And his definition has been recognised. In this context, NP toxicity refers to the ability of the particles to adversely affect the normal physiology as well as to directly interrupt the normal structure of organs and tissues of humans and animals. It is widely accepted that toxicity depends on physiochemical parameters such as particle size, shape, surface charge and chemistry, composition, and subsequent NPs stability.

The size of NPs is not more than 100 nm micro. They can be obtained by many ways: wet chemical treatment (chemical reactions in solution), mechanical processing (milling and grinding technology), vacuum deposition, and gas phase synthesis. Its form may be latex body, polymer, ceramic particle, metal particles, and the carbon particles. According to the different preparation methods, those NPs can have different size, chemical composition, and shape and can be with or without surface coating. Each of these factors can affect the interactions between the nanomaterials and cells or tissues. NPs can permeate membrane cells, and spread along the nerve cells synapses, blood vessels, and lymphatic vascular. At the same time, NPs selectively accumulate in the different cells and certain cellular structure. NPs of strong permeability not only provide the effectiveness for the use of drugs, at the same time, but also give rise to potential threats on the health of human body.

The development of NPs for biomedical applications including medical imaging, magnetic hyperthermia, and gene or drug delivery is currently undergoing a dramatic expansion. For biomedical applications, emerging nanostructures requires stringent evaluations for their biological security. There are a number of different classes of NPs promising for biomedical purposes.

Due to the unique structure, size, and shape, much effort has been dedicated to analyzing biomedical applications of nanotubes. At present, nanotubes for biomedical application include carbon nanotubes, silicon dioxide nanotubes, boron nitride nanotubes, titanium dioxide nanotubes, and organic nanotubes, of which carbon nanotubes are the most widely used materials.

Here, we will focus on the current understanding of the biocompatibility and toxicity of NPs and nanotubes. This paper proceeds as follows. In later sections, the NPs and nanotubes are reviewed in two separate sections. Section 2 reviews the biocompatibility and toxicity of NPs in the aspect of hemocompatibility, histocompatibility, cytotoxicity, and neurotoxicity. Section 3 is a description of main types of nanotubes. Considering the attention that carbon nanotube has received, the section of nanotubes is structured a little differently from that of the NPs.

2. Biocompatibility and Toxicity of Nanoparticles

2.1. Biocompatibility of Nanoparticles. For biomedical applications, those NPs enter the body and contact with tissues and cells directly, thus it is necessary for exploring their biocompatibility.

2.1.1. Hemocompatibility. NPs are used as vectors for the applications in drug delivery, gene delivery, or as biosensors, where a direct contact with blood occurs. Here some NPs are examined for their blood-compatible behaviors.

Recently, blood cell aggregation and haemolysis studies, coagulation behaviors experiments have been carried out evaluating blood compatibility of NPs in vitro conditions,of which hemolysis is considered to be a simple and reliable measure for estimating blood compatibility of materials [2].

Chouhan and Bajpai [3] has adopted Hemolysis assay to judge the in vitro blood compatibility of the prepared PHEMA NPs. Hemolysis assay experiments were performed on the surfaces of the prepared particles. The results indicate that for NPs with 12.37 mM HEMA and 1.06 mM EGDMA percentage hemolysis is lowest. This clearly suggests a moderate level of biocompatibility.

Sanoj Rejinold et al. [4] have studied the formulation of curcumin with biodegradable thermoresponsive chitosan-g-poly (N-vinyl caprolactam) NPs (TRC-NPs) for cancer drug delivery. Fresh human blood was used in this study. Hemolysis assay was carried out to evaluate the blood compatibility of bare and curcumin-loaded TRC-NPs. The results showed that the hemolytic ratio of the sample was within the range of less than 5%, the critical safe hemolytic ratio for biomaterials according to ISO/TR 7406, which indicated that the damage of the sample on the erythrocytes was little.

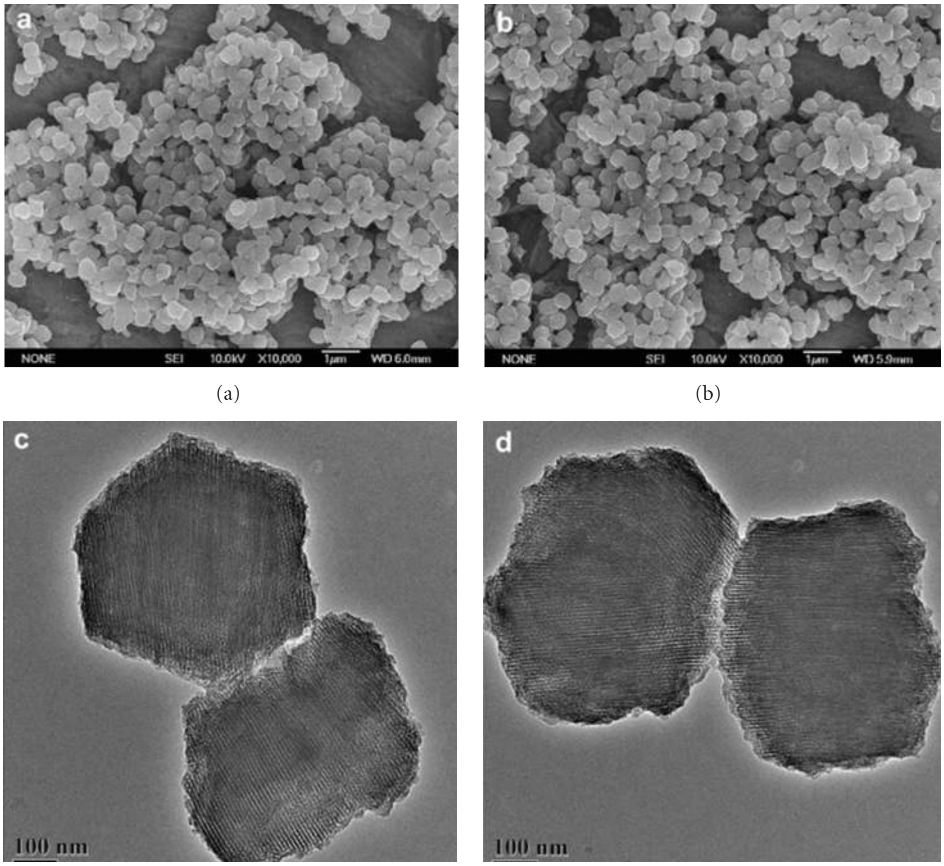
The blood compatibility of the carrier MSNs-RhB was evaluated by investigating the hemolysis and coagulation behaviors in a broad concentration range ($50{\sim}500\ \mathrm{mgmL^{-1}}$) under in vitro conditions [5]. The results suggested that MSNs-RhB possessed good blood compatibility and also, SEM and TEM analyses in Figure 1 indicated that both MSNs and MSNs-RhB had a subsphaeroidal morphology, a high dispersivity and uniform particle size of about 400 nm. In this work, He et al. [5] evaluated the blood compatibility of SBA-15-type MSNs and MSNs-RhB with negative and positive surface potentials, respectively, by investigating their hemolysis and coagulation behaviors. As to their coagulation behaviors, PT was used to evaluate the extrinsic and common coagulation pathways, APTT was used to evaluate the intrinsic and common coagulation pathways, and Fib was used to evaluate the abnormality of coagulation factor I. The hemolytic phenomena of SBA-15-type MSNs and MSNs-RhB are almost invisible by direct observation.

This is utterly different from the dry mesoporous silica powder previously reported by Dai et al. [6], because all hydrophilic mesoporous channels of MSNs and MSNs-RhB have been fully filled with PBS during experimental operation in the present study, and no space is left for further water absorption when mixed with plasma. Thus both MSNs and MSNs-RhB had not effected the normal coagulation/anti-coagulation functions of plasma, that is, the blood compatibility of SBA-15-type MSNs-RhB is satisfactory. The aggregations of the blood cells on interaction with the NPs are shown for RBCs, WBCs, and platelets. It revealed no aggregation of blood cells on incubation of NPs at a higher interaction ratio of 10 mg/mL. Polyethylene imine (PEI) which was used as positive control showed aggregation whereas saline used as negative control did not show any aggregation. Citrate-capped NPs also revealed no aggregation of blood cells on incubation with blood as reported earlier [7]. The same was visible with the haemolytic property of the NPs. The haemolysis induced by gold NPs is shown which were well within the acceptable limits of 1% [8]. Stability in physiologically relevant media, where saline levels are high, is a significant issue for the use of gold NPs in biological applications and assays. Therefore, stability in PBS may be taken as an initial screening test for compatibility with physiological conditions [9]. Regarding the application of gold NPs in biomedicine (sensing and drug delivery applications), they should be easily dispersible at neutral pH and should be stable.

Most studies are aimed at attempting to understand the blood compatibility of foreign materials and their investigation have shown that the blood compatibility was affected by various properties of the material surface. The response of blood in contact with the material depends on physicochemical features such as surface area, surface charge, hydrophobicity/hydrophilicity, and so forth. As for NPs, the size effect, structure, and surface are the decisive factors in these responses [10].

2.1.2. Histocompatibility. Targeted drug delivery is one of the most intensively explored areas of research and the use of NPs for diagnostic purposes has already entered the biomedical field. The current review is focused on biocompatibility of several representative types of nanomaterials: super paramagnetic iron oxides (SPION), dendrimers, mesoporous silica particles, gold NPs, and carbon nanotubes (CNTs).

In general, SPION are classified as biocompatible, showing no severe toxic effects in vitro or in vivo [11]. In primary human macrophages, no immunomodulatory effects



(a) (b) (c) (d)

Figure 1: SEM and TEM images of samples MSNs ((a) and (c), resp.) and MSNs-RhB ((b) and (d), resp.). The scale bars of (a), (b), (c) and (d) correspond to 1 mm, 1 mm, 100 nm and 100 nm, respectively [5].

were observed when cells were exposed to 30 nm dextran-coated SPION [11]. However, when primary peritoneal macrophages from rats and mice were exposed to 20 nm and 60 nm dextran-coated SPION, an increased secretion of anti-inflammatory cytokines, and reduced production of proinflammatory cytokines occurred [12]. In contrast, an increase in proinflammatory cytokines in a murine macrophage cell line was observed, accompanied by a decrease in the phagocytic function of these cells upon exposure to dextran-coated SPION [13]. These studies underline the importance of using different cellular systems for nanotoxicological studies, including primary human cell types. Jain et al. [14] have reported that SPION neither cause any effect in liver function when administered in vivo in rats nor do the particles induce oxidative stress. Our own studies demonstrate that dextran-coated SPION are nontoxic to primary human monocyte-derived macrophages and dendritic (antigen-presenting) cells (Kunzmann et al., unpublished observations).

Dendrimers exhibit a generation-dependent toxicity with higher generation dendrimers being the most toxic. The extent of cytotoxicity induced by dendrimers also depends on surface charge, whereby cationic dendrimers are more toxic than anionic dendrimers. A marked decrease in cytotoxicity can also be achieved when the surface is modified with PEG. Cationic dendrimers induce disruption including formation of pores in membranes [15]. They can induce apoptosis caused by mitochondrial dysfunction [16]. Cationic dendrimers can cause substantial changes in red blood cell morphology and hemolysis in a generation-dependent manner, whereas anionic dendrimers have no such effect. Cationic dendrimers were shown to induce caspase-dependent apoptosis and negatively influence proliferation in a murine macrophage cell line [17]. These effects could not be observed in two other murine cell lines, highlighting the importance of cell type specific differences. PAMAM dendrimers of generation 3.5 (G3.5) were shown to affect mitochondrial membrane potential in isolated rat liver mitochondria [18]. Glucosamine-conjugated dendrimers inhibit the synthesis of proinflammatory cytokines in LPS-treated human dendritic cells and macrophages. These dendrimer conjugates also have an inhibitory effect on toll-like receptor 4 (TLR4), a receptor that triggers LPS-induced stimulation of immune-competent cells [19]. Shaunak et al. evaluated the dendrimer conjugates in a rabbit model of scar tissue formation after glaucoma filtration surgery and found that the long-term success of the surgery increased from 30% to 80% [19]. The authors suggested that these dendrimer conjugates could be utilized to prevent scar tissue formation. The transcriptional profile of monocytes exposed to phosphorylated dendrimers revealed over expression of genes involved in anti-inflammatory responses [20]. Anti-inflammatory effects were also reported in vivo when simple modified PAMAM dendrimers were injected into rats [21]. However, the detailed mechanisms are still unknown.

Silica-NPs-demonstrated a good degree of biocompatibility [22, 23]. Silica-coated NPs, or silica NPs, have been demonstrated to enter the cell without affecting cell survival. These insights push research toward the development of silica NPs based drug delivery systems and biosensors [24–26]. Bardi et al. [27], developed and characterized NH2 functionalized CdSe/ZnS quantum dot (QD)-doped SiO2 NPs with both imaging and gene carrier capabilities. They show that QD-doped SiO2 NPs are internalized by primary cortical neural cells without inducing cell death in vitro and in vivo. Moreover, the ability to bind, transport, and release DNA into the cell allows GFP-plasmid transfection of NIH-3T3 and human neuroblastoma SH-SY5Y cell lines. QD-doped SiO2 NPs properties make them a valuable tool for future nanomedicine application.

The use of colloidal gold has a long history in coatings and glassware as a result of their high scattering power, variability of bright and intense colors, and stability. Furthermore, gold NPs can be readily functionalized with probe molecules such as antibodies, enzymes, and nucleotides. These hybrid organic-inorganic nanomaterials are the active elements of a number of biosensor assays, drug and gene delivery systems, laser confocal microscopy diagnostic tools, and other biomaterial-based imaging systems [28]. There have been many studies on the biocompatibility of gold NPs. In an attempt to mimic the respiratory tract after inhalation, Brandenberger et al. [29] devised an epithelial-airway model consisting of alveolar epithelial-like cells (the A549 lung carcinoma cell line), human monocyte-derived macrophages, and dendritic cells. After exposure to 15 nm gold NPs using an air-liquid interface exposure system, no induction of oxidative stress or inflammatory responses was noted. However, the system was responsive to proinflammatory LPS. No synergistic or suppressive effect was seen in the presence of gold NPs, suggesting that the gold NPs do not elicit immune reactions. On the other hand, gold NPs conjugated with peptides were recognized by primary murine macrophages and induced an immune response as evidenced by secretion of IL-6, IL-β, and TNF-α [30]. Therefore, the peptide coating on gold NPs is an important factor to enhance the immune response. Indeed, recent studies have shown that the conjugation of peptides on the surface of NPs may enhance the immune response [30]. Murine bone marrow macrophages were thus found to be able to recognize gold NP-peptide conjugates, while peptides or NPs alone were not recognized. The latter studies shed light on the design of NPs conjugates for modulation of immune responses in the fight against allergies, cancer, and autoimmune diseases. The role of plasma proteins attaching to NPs following entry into circulation also merits attention as this could potentially interfere with or modulate the presentation of other ligands attached to the particles.

2.2. Toxicity of Nanoparticles

2.2.1. Toxicology of Nanoparticles [31]. Interaction mechanisms between NPs and living systems are not yet fully understood. The complexity comes with the particles' ability to bind and interact with biological matter and change their surface characteristics, depending on the environment they are in. Scientific knowledge about NPs cell-interaction mechanisms has been accumulating in recent years, indicating that cells readily take up NPs via either active or passive mechanisms. Intracellularly, however, mechanisms and pathways are more difficult to understand. Even particles of the same material can show completely different behaviour due to, for example, slight differences in surface coating, charge, or size. This makes the categorisation of NPs behaviour, when in contact with biological systems, intricate and thus nanoparticle hazard identification is not straightforward. This is one of the main distinctions between nanotoxicology and classical toxicology where, in the latter, characterisation of toxicants is, in general, protocolised with a well-established set of methodologies available, employing a mass-based dose metric. However, with NPs the dose metric is not straightforward, as discussed below. Furthermore the protocolization of bioassays involving nanomaterials is still under development and has, in general, not yet been internationally validated. In addition, there are many more variables to consider when working with nanomaterials and these include material, size, shape, surface, charge, coating, dispersion, agglomeration, aggregation, concentration, and matrix.

The complexity increases when moving from in vitro to in vivo models. Hazard identification on the in-vivo level, with regards to nanomaterials, is still at an early stage. Major entry routes (lung, gut, and possibly skin) as well as putative targets (lung, liver, heart, and brain) have been identified. However, more research is required to understand mechanisms and pathways in the body. What seems clear is that exposure to insoluble nanoscale particles of b50 nm appears to be "new," when compared to the evolutionary history of the preindustrial world. Furthermore, such NPs appear to be able to high jack a preexisting transport mechanism through the body using endocytotic mechanisms, in the same manner that viruses employ. Therefore, because widespread translation of NPs within the body seems to be likely if the body is exposed, we need to take any toxicological risks seriously.

2.2.2. Cytotoxicity. Depending on the mode of administration and sites of deposition, toxicity may vary in severity. Therefore, to maintain clinical relevance, information on toxicity is presented using a system-based approach focusing on lung, dermal, liver, and nervous system targets. Figure 2 summarizes the advantages and disadvantages of each of the routes.

All eukaryotic cells (such as lung cells) contain functionally distinct, membrane-enclosed compartments. The main types are the nucleus and the organelles which include mitochondria, endoplasmic reticulum, Golgi apparatus, peroxisomes, lysosomes, and endosomes. Nucleus and

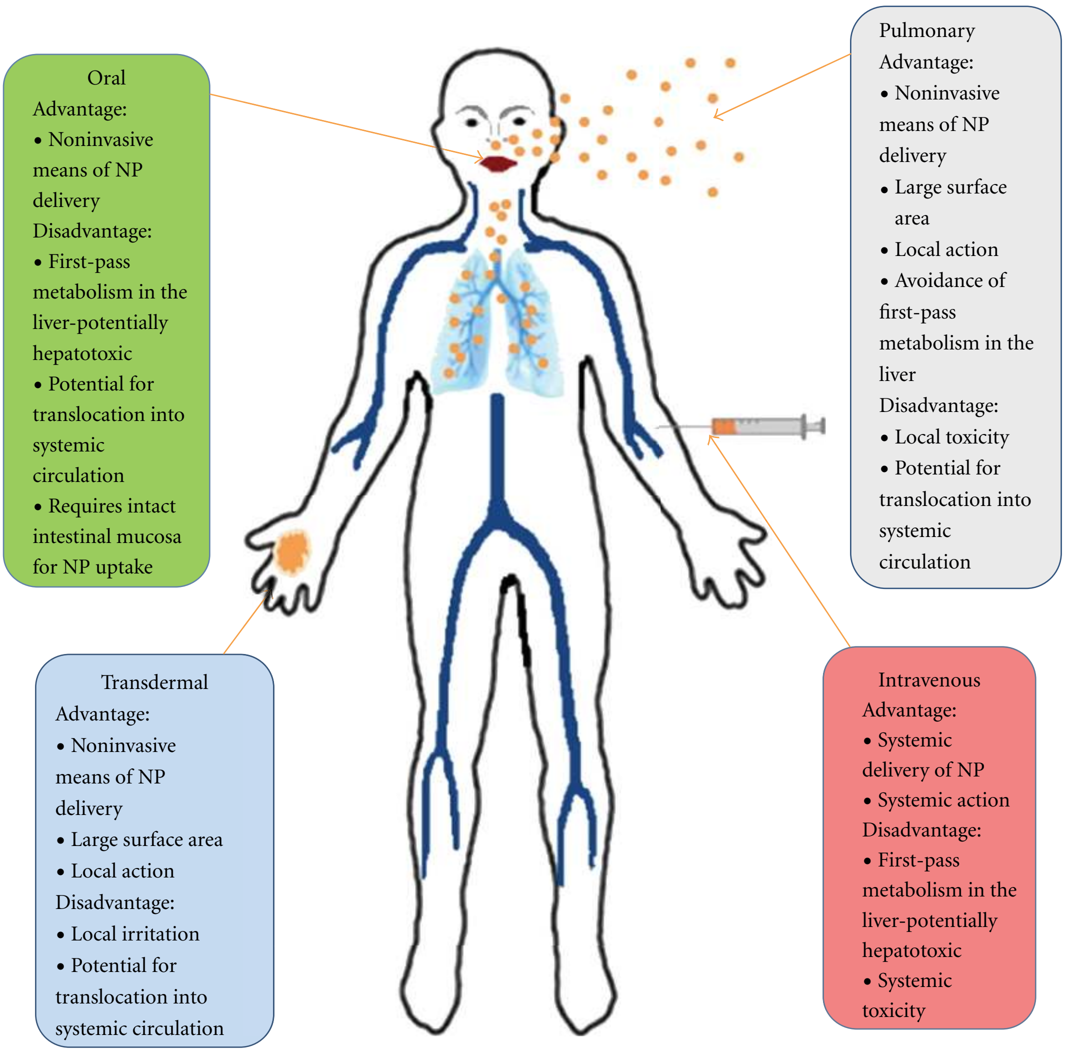


Figure 2: Routes of administration of nanoparticles and their advantages and disadvantages [32].

organelles are enclosed by a lipid bilayer containing distinct proteins. NPs can cross the membranes of organelles since they have been localized in lysosomes, mitochondria, and the nucleus, the mechanisms of internalization are, however, not known so far.

In this paper we focus on the cytotoxic effects of frequently used NPs, such as Metal and metallic oxide NPs, Polymeric NPs, Quantum dots, Silica (SiO2) NPs, to explain this topic.

Lung Cells. As NPs get in contact with the skin, the gastrointestinal tract, and the respiratory tract, these biological compartments are "designed" to act as barriers to the passage of nanosized materials into the organism. Because the lung is considered by far the most important portal of entry for NPs into the human body this overview will mainly focus on the lung as a potential barrier for inhaled NPs. It should however be noted that evidence has been published that NPs can also deposit on the olfactory epithelium and directly be translocated to the brain [33]. Current related researches are mainly focused on the impact of NPs on alveolar macrophages and fibroblasts and bronchial epithelial cells. Studies have already shown that NPs can remarkably weaken the phagocytic capacity of macrophages, which causes decline in lung's clearance ability. Nanocarrier systems (polymeric NPs, silica (SiO2) NPs, silver NPs, carbon nanotubes) for pulmonary drug delivery have several advantages which can be exploited for therapeutic reasons and, thus, intensively studied

Polymeric NPs are biocompatible, surface modifiable, and capable of sustained drug release. They show potential for applications in the treatment of various pulmonary conditions such as asthma, chronic obstructive pulmonary disease (COPD), tuberculosis (TB), and lung cancer as well as extra pulmonary conditions such as diabetes [34–36]. Already, there is a multitude of organic nanopolymers including collagen, gelatin, chitosan, alginate, and bovine serum albumin (BSA). Furthermore, the last three decades has seen a rise in the development of synthetic polymers such as the biocompatible and biodegradable poly(lactic-co-glycolic acid) (PLGA) for use as drug carrier devices [37, 38]. While such drug-loaded nanoconfigurations demonstrate promising alternatives to current cancer treatment, cytotoxicity needs to be evaluated. PLGA NPs successfully improve therapeutic outcome and reduce adverse effects via sustained and targeted drug delivery. Additionally, the use of biological capping materials such as chitosan or BSA further reduce toxicity while their biocompatibility and biodegradative capacity making them an intuitive choice for NPs surface modification. Romero et al. demonstrated a reduction in cytotoxicity of PLGA NPs stabilized with BSA compared to synthetic coating materials in cultured lung cancer cells [37]. Albumin, the most abundant serum protein, was found to be highly biocompatible making it a useful stabilizer for drug delivery vehicles. Similarly, chitosan-stabilization resulted in near-total cellular preservation and improved pulmonary mucoadhesion in an in vivo lung cancer model [39]. Biological capping materials reduce cytotoxicity by mimicking the physiological environment, thus “hiding” from the immune system. However, the possibility of enzymatic degradation due to biophysical resemblance needs further investigation.

Silica (SiO2) NPs have found extensive applications in chemical, mechanical polishing, and as additives to drugs, cosmetics, printer toners, varnishes, and food. Recently, the use of silica NPs has been extended to biomedical and biotechnological fields, such as biosensors for simultaneous assay of glucose, lactate, l-glutamate, and hypoxanthine levels in rat striatum, biomarkers for leukemia cell identification using optical microscopy imaging, cancer therapy, DNA delivery, drug delivery, and enzyme immobilization. Silica NPs have been shown to have a low toxicity when administered in moderate doses [40]. Unfortunately, silica NPs also tend to agglomerate and have been demonstrated to lead to protein aggregation in vitro at dose of 25 μg/mL [41]. Oxidative stress has been implicated as an explanation behind silica NPs cytotoxicity both in vitro and in vivo [42–45]. All these studies have reported cytotoxicity and oxidative stress, as determined by increasing lipid peroxidation (LPO), reactive oxygen species (ROS), and decreasing cellular glutathione (GSH level), but no similarity exists regarding dose-response. In the present study, we did not found significant difference in the cytotoxicity and oxidative stress caused by the two sizes 10 nm and 80 nm of amorphous silica NPs. A similar result was observed for 15 nm and 46 nm silica NPs by Lin et al. [46]. Present studies suggest that it is theoretically feasible and within acceptable safety limits to use moderate doses of silica NPs; however, high-dose toxicity profiles warrant further investigations.

The most common route of pulmonary exposure to silver NPs (AgNP) is via the occupational inhalation of airborne particles during manufacturing. The current American Conference of Governmental Industrial Hygienist’s (ACGIH) limit for silver dust exposure is 100 μg/m^3. In order to evaluate potentially acute and delayed adverse pulmonary effects of AgNP, Sung et al. have carried out a series of inhalation studies focusing on the acute, subacute (28 days) and subchronic (90 days) toxicity of AgNP in rats [47–49]. In the acute setting,rats were exposed to different particle concentrations in a whole-body inhalation chamber for 4 consecutive hours and were subsequently observed for a further 2 weeks. At the highest concentration used (750 μg/m^3; 7.5 times higher than the limit), no significant body weight changes or clinical changes were observed. Furthermore, lung function tests revealed no statistical differences between exposed and control groups. Repeated administration of AgNP for 4 weeks showed similar results. In contrast, subchronic inhalation for 13 weeks at a maximum concentration of 515 μg/m^3 (5 times the limit) revealed time- and dose-dependent alveolar inflammatory and granulomatous changes as well as decreased lung function [50]. Such results suggest that while high-dose chronic exposure to AgNP has the potential to cause harm, under current guidelines and limits, such excessive particle inhalation would seem unrealistic.

Dermal Cells. The skin is the largest organ of the body and functions as the first-line barrier between the external environment and the internal organs of the human body. Consequently, it is exposed to a plethora of nonspecific environmental assaultswithin the air as well as to distinct and potentially toxic substances within creams, sprays, or clothing. Topically applied NPs can potentially penetrate the skin and access the systemic circulation and exert adverse effects on a systemic scale. In this part, we will explain cytotoxic effects of TiO2 NPs and gold NPs.

TiO2 NPs have several properties which make them an advantageous ingredient for commercial sunscreens and cosmetics. They exhibit UV-light blocking properties and confer better transparency and aesthetics to creams. In vitro studies demonstrated cell type-dependent TiO2 toxicity affecting cellular functions such as cell proliferation, differentiation, mobility, and apoptosis [51, 52]. Such adverse effects, however, could not be replicated in vivo. In order to assess penetrative capacities, dermal infiltration studies have been carried out on human volunteers using different investigative techniques. Lademann et al. investigated the penetrative effect of repeated administration of TiO2-containing sunscreen on the skin of volunteers [53]. Tape stripping and histological appraisal of skin biopsies revealed that TiO2 penetrated into the open part of a hair follicle as opposed to the viable layers of the epidermis or dermis. Furthermore, the titanium amount in any given follicle was less than 1% of the applied total amount of sunscreen. Surface penetration via hair follicles or pores was also suggested by a study conducted by Bennat and Muller-Goymann where skin permeation was greater when sunscreen was applied to relatively hairy skins [54]. Mavon et al. demonstrated near total recovery of sunscreen after 15 tape strippings with no TiO2 deposition in hair follicles or skin layers [55]. It could be argued that different degrees of permeation and toxicity correlate with surface coatings and functionalizations of TiO2 NPs as well as with the number of follicular pores within the skin facilitating particle uptake.

Due to facile means of synthesis and the potential for biofunctionalization, gold NPs (AuNP) are being investigated for clinical applications including dermal drug-delivery [56]. Sonavane et al. demonstrated size-dependent permeationon excised rat skin after topical application of differently sized AuNP (15, 102 and 198 nm) [57]. Smaller NPs penetrated deeper into the tissue than larger ones which were mainly accumulated in the more superficial epidermis and dermis. These findings may have important implications with regards to efficient NP-based dermal drug delivery. Au compounds are generally considered safe and have been in routine clinical use for many years, for example, in the treatment of rheumatoid arthritis [58]. However, once reduced to nanometer scale, particles are known to undergo profound changes in terms of their biochemical properties which necessitates renewed investigations into their cytotoxic profile. Despite the relative wealth of toxicity studies focusing on AuNP, contradictory results remain the main obstacle to transition into the clinical setting. Several studies have demonstrated cellular uptake of AuNP to be a function of time, particle size, and concentration. In a study by Murphy et al., human dermal fibroblasts were exposed to AuNP for a period of up to 6 days [58]. Three sets of NP concentrations were obtained for each of two different sizes. Larger particles, 45 nm, exhibited marked cytotoxicity at a concentration of 10 μg/mL compared to smaller particles, 13 nm in size, which only displayed cytotoxic signs at the much higher concentration of 75 μg/mL. These results conflict with those obtained by Mironava et al. who reported maximum toxicity for a particle size of 1.4 nm [59]. Such differences may be explained by the distribution pattern of particles within cells and require more research.

Liver Cells. Being the site for first-pass metabolism, the liver is particularly vulnerable to NP toxicity and has consistently been shown to accumulate administered substances, even long after cessation of exposure. Thorough evaluation of NP-mediated hepatocellular toxicity thus remains of prevailing importance. Lipid peroxidation assay, comet assay, and oxidative DNA damage are commonly used to study the impact of NPs on liver cells. Gold NPs, silver NPs, silica NPs, and QDs have been intensively studied for clinically application reasons. The effect of surface structure and surface modification of NPs are important factors of their interaction with cells. Here we use QDs to elaborate it.

Semiconductor nanocrystals, or QDs, may be used in a variety of biomedical applications. The general structure of QDs comprises an inorganic core-shell and an organic coating to which biomolecules may be conjugated to enable targeting to specific areas within the body. Such close proximity and interaction with the physiological environment necessitates toxicological evaluation of these particles. Cell-based studies focusing on QD-induced adverse effects that found that toxicity most likely arises from the liberation of metal ions released from the heavy metal core [60]. Oxidative environments further promote degradation and metal-ion leaching. The liver is of particular importance with regards to bio-toxicity because of first-pass metabolism and potential accumulation and deposition within the organ, as shown by Derfus et al. [61]. QD size was also postulated to be a major parameter in organ-specific deposition with smaller particles (<20 nm) extravagating through capillary fenestrae that are large enough in the liver (~100 nm in size) [62]. The long half-life clearly has implications for organ toxicity, particularly in view of the liver's untoward propensity to heavy metal ion poisoning which makes exposure to QDs potentially very hazardous. Surface coating to protect the core from degradation has been shown to reduce toxicity [63]. Conventionally, QDs are coated with a layer of zinc sulphide (ZnS) or mercaptoacetic acid. However, evidence of continued cellular toxicity after prolonged periods of time suggests either inadequate core coverage or the need for a different type of coating material [64]. Das et al. carried out a series of experiments assessing additional surface coatings for their respective cytotoxicities [65]. CdTe/CdSe cored QDs with a ZnS shell were additionally covered with organic, carboxylated (COOH), amino (NH2), or poly(ethylene glycol) (PEG) coatings. Cytotoxicity was tested on exposure to each type separately by measurement of macrophage cell viability and LDH release. All QDs were shown to induce significant cytotoxicity after 48 h and coating materials as well as liberated Cd ions were suggested to be the causative agents. It is likely that a breakdown of physically labile surface material resulted in ion liberation and subsequent toxicity. Recently, Seifalian and colleagues have demonstrated that the novel synthetic nanomaterial polymeric oligohedral silsesquioxane (POSS), when incorporated onto CdTe-cored QDs, shows significantly enhanced cytocompatibility more than conventionally used materials, even without ZnS shelling (unpublished data). POSS was shown to be nontoxic by preventing ion leakage from the core. These results underline the importance of the type of coating material used and suggest that the most important factor influencing QD toxicity remains heavy metal-ion leakage from the core due to inadequate surface coverage.

2.2.3. Neurotoxicity. The central nervous system is composed of two parts: the brain and the spinal cord. Both of them are delicate organs in human body which must be protected from the injury to xenobiotics. Recent observations suggest that several NPs, such as polysorbate 80-coated PBCA NPs and pegylated PLA immunonanoparticles, are able to cross BBB [66, 67] through intravenous administration and followed by the accumulation in the brain. However, due to their special physicochemical properties, such as large surface area, the NPs may cause neurotoxicity after entering into the brain. Therefore, the evaluation of the potential neurotoxic effects of these NPs on CNS function is required, as specific mechanisms and pathways through which NPs may exert their toxic effects remain largely unknown. So far, there are already some reports, but not many, which observed the neurotoxicity of NPs both in vitro and in vivo [68, 69]. As a large variety of colloidal dispersions of super paramagnetic iron oxide nanoparticles (SPIONs) have been developed and explored for a range of new biological, biomedical, and diagnostic applications with regard to their magnetic properties [70, 71]. Here we will give a description of the toxicity effect of super paramagnetic NPs on the brain.

SPIONs and ultrasmall SPIO nanoparticles (USPIONs) consist of an iron oxide core and a variable carbohydrate coating which determines cellular up take and biological half-life. The degree of surface coverage has been postulated to be the main parameter in cellular uptake as incomplete surface coverage was shown to promote opsonization and rapid endocytosis whereas fully coated SPION escaped opsonization which, as a result, prolonged plasma half-life [72]. However, more recently, particle size as opposed to coating degree has been suggested to exert chief influence on the rates of uptake by macrophages [73]. Being one of the few FDA approved NPs for the use in MRI, SPIONs most commonly find applications in the imaging of the vasculature and lymph nodes [74–77]. However, recent reports from both animal models and human subjects have shown their efficacy in visualizing intracerebral malignancies and neurological lesions within the CNS [78]. Despite such routine use of SPION, the long-term effects and potential neurotoxicity have, as yet, not been evaluated extensively. The unique physiochemical properties shared by all NPs, such as nanometer size and a large surface area to volume ratio, make SPION particularly valuable for novel therapeutic and diagnostic applications. However, such dimensional reductions may potentially induce cytotoxicity and interfere with the normal components and functions of the cell [79]. Previous in vitro studies have shown the capacity for SPION to induce ROS generation, impair mitochondrial function and cause leakage of LDH-all of which could incite neurotoxicity as well as potentially aggravate pre-existing neuronal damage [80]. Furthermore, toxicity reports demonstrated an association between particle size, type of surface coating and breakdown products, concentration, and the degree of opsonization and cytotoxicity in cultured cells [81]. For example, Berry et al. utilized fibroblast cultures to demonstrate the ability to tune particle toxicity according to particle coating. They compared the in vitro toxicity of plain uncoated magnetic iron oxide NPs (P particles) with either dextran-derivatized (DD) or albumin-derivatized (AD) NPs. P particles as well as DD particles exhibited similar toxicities, whereas AD particles managed to induce cell proliferation [82]. In a study by Muldoon et al., the distribution, cellular uptake, and toxicity of three FDA-approved SPION of different sizes and surface coatings were compared to each other and to a laboratory reagent [83]. Firstly, inoculation of ferumoxtran-10 (USPION: 20–50 nm in size, complete surface coverage with native dextran), ferumoxytol (USPION: 20–50 nm in size, complete surface coverage with semisynthetic carbohydrate) and ferumoxide (SPION: 60–185 nm in size, incompletely coated with dextran) as well as the lab reagent MION-46 into tumor-bearing rat brains demonstrated direct uptake of ferumoxtran-10 into tumor tissue and long-term retention within the cancerous lesion (5 days). However, uptake seemed NP dependent. Ferumoxide inoculation did not yield tumor enhancement which suggests size and surface coverage dependence. The second step involving osmotic BBB disruption to evaluate transvascular SPION delivery and neurotoxicity displayed no evidence of gross pathology implying the feasibility of intracerebral injection of clinical USPION into humans.

3. Biocompatibility and Toxicity of Nanotubes

At present, nanotubes for biomedical application include carbon nanotubes, silicon dioxide nanotubes, boron nitride nanotubes, titanium dioxide nanotubes, and organic nanotubes, of which carbon nanotubes are the most widely used materials. So far, there have been many great studies into it.

3.1. Carbon Nanotubes. Carbon nanotubes are made from rolled up sheets of graphene and are classified as single-walled (SWCNTs) or multiwalled carbon nanotubes (MWCNTs) (as shown in Figure 3) depending on the constituent numbers of graphene layers. Due to their unique size and shape, much effort has been dedicated to analyzing biomedical applications of CNTs. Such extensive potential requires the meticulous evaluation of toxicity. This widespread use of different types of NPs in the biomedical field raises concerns over their increasing access to tissues and organs of the human body and, consequently, the potential toxic effects. Carbon nanotubes (CNTs) are cylindrical graphene sheets. Due to their unique structure, CNTs can be used for hyperthermic ablation of cancer cells due of their strong optical absorption in the NIR wavelength region, as well as for drug delivery to cancer cells owing to their high surface areas.

CNTs are hydrophobic in nature and thus insoluble in water, which limits their application in biomedical and medicinal chemistry. Therefore, various functionalization methods like adsorption, electrostatic interaction, and covalent bonding are being utilized with a number of compounds and polymers to render a hydrophilic character to CNTs so as to avoid their aggregation and to facilitate their use in biomedical applications. Recent developments with CNTs span the areas of gene therapy, drug delivery, thermotherapy, imaging, and anticancer treatments.

3.1.1. Biocompatibility of Carbon Nanotubes. Carbon nanotubes (CNTs) have attracted broad attention because of their excellent electrochemical, mechanical, and electrical characteristics. In recent years, many research efforts have focused on the exploration of the application of both single-wall (SWCNT) and multiwall (MWCNT) carbon nanotubes in the biological and biomedical field as nerve cell stimuli, diabetes sensors, cancer therapy, drug delivery carrier, bone scaffold materials, and so forth [85, 86].

Interaction with Cells. Among CNTs, single-wall CNTs consist of a single layer of graphite lattice rolled into a perfect cylinder, whereas sets of concentric cylindrical graphite shells form multiwall CNTs (MWCNTs). Neurobiology is one of the fields where the potential applications seem to be very promising [87]. Neurons and neuronal cell lines can grow and differentiate on CNT substrates [88, 89].

It is known that the functionalized CNTs (f-CNTs) can be used to control the number of growth cones, neurite outgrowth, length, and branching during neuronal cell growth on f-CNTs [90]. The neuronal environment with positively charged multiwalled carbon nanotubes (MWCNTs) has improved neurite outgrowth and branching compared to neutralor negatively charged MWCNTs [91, 92].

Bardi et al. [93] show that multiwall CNTs (MWCNTs) coated with Pluronic F127 (PF127) surfactant can be injected in the mouse cerebral cortex without causing degeneration

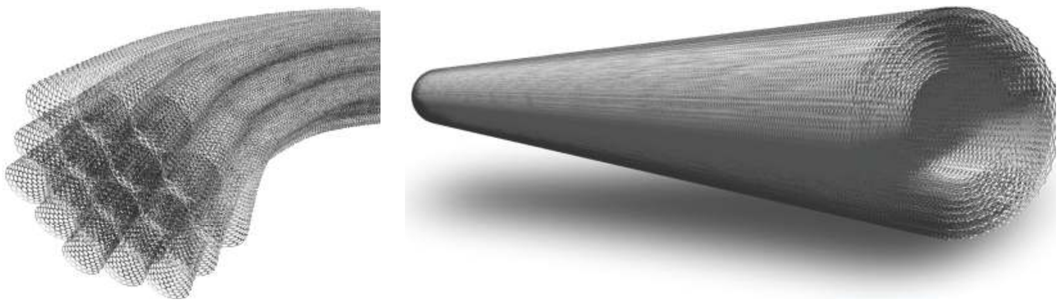

(a) (b)

Figure 3: (a) Single-walled carbon nanotubes (SWCNTs); (b) multiwalled carbon nanotubes (MWCNTs) [84].

of the neurons surrounding the site of injection. These results suggest that PF127-coated MWCNTs do not induce apoptosis of cortical neurons. Moreover, the presence of MWCNTs can reduce PF127 toxicity.

In 2011, to evaluate the effects of the surface roughness and functionalization modifications of the SWCNT papers, Yoon et al. and so forth [94] investigated the neuronal morphology, mitochondrial membrane potential, and acetylcholine/acetylcholinesterase levels of human neuroblastoma during SH-SY5Y cell growth on the treated SWCNT papers. Their results demonstrated that the plasma-chemical functionalization caused changes in the surface charge states with functional groups with negative and positive charges and then the increased surface roughness enhanced neuronal cell adhesion, mitochondrial membrane potential, and the level of neurotransmitter in vitro. The cell adhesion and mitochondrial membrane potential on the negatively charged SWCNT papers were improved more than on the positively charged SWCNT papers. Also, measurements of the neurotransmitter level showed an enhanced acetylcholine level on the negatively charged SWCNT papers compared to the positively charged SWCNT papers.

It has been demonstrated that CNT support the growth of osteoblastic cells by stimulating the production of extracellular matrix (ECM), a central step during the formation of bone tissue [95].

In order to investigate the interaction of cells with modified multiwalled carbon nanotubes (MWCNTs) for their potential biomedical applications, the MWCNTs were chemically modified with carboxylic acid groups (–COOH), polyvinyl alcohol (PVA) polymer and biomimetic apatite on their surfaces [96]. In this study, human osteoblast MG-63 cells were cultured in the presence of the surface-modified MWCNTs. There were no obvious changes in cell morphology in osteoblastic MG-63 cells cultured in the presence of these chemically modified MWCNTs. The surface modification of MWCNTs with apatite achieves an effective enhancement of their biocompatibility. Recently, a new study [97] indicated that MWCNTs might stimulate inducible cells in soft tissues to form inductive bone by concentrating more proteins, including bone-inducing proteins. In this study, they evaluated human adipose-derived MSCs (HASCs) cultured on MWCNTs compacts, comparing on graphite compacts, with and without the adsorption of FBS and recombinant human bone morphogenetic protein-2 (rhBMP-2) in advance in order to find out how CNTs affect differentiation of HASCs. Larger mineral content was found on the MWNTs compacts than on the GP compacts at day 7. In vivo experiment showed that the MWNTs could induce ectopic bone formation in the dorsal musculature of ddy mice while GP could not.

Surface-coating treatment with multiwalled carbon nanotubes (MWCNTs) was applied to 3D collagen scaffold for bone tissue engineering. In Hirata et al. [98] study, the effect of the MWCNT coating on differentiation of rat primary osteoblasts and the tissue response around MWCNT-coated sponges were investigated. Rat primary osteoblasts (ROBs) were cultured on an MWCNT-coated collagen sponge (MWCNT-coated sponge) in a 3D dynamic flow cell culture system and differentiation markers were measured. Significantly more bone formation was observed around the MWCNT-coated sponges than around the uncoated sponges and new bone attached to MWCNTs directly at 28 and 56 days after implantation in the femur. Moreover, at 28 days after implantation of the MWCNT-coated sponge with osteoblasts cultured for 1 day, bone tissues were successfully formed in the pores according to its honeycomb structure. Therefore, MWCNT coating appears to be effective for bone tissue engineering.

As Drug and Vaccine Delivery Vehicles. Carbon nanotubes (CNTs) could be one of the most advanced nanovectors for the highly efficient delivery of drugs and biomolecules owing to their large surface with unique optical and electrical properties. They can be conjugated noncovalently or covalently with drugs, biomolecules and NPs towards the development of a new-generation delivery system for drugs and biomolecules.

CNTs can interact with mammalian cells and enter cells via cytoplasmic translocation [99–102]; they therefore can deliver a range of therapeutic reagents into the cell. For example, plasmid DNA has been internalized by the cell, and the expression of the plasmid-carried marker genes has been enhanced [102–105]. Other macromolecules, including proteins [106], polymers [107], and single-stranded DNA [108] have also been internalized by coating onto CNTs and through the interaction of CNTs with mammalian cells.

Based on the dosage differences in target organelles, Yang et al. [109] successfully used SWCNTs to deliver acetylcholine into brain for treatment of experimentally induced Alzheimer disease with a moderate safety range by precisely controlling the doses, ensuring that SWCNTs preferentially enter lysosomes, the target organelles, and not mitochondria, the target organelles for SWCNT cytotoxicity.

To evaluate the acute response of blood leukocytes to CNTs in vitro, Medepalli et al. [110] recreated two specific events: (a) a direct-exposure event that may occur due to presence of CNTs in circulation and (b) presentation of CNTs to blood leukocytes via antigen presenting cells. The potential for activation of different leukocyte subpopulations was then evaluated by profiling various early activation markers using flow cytometry. To ensure relevance to gene and drug delivery, these experiments utilized single-walled CNTs (SWCNTs) functionalized with single-stranded (ss)-DNA fragments consisting of guanine-thymine (GT) repeated sequences, which have potential to serve as a backbone for transport of biomolecules and also as a surfactant to prevent aggregation. Results from this study demonstrate that ss-DNA-functionalized SWCNTs does not elicit an acute immune response from blood leukocytes through either direct or indirect interactions as verified by the expression of early leukocyte activation markers.

As Biosensors. Carbon nanotubes show great potential for use as highly sensitive electronic (bio)sensors. Single-walled carbon nanotubes (SWNTs) arguably are the ultimate nanosensor in this class for a number of reasons: SWNTs have the smallest diameter (~1 nm), directly comparable to the size of single molecules and to the electrostatic screening length in physiological solutions [111]. Furthermore, the low charge-carrier density of SWNTs [112] is directly comparable to the surface charge density of proteins, which intuitively makes SWNTs well suited for electronic detection that relies on electrostatic interactions with analyte (bio)molecules. Finally, the SWNT consists solely of surface such that every single carbon atom is in direct contact with the environment, allowing optimal interaction with nearby molecules. Although an appreciable amount of biosensing studies has been conducted using carbon nanotube transistors, the physical mechanism that underlies sensing is still under debate [113]. Several suggested that mechanisms are electrostatic gating [114], changes in gate coupling, carrier mobility changes, and Schottky barrier effects [115].

Recently, Zelada-Guillén et al. [116] have reported the first biosensor that is able to detect *Staphylococcus aureus* in real time. A network of single-walled carbon nanotubes (SWCNTs) acts as an ion-to-electron potentiometric transducer and anti-*S. aureus* aptamers are the recognition element. In this study, both biosensor types demonstrated great versatility in selectivity assays, which suggests the applicability of SWCNT/aptamer-based potentiometric biosensors in the highly selective identification of *S. aureus*.

3.1.2. Toxicity of Carbon Nanotubes. CNTs has certain toxicity, including lung toxicity and embryonic toxicity. Through covalent modification and adding surfactants to the CNTs, the improvement of the living creature exploitation degree, and reducing the biological toxicity can be achieved.

CNTs may eliminate quickly in vivo from the blood, is mainly detained in the liver, the spleen and the lung.

Liver is the dominant site of accumulation after intravenous (iv) or intraperitoneal (ip) administration of CNTs, but only few studies were conducted in order to establish the impact of CNTs over the liver [117]. Also, only few studies have been conducted regarding ip delivery of CNTs [118]. Last year, Clichici et al. and so forth [119] have found that ss-DNA-MWCNTs induce oxidative stress in plasma and liver, with the return of the tested parameters to normal values, 6 h after ip injection of nanotubes, with the exception of reduced glutathione in plasma. Results demonstrate that ss-DNA-MWCNTs produce oxidative stress and inflammation, but with a transient pattern. Given the fact that antioxidants modify the profile not only for oxidative stress, but also of inflammation, the dynamics of these alterations may be of practical importance for future protective strategies.

The research [120] indicated that in 2 months water-soluble SWCNTs does not cause the mouse spleen organization refining various biochemistry target change, the histopathology inspects the nonspleen damage; But along with detection time's extension, possibly causes spleen's immune response.

Porter et al. [121] conducted an in vivo dose-response and time course study of MWCNT in mice in order to assess their ability to induce pulmonary inflammation, damage, and fibrosis using doses that approximate estimated human occupational exposures. The data reported indicate that MWCNT exposure rapidly produces significant adverse health outcomes in the lung. Furthermore, the observation that MWCNT reach the pleura after aspiration exposure indicates that more extensive investigations are needed to fully assess if pleural penetration results in any adverse health outcomes.

Recently, Pietroiusti et al. [122] have tested the effect of pristine and oxidized single-wall carbon nanotubes (SWCNTs) on the development of the mouse embryo. No fetal and placental abnormalities were ever observed in control animals. In parallel, SWCNT embryo toxicity was evaluated using the embryonic stem cell test (EST), a validated in vitro assay developed for predicting embryo toxicity of soluble chemical compounds, but never applied in full to NPs. The EST predicted the in vivo data, identifying oxidized SWCNTs as the more toxic compound.

Toxicity of CNTs and its mechanism have been widely investigated, which is differing from composition, length, diameter and sizes. Exposure to pristine CNT has been shown to cause minimal cytotoxicity at higher concentrations (both in vivo and in vitro), while chemically functionalized CNT enhanced for drug delivery has not demonstrated any toxicity thus far. However, CNT aggregation has plagued research in this area and the impact of this key variable is unclear at this stage.

3.2. Other Nanotubes. Silicon dioxide nanotubes, boron nitride nanotubes, titanium dioxide nanotubes, organic nanotubes are emerging used nanotubes. Until now, reports about their biomedical application are still not sufficient. Simple descriptions of their biomedical studies are given here to help us get a better understanding about them.

3.2.1. Silicon Dioxide Nanotubes. Silica nanotubes (SNTs) have become a promising material in biomedical applications, owing to their unique properties. The tube-structured SNTs are endowed with two physically distinct domains: the inner void and the outer surface. Differential functionalization of the inner and outer surfaces of SNT could provide a facile and effective means to integrate multifunctionality with SNT technology [123]. For example, various nanosized biomaterials and therapeutics, such as magnetic particles, imaging agents, and drugs, can be loaded inside the vacant inner space of SNT to make them potent multifunctional materials. Figure 4(a) shows a TEM micrograph of MSNTs with a length of 6–10 μm and a diameter in the range 400–600 nm. From the TEM image of NH_2-MSNTs (Figure 4(b)) it can be seen that the samples retained the same morphology as the as prepared MSNTs after modification with APTS. A TEM micrograph of MSNTs coated with PAH/PSS multilayers is presented in Figure 4(c). Similar results for the thickness of the ALG/CHI multilayer assembled on NH_2-MSNTs can be determined from the TEM micrograph of Figure 4(d).

Biocompatibility and facile modification through well-known silane chemistry [125–127] make SNTs even more attractive tools in various biomedical applications, such as in drug or gene delivery vehicles. Nevertheless, SNTs have encountered a fundamental impediment in gene delivery as they acquire a negative charge in aqueous solution due to the presence of a large number of hydroxyl groups on their surface. Therefore, to achieve efficient gene delivery, the surface of the SNT must be rendered positive by conjugating cationic materials. These cationic materials then condense and load DNA, having a negatively charged phosphate backbone and transport it to the target sites, especially intracellular regions.

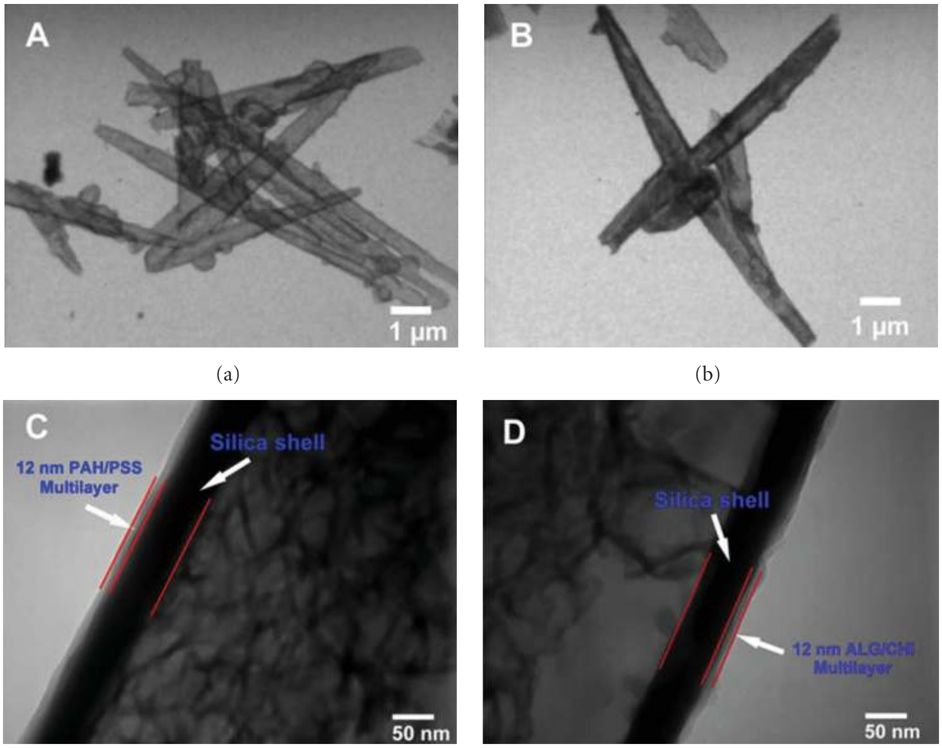
The Wu group was the first to introduce SNT as a therapeutic cargo for gene delivery [128]. In their report, the inner surface of SNT was functionalized with 3-(aminopropyl)trimethoxysilane to generate a polycationic surface and, as per confocal microscopy, 60e 70% of the cells were transfected during incubation. The Ran group [129] have functionalized SNT with a magnetic-fluorescent nanocomposite and LMW BPEI to construct a device that can act as an efficient gene delivery carrier and as a MRI agent. The success of this dual-modality nanoconstruct should drive further research into multipurpose therapeutic biomaterials.

3.2.2. Boron Nitride Nanotubes. A boron nitride nanotube (BNNT) is a structural analog of a carbon nanotube: alternating B and N atoms entirely substitute for C atoms in a graphitic-like sheet with almost no change in atomic spacing [130]. Despite this structural similarity with carbon nanotubes (CNTs), BNNTs own superior mechanical, chemical, and electrical properties [131, 132]. In the latest years, several examples of CNT exploitation in biotechnology have been proposed [133], while the biomedical applications of BNNTs have remained largely unexplored [134], having the first study about BNNT-cell interactions been performed by Ciofani et al. [135].

Figure 5 shows the SEM and TEM images of the as-received BNNTs SEM image shows nice clean BNNTs, whereas TEM picture shows the presence of both long cylindrical tubes and bamboo type structures. BNNTs have excellent elastic modulus of 1.22 TPa (similar to CNTs) and are thus a potential candidate as reinforcement. A recent study through the molecular dynamic approach has shown the tensile strength of single-walled BNNTs to be P24 GPa [137]. Also, BNNTs are very flexible and hence their reinforcement will not adversely affect the ductility of the scaffolds [138]. BNNTs were first synthesized in 1995 but there are very few studies [139–144] on BNNT reinforced composites. Researchers have used BNNTs as reinforcement in glasses mainly to increase the strength and fracture toughness [139, 140]. Only one report is available on ceramic-BNNT composite [141], where enhanced superplasticity in Al2O3 and Si3N4 with BNNT addition is observed. Few studies on polymer-BNNT composites have been reported including nonbiodegradable polymers like polyaniline [142], polystyrene [143], and copolymer of vinylidene chloride and acrylonitride [144]. These studies have justified the role of BNNT in terms of improvement in mechanical and optical properties. BNNTs have higher chemical stability than CNTs in oxidative atmosphere, with their oxidation starting at 1223 K compared to CNTs at 773 K [145]. Although human body temperature is 310 K, the chemical inertness of BNNTs may still be an added advantage when they are exposed in the living body.

Given its proposed biomedical application, cytotoxicity of BNNTs is a very important issue. Recently, Chen et al. [146] have shown BNNTs to be noncytotoxic to human embryonic kidney cells (HEK-293) and reported that BNNTs do not inhibit cell proliferation even after 4 days. Ciofani et al. [147] demonstrated good cytocompatibility and cellular uptake of polyethyleneimine- (PEI-) coated BNNTs in a human neuroblastoma cell line (SH-SY5Y). Both these studies indicate safe use of BNNTs in bioapplication. The application of BNNTs in orthopedic scaffold material requires their cytotoxic behavior to be investigated with bone cells, for example, osteoblasts. Since PLC matrix is biodegradable, BNNTs may get exposed to the bloodstream after the scaffold degrades. BNNTs, exposed in the bloodstream, interact first with macrophages. Macrophages internalize the foreign elements entering in the bloodstream to prevent any harmful reaction. Hence, the cytotoxicity test of BNNTs on macrophages is also very important. No studies have yet been performed on cytotoxicity of BNNTs with osteoblasts or macrophages. It must also be emphasized that no report exists on any biodegradable polymer-BNNT composites up to now.

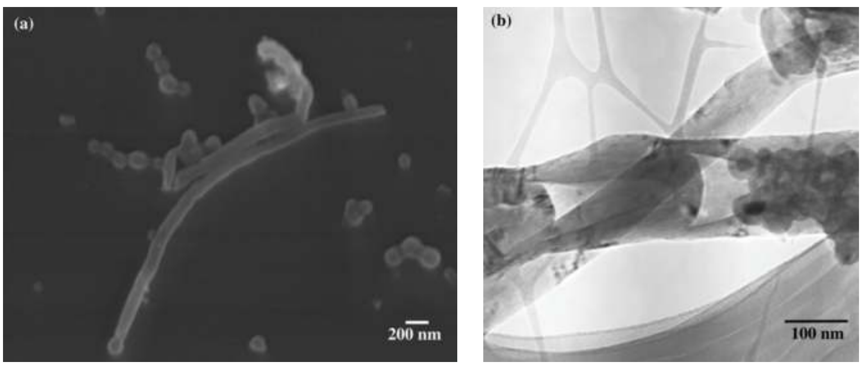
3.2.3. Titanium Dioxide Nanotubes. In 2001, Gong and coworkers [148] reported the fabrication of vertically oriented highly ordered TiO2 nanotube arrays up to



(a) (b)

(c) (d)

Figure 4: TEM images of (a) MSNTs, (b) NH2-MSNTs, (c) PAH/PSS-MSNTs, and (d) ALG/CHI-NH2-MSNTs [124].

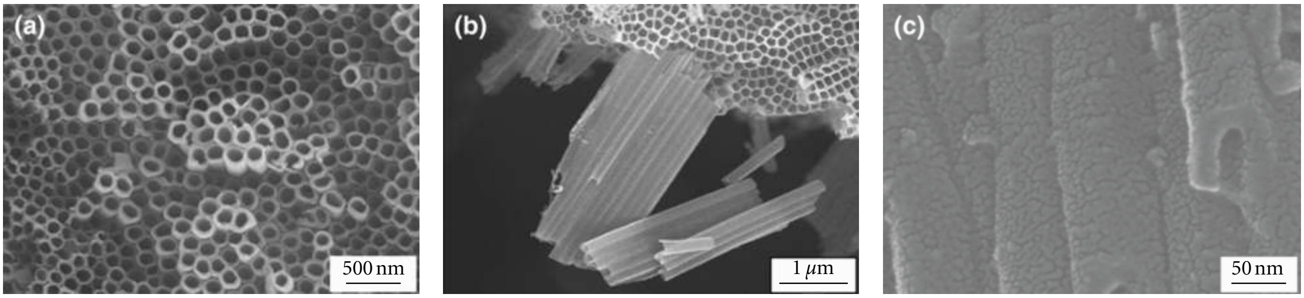


(a) (b)

Figure 5: (a) SEM image of the as-received BNNTs. (b) TEM images of the as-received BNNTs showing the presence of both tubular- and bamboo-type structures [136].

approximately 500 nm length by anodization of titanium foil in an aqueous HF electrolyte. Since then, substantial efforts have been devoted to the self organisation and growth of TiO2 [149]. Titanium dioxide nanotube layers are used as photocatalysts in water and environmental purification, as well as biological and biomedical applications [150–152]. In particular, titanium dioxide nanotubes are used as a biomaterial for implants, drug delivery platforms, tissue engineering, and bacteria killing [153–155]. Another interesting propriety of TiO2 is its tunable wettability effect [156]. The ability to modify surface topography and to control wetting behavior is useful for biomedical applications. Surface roughness, contact angle, and surface energy are the main factors in understanding the biology media and material interaction. We can see the SEM images of the ordered anodized titanium oxide nanotube arrays in Figures 6(a) and 6(b). Figure 6(c) shows Silica coated TiO2 nanotubes prepared on the above anodized TiO2 via a sol-gel method.

In 2010, Feschet-Chassot et al. [158] used the ciliated protozoan T. pyriformis to predict the toxicity of titanium dioxide nanotube layers towards biological systems. The contact angle measurements show clearly the correlation between surface topography and surface wettability. They have shown the ability of the titanium dioxide nanotube



(a) (b) (c)

Figure 6: SEM images of TiO2 nanotube arrays anodized at constant potential. (a) Top view, (b) side view, and (c) silica-coated titania nanotube [157].

layers to degrade AO7. Such surfaces do not show any characteristic in vitro toxicity effect in a biological system.

3.2.4. Organic Nanotubes. Organic nanotubes (ONTs) self-assembled from amphiphiles are one of the tubular nanomaterials that have attracted many interest in the field of nanotechnology because of their uniform tubular morphology with a hollow nanospace and a hydrophilic biocompatible surface [159]. Application of pristine ONTs has been found in nanopipettes, photovoltaic devices, and nanocontainer for and gene. Furthermore, the surface functionalization of ONTs has become a key methodology to utilize them for many purposes, such as sensor for guest protein, pathogen detection chips, and biomimetic catalyst [160].

In the meantime, the use of tubular nanomaterials as nonviral gene transfer vector has been growing fast. Inorganic ones, mainly carbon and silica nanotubes, were functionalized with various positive materials and their gene transfer ability has been extensively investigated. To the best of knowledge, two attempts on the usage of ONTs in gene delivery have been reported. In the first example, lipid microtubules were embedded in an agarose gel as a reservoir for the sustained release of plasmid DNA, but not as a DNA transfer vector [162]. In the second example, cationic nanotubes self-assembled from dipeptide were able to associate single-stranded DNA on their outer surface for the intracellular delivery [163]; however, they were transformed to spherical vesicles under dilute condition before cellular internalization. These limited reports indicated that the utility of ONTs as nonviral tubular gene transfer vectors has not been fully demonstrated.

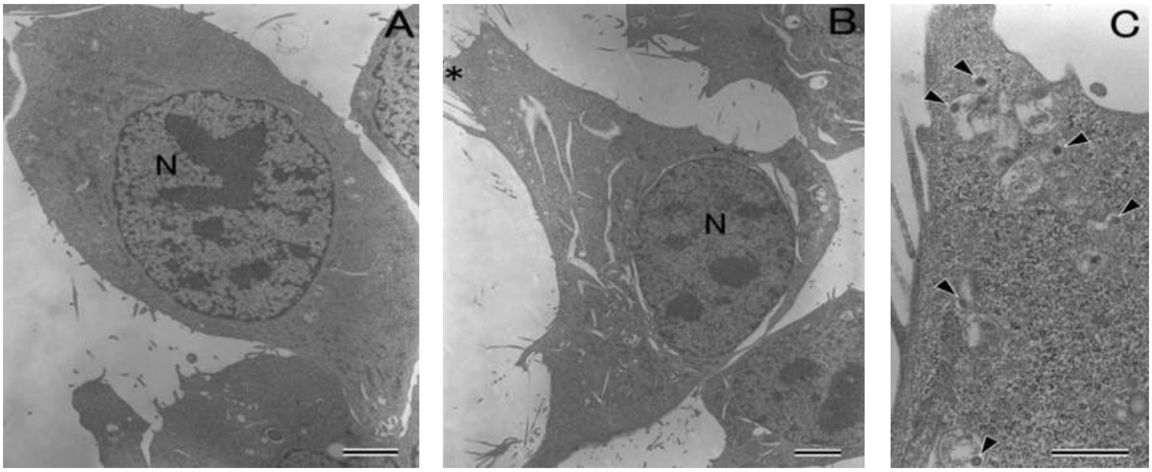
The drug loading of ONTs was susceptible to the effect of ionic strength and H^+ concentration in the medium, and drug release from ONTs was promoted at lower pH, which is favorable for the release of drugs in the endosome after cellular uptake [161] and Figure 7 shows that ONT1 was taken up to the cells. Moreover, ONT could be modified chemically with folate by simply mixing with a folate-conjugate lipid. Also in 2011, another study [164] demonstrated the usefulness of functionalized ONT in gene delivery, and the functionalized ONT represents a novel type of tubular nonviral gene transfer vector. These novel, biodegradable organic nanotubes have the potential to be used as drug carriers for controlled and targeting drug delivery.

4. Conclusions

Nanoparticles, of large surface area and high specific surface energy, are thermodynamically unstable system. After the NPs enter the organism by various means, they will agglomerate, dissolve, and meet with other changes as a result of the environmental impact of the body (such as protein concentration and high ionic strength, high acidity). When NPs agglomerate, the physical and chemical properties may change, thus affect the biological effects. For metal and metallic oxide NPs, solubility problems are more important. The release of metal ions of dissolved NPs, at least part of them contributes to the toxicity that we observed. The biological characteristics which NPs demonstrated have significant correlations with structures and the nature of their own. Therefore, people are considering changes in NPs themselves to reduce their toxicity and improve the biocompatibility.

Surface modification of NPs and artificial control of NPs size and shape, are effective ways to reduce the toxicity of NPs. But some scholars believe that artificially coated and modified NPs have lost their original features, which from a fundamental sense not the original NPs can be compared with. Surface modification methods can be divided into the surface coating and chemical modification. Through the surface modification of NPs, the inherent toxicity of NPs can be reduced, which also can greatly improve the biocompatibility of NPs.

To use NPs safely in biomedicine, a detailed understanding of biocompatibility and toxicity of NPs is needed. As we can see, more and more data are becoming available regarding NPs toxicity, but highly effort is still required in order to truly advance our knowledge in this field. Currently, researchers may carry out these studies from these aspects: considering various forms of particles respectively, considering the dose-response relationship, in vivo and in vitro experiments, setting about establishing a database of toxic nanoscale to further clarify the division of nanoscale toxic nanosize range. Meantime, deep studies about the



(a) (b) (c)

Figure 7: Transmission electron micrographs showing untreated C26 cells (a) and C26 cells incubated with ONT1 for 24 h (b) and a high magnification image of the surrounding cell (indicated by an asterisk in (b)) (c). N: nucleus; arrowhead: ONT1, bars = 2 μm (a) and (b) and 500 nm (c) [161].

interaction between cells from different tissues and NPs are also necessary.

As a novel kind of nanomaterials with wide potential applications, adverse effects of carbon nanotubes (CNTs) have recently received significant attention after respiratory exposure. Toxicity of CNTs and its mechanism have been widely investigated, which is differing from composition, length, diameter, and sizes. Exposure to pristine CNT has been shown to cause minimal cytotoxicity at higher concentrations (both in vivo and in vitro), while chemically functionalized CNT enhanced for drug delivery have not demonstrated any toxicity thus far. However, CNT aggregation has plagued research in this area and the impact of this key variable is unclear at this stage.

Acknowledgments

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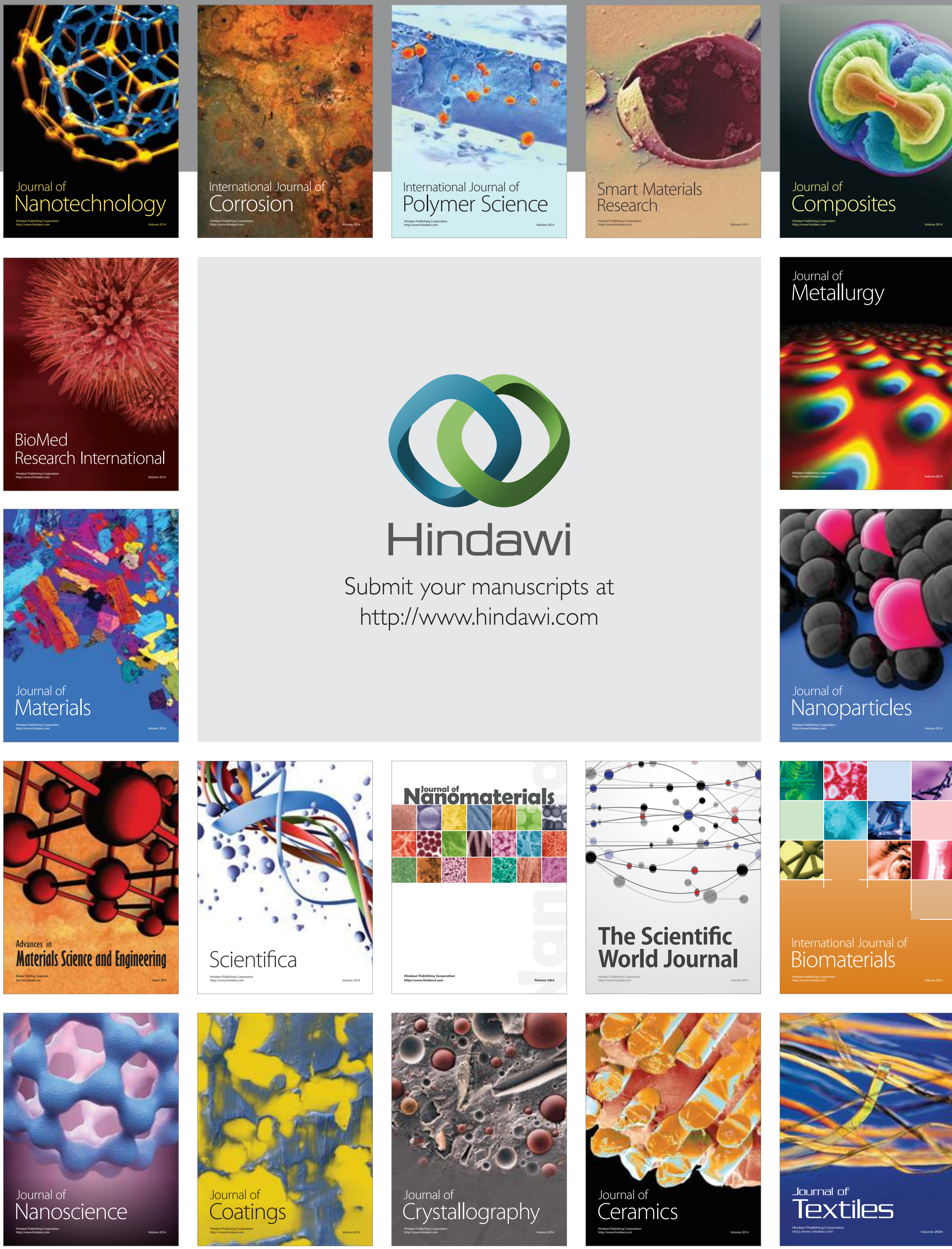
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