Chapter 15
Nanomaterials: Properties, Toxicity, Safety, and Drug Delivery

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Abstract The nanotechnology field has considerably increased in recent years, playing an important role in the pharmaceutical industry. However, this emerging science presents uncertainties and shortcomings regarding toxicological effects in human and ecological systems. It was possible to achieve a range of drugs and cosmetics that have specific properties using nanotechnology. In drug delivery systems, nanotechnology has demonstrated great potential because of its ability to induce desired pharmacological responses. The nanocomposites used in the production of sunscreens provide effective protection against damages caused by exposure to ultraviolet radiation. However, recent studies have shown the toxicity of some UV filters to health and the environment. These studies demonstrated that the compounds of sunscreens are capable of reaching the marine environment after released from human skin during the bath through water treatment plants. It is important to know the physical characteristics and chemical composition of the working nanomaterial before starting a research because that information will be relevant keys to a better understanding about the risks evaluation of the study

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object. The comparisons of biological/toxicological data between nanomaterials should be evaluated by a detailed physical characterization of each material in order to demonstrate similarities and differences between all substances. Factors such as size, aggregation/agglomeration state, aggregates/clusters, surface area and shape of the nanomaterials should be considered for the risk assessments they may cause to humans and the environment.

Keywords Pharmaceutical industry · Nanomaterials · Toxicity
Safety · Drug Delivery

15.1 Introduction

Nanotechnology became a revolutionary science in the biology and medicine fields. Among the various approaches to the use of nanotechnology in medicine, we have nanoparticles (NPs), which offer some peculiar advantages, such as sensors, image enhancers, and drug delivery. Several nanoparticle varieties with biomedical relevance are already available in the market, including polymer nanoparticles, metal NPs, liposomes, micelles, quantum dots, dendrimers, and nanoassemblies (Daraee et al. 2014).

Due to its enormous potential in new product development, new applications with higher performance, and new functionalities, the field of nanotechnology has increased considerably in recent years. However, this emerging science still presents uncertainties and shortcomings regarding toxicological effects in humans and the environment (Pini et al. 2016).

Studies on assessment of hazards of nanotechnology focus on the unconventional behavior of nanomaterials leading to unexpected mechanisms of transport and toxicity in human and ecological systems, due the peculiar size and functionality of those materials (Gavankar et al. 2012).

Some metal oxide compounds such as cerium (CeO_2), zinc (ZnO), and titanium (TiO_2) have extensive industrial and commercial applications and can be applied in the fields of biofuels, construction, pharmaceutical, as catalyst agents, etc. These compounds found on high demand products, especially in sunscreen form, are at great risk of releasing into the environment, which is followed by increasing humans exposure, creating impacts on human health and ecosystems that should be more investigated (Sendra et al. 2017; Forest et al. 2017).

Sunscreen production has increased significantly in recent years, entering the best-selling cosmetic category in the skin care industry. UV filters, incorporated into the sunscreen formulations, are classified in organic and/or inorganic, and metal oxides NPs are part of the latter category. Recent studies have proven the toxicity of these filters (Sendra et al. 2017).

Current researches showed that components of sunscreens are capable of reaching the marine environment after the release from human skin during skin washing. In wastewater treatment plants, high concentrations of these compounds

were observed (Sendra et al. 2017). These NPs have lipophilic properties, persistence, and stability against biodegradation, which allows food chain accumulation (Santos et al. 2012; Sendra et al. 2017). Bioaccumulation can cause hormonal effects and genotoxicity in marine creatures as presented by Fent et al. (2008) and Sendra et al. (2017).

Carbon nanotubes (CNTs) and carbon nanofibers (CNFs) are some of the most promising materials from the field of nanotechnology. The introduction of these materials and its products has considerably grown in the last decade. However, safety and health, especially during manipulation, also raised concerns. Manipulators are the first people in society to be exposed to these products, and there is great need for safety and knowledge about these nanomaterials in order to build a sustainable developing enterprise (NIOSH 2013).

A rigorous study should be made about the nature of these materials, such as the physicochemical properties among other analyzes that may define the mechanisms of inhalation toxicity. Thus, all types of CNT and CNF should be considered a respiratory risk, and exposures should be controlled in a reduced manner according to the Risk Assessment and Recommended Exposure Limit (REL) (NIOSH 2013).

Nanomaterials from noble metals have attracted considerable attention from researchers due to their specific mechanical, electrical, optical, and catalytic properties when compared to their bulk materials. Silver nanoparticles (AgNPs), for example, have been widely applied in consumer products including textiles, disinfection of medical devices, and household appliances, as well as their potential water treatment capacity. Thus, with the significant increase in AgNPs production, application, and market demand, it is inevitable that release of AgNPs into the environment at high concentrations may affect normal wastewater behavior. According to the World Health Organization, the maximum permissible concentration of silver in drinking water is set at 0.1 mg/L (Huang et al. 2017).

Nanoparticles mediated drug delivery systems have demonstrated great potential because of their ability to induce desired pharmacological responses. Solid lipid nanoparticles (SLNs), nanostructured lipid carriers (NLCs), and lipid drug conjugates (LDCs) are the modified versions of nanoparticle delivery systems, which are based on a solid lipid matrix (Jain et al. 2014).

Although nanomaterials are being studied to be used as drug delivery devices, for example in cancer treatment. There is also a great potential for combining diagnostic and therapeutic capabilities in one device (Cattaneo et al. 2010; Hull et al. 2014). Although great effort is being made in the development of nanodevices for medicine, much information is still needed to determine the effects of long-term nanomaterials on human health (Hull et al. 2014).

In this chapter, we have discussed the possible hazards of nanomaterials in human health and in the environment.

15.2 Health and Environmental Impact of Nanotechnology

Over the past 10 years, the field of environmental nanotechnology has witnessed a remarkable development in the diversity of materials designed for pollution management as well as the myriad applications of nanotechnology in many subfields of environmental science and engineering. However, nanotechnology has raised public concerns about the widespread use of these nanomaterials that have been manufactured in a wide range of consumer products. These nanomaterials can cause ecological and health influences due to their excessive release into the environment (Lien et al. 2016).

15.2.1 Risk Associated with Toxicity of NPs

Risk assessment is related to everything that can go wrong, how it is likely to happen, and the consequences of this event. As a regulatory platform, risk assessment is the guiding principle for assessing environmental and product risks, including nano-activated technologies. Regarding chemicals and nanomaterials, risk assessment has historically been based on empirical data detailed by exposure and risk, such as dose-response models, which describe the change in effect in a system caused by different levels of exposure of a stressor over a given exposure time (Fadel et al. 2014).

NPs may be unsafe for the biological system. Some research on the toxicity of these nanomaterials indicates that some of these products can enter the human body, becoming toxic at cellular level in tissues and organs. The materials composing these particles may or may not be carcinogenic or allergenic, and even inert NPs have harmful effects due to some toxic species absorbed or the formation of toxic agents that are the products of reactions with body fluids. Some NPs have catalytic properties that are highly reactive with oxygen and can cause tissue damage including inflammation and other toxic effects, which can cause asthma and atherosclerotic heart disease (Vishwakarma et al. 2010).

According to Hull et al. (2014), the potential effects of nanomaterials on human health will depend on key factors such as:

1. The likelihood of exposure of humans to nanomaterials, as well as bioavailability and associated doses (occupational exposure versus environmental exposure) (Hull et al. 2014; Magdolenova et al. 2014).
2. The physical and chemical characteristics of nanomaterials at the time of exposure (after environmental processing) (Lowry et al. 2012; Magdolenova et al. 2014).

3. The exposure pathway or point of entry into the body (dermal and ocular contact, inhalation, ingestion or digestion) (Abbott and Maynard 2010; Quadros et al. 2013).

The NPs can more easily be transported in the human body crossing many biological barriers, thus reaching the most sensitive organs. Some scientists have proposed that NPs with size smaller than 10 nm act in a gas-like fashion and can easily penetrate human tissues, disrupting the cell's usual biochemical environment. Human and animal test studies have shown that after inhalation and through oral exposure, NPs can be delivered to the liver, heart, spleen, brain, lungs, and gastrointestinal tract (Bahadar et al. 2015).

It is believed that the toxicity screening plan for nanomaterials should have three key elements—physical and chemical characterization, evaluation of cellular tissues, and animal testing and studies (Vishwakarma et al. 2010).

The respiratory tract and the skin present two main possibilities for contamination by nanomaterials, since the NPs have a very small size and can easily penetrate the tissues. Due to inhalation exposure, these NPs can be easily airborne into the respiratory tract. In addition, agglomeration of NPs may occur in longer chains, which may change behavior both in the external and in the internal environment. The toxicity can be influenced by the nanostructure, which has a high surface area, unusual morphology, very small diameter, and alteration due to segregation that may occur after deposition (Ray et al. 2009). Stahlhofen et al. (1989) reported that deposition of 20 nm particles is 2.7 times greater than 100 nm particles, and 4.3 times greater than 200 nm particles.

The skin may be exposed to solid particles at the nanoscale through intentional or unintentional means. Intentional dermal exposure to nanoscale materials may include the application of lotions, creams, dressings for wounds, and detergents containing silver nanomaterials. Nano-TiO_2 and nano-ZnO materials are components of sunscreens or fibrous materials coated with nanoscale substances for water or stain repellent properties. Human skin contact with these oxides occurs through the use of these products. Unintentional exposure involves dermal contact with anthropomorphic substances generated during the manufacture or combustion of nanomaterials. The mechanism for this process is still unclear (Ray et al. 2009).

15.2.2 Relation of Nanomaterials Effect Between the Plants and Animals Food Chain

There is a close link between the components of the plant–animal/human system, through food contamination. The NPs manufactured through plant and/or herbal products have become a major challenge for life and environmental scientists. This situation is made even more difficult by the lack of discussion and misunderstanding in interaction mechanisms of the manipulated nanoparticle with the plant–

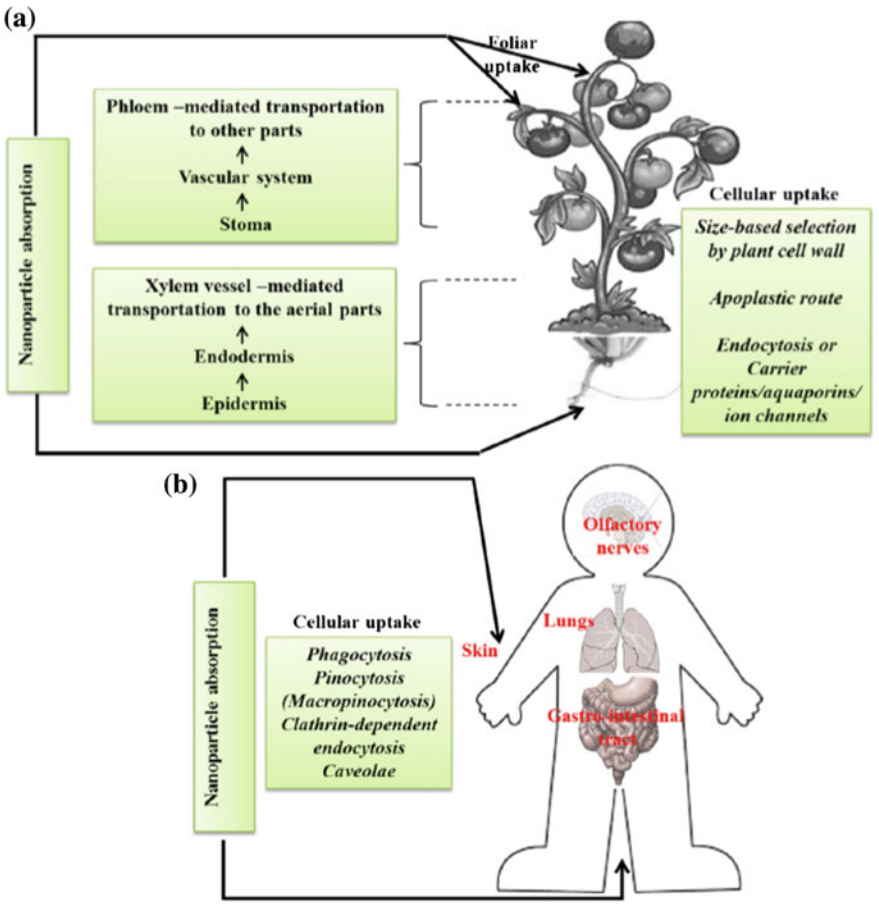

Fig. 15.1 Release of nanoparticles into the environment (Modified by Anjum et al. 2016). With permission from Environmental Research

animal/human system, which can be better observed in Fig. 15.1. (Anjum et al. 2016).

The plants interact very strongly with their surrounding environment, which sometimes presents considerable contamination by dangerous substances, among them the NPs are of prime importance. Metal-based NPs have numerous applications because of their peculiar physicochemical properties. The human and animal system may be at great risk through nanoparticle-laden plants or herbal food products. The literature for this subject is still scarce mainly in the interaction of NPs with plants, and also the phenomena of nanoparticle transport in plants still need to be better studied. Figure 15.2a shows a schematic representation of the processes and mechanisms underlying the uptake/accumulation of NPs and the

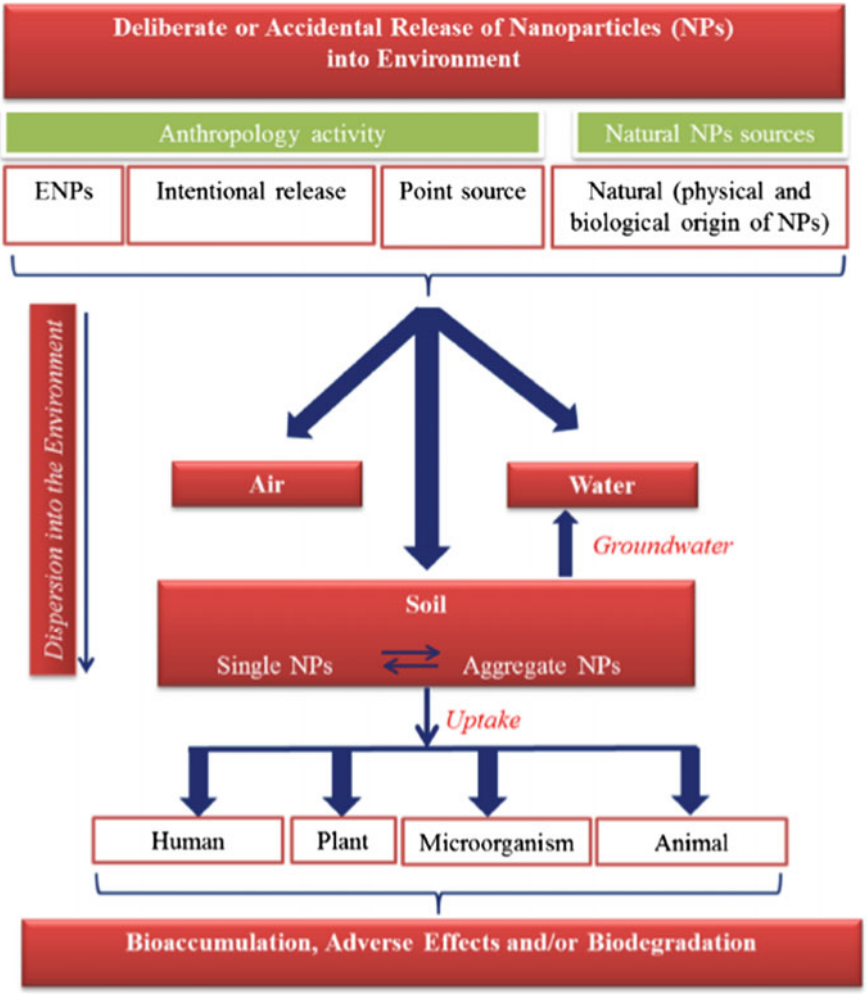

Fig. 15.2 Scheme of the relationship between the transport of nanoparticles in plant **a** and human **b** systems (Anjum et al. 2016). With permission from Environmental Research

transport of NPs in the leaves and parts of edible plants (Anjum et al. 2016). And Fig. 15.2b shows how it can behave in human system.

At the cellular level of the roots, the NPs have to interact first with the plant's cell wall, before entering into the cells and performing the intracellular transport as shown in Fig. 15.2a. The plants have the microfibrils of cellulose, hemicelluloses and also present molecules of lignin and pectin in their structure, this ends up forming a porous network that restricts the entry of large aggregates or agglomerates of NPs. However, small aggregates or individual particles may enter the apoplastic and/or symplastic flow after the diffusion of these particles through the

pores. The interaction of NPs with transport proteins, aquaporins, ion channels, and organic chemicals can facilitate their entry into plant cells through the symplastic route, an important and highly regulated route for the transport of NPs in large cultures (Rico et al. 2013).

The food chain (animal/human) can easily be contaminated by NPs, which leads to bioaccumulation. Thus, more studies are needed to gather information about NPs of the metallic components accumulation in edible tissues of plants and seeds, in order to better understand the potential toxic effects evaluation of these nanomaterials (Rico et al. 2013. Anjum et al. 2015; Anjum et al. 2016).

15.2.3 Exposure of Animals to NPs

Eom et al. (2016) performed tests on 40 rabbits, exposing their ocular surface to TiO_2 nanoparticles, these authors observed that after a period, the eyes of animals suffered damage. The authors further observed that although the Mucin 5AC (MUC5AC) (mucosal glycoprotein responsible to produce viscosity) increased the level of tear production to protect an ocular area after a single exposure to TiO_2, decreased to normal levels after repeated exposures. The area of conjunctival PAS-positive goblet cells decreased significantly after single and repeated exposures. The TiO_2 nanoparticles exposure in rabbits appears to induce the escape of goblet cells, resulting in reduced ocular protection provided by MUC5AC due to this exposure.

Grassian et al. (2007) reported a study with inhalation exposure using TiO_2 nanoparticles of approximately 2–5 nm. They showed that nanoparticles aggregate to form aerosol in the exposure chamber with geometric mean of the mobility diameter between 120 and 130 nm. Analysis of lung responses in rats after subacute exposures to these clusters showed a significant inflammatory response among animals necropsied at 0, 1, or 2 weeks (Ray et al. 2009).

Chupani et al. (2017) have studied the effect of dietary intake of carp (*Cyprinus carpio* L.) on ZnO nanoparticles. The authors have shown that this exposure affected the immune system in the carp. To a certain extent, fish homeostasis was affected after a six-week exposure of ZnO nanoparticles. The proteins and regulated pathways that were related to immunological and coagulation systems could be a response to homeostasis disturbance in fish treated with ZnO nanoparticles. These authors provided interesting results that have paved the way for biological beings to be affected by these NPs.

Asharani et al. (2008a, b) performed tests on zebra fish (*Danio rerio*). These authors used starch and bovine serum albumin (BSA) as leveling agents, synthesizing silver nanoparticles (AgNPs) to study their deleterious effects and the distribution pattern in the embryos of this species of fish. The transmission electron microscopy (TEM) analyses of the embryos demonstrated that the NPs were distributed in the brain, heart, yolk, and blood of embryos. Their results indicate that AgNPs induce dose-dependent toxicity in embryos, which hampers normal

development. Microscopic images could confirm this behavior. AgNPs can be toxic because they release silver ions, which are well known for their antibacterial and destructive behaviors.

15.2.4 *Effect of Nanoparticles Used in Sunscreens*

The production of sunscreens has increased significantly in recent years. It is the best-selling cosmetic category in the skin care industry. However, recent studies have proven the toxicity of these filters to humans. Metal oxide nanoparticles are commonly used as inorganic UV filters (Sendra et al. 2017). Cerium belongs to the elements of the lanthanides also known as metals. Cerium oxide nanoparticles (CeO_2), also known as nanoceria, are widely used as a component of UV filter manufacturing (Forest et al. 2017).

Because of this large use, the risk of release of CeO_2 nanoparticles into the environment and their exposure to humans is potentially increasing, while its impact on human health and ecosystems is not yet fully understood. This observation led the Organization for Economic Cooperation and Development (OECD) to classify these nanoparticles as priority materials for toxicological evaluation since 2010 (Forest et al. 2017).

The human skin is generally strongly exposed to solid nanoparticles by the application of lotions or creams containing TiO_2 or ZnO nanoparticles as sunscreen components or lotions with repellent properties. Since the manufacture and use of nanoparticles are increasing, humans are more likely to be exposed to these nanomaterials (Ray et al. 2009).

Although in the form of larger particles, these compounds protect the skin against UV radiation, in the form of nanoparticles, absorbing the UV radiation, carrying out the photocatalysis, and as a result releases reactive oxygen species, which have great capacity to cause changes in the DNA. Some studies suggest that this photocatalytic process may not be significant. In contrast, other recent studies assume that nanoparticles may, in certain circumstances, violate this barrier. However, these studies are carried out on the scale of laboratory animals, not yet being tested in humans (Tran and Salmon 2011).

15.2.5 *Drug Delivery and Nanoparticles*

According to Farokhzad and Langer (2009), nanotechnology products are able to play a very important role in the therapeutic area that is important for pharmaceutical companies. Using this technology, it is possible to:

(a) Achieving a better supply of poorly water-soluble drugs;
(b) Targeted delivery of drugs in a manner specific to cells or tissues;
(c) The transcytosis of drugs through tight epithelial and endothelial barriers;
(d) Delivery of large macromolecule drugs to intracellular sites of action;
(e) Co-supplying two or more drugs or therapeutic modality for combination therapy;
(f) Visualizing drug delivery sites by combining therapeutic agents with imaging modalities;
(g) Real-time reading of the in vivo efficacy of a therapeutic agent. In addition, the complexity of manufacturing nanotechnology therapeutics may also create a significant obstacle effect for generic drug companies to readily develop equivalent therapeutics. These are just some of the many compelling reasons that nanotechnology holds huge promise for drug delivery.

In the treatment of the disease, nanomaterials are currently being explored to serve as drug delivery devices, for example, on cancer treatment. There is also great potential for combining diagnostic and therapeutic capabilities in a device, thus the newly invented term "theranostics," (Cattaneo et al. 2010; Hull et al. 2014). Although great effort is being made in medicine nanodevices development, much information is still needed to determine the effects of long-term nanomaterials on human health (Hull et al. 2014).

According to Farokhzad and Langer (2009), there are a number of very important parameters to develop a successful mechanism for the manufacture of drug delivery vehicles, among them we can mention:

(a) The use of biocompatible materials with robust simple processes for the assembly of biomaterials, conjugation chemistry, and purification steps;
(b) Ability to optimize in parallel the myriad of biophysical and chemical parameters of the delivery vehicles of drugs which have pharmaco-kinetic properties and possible cell uptake;
(c) Development of scalable operations of large-scale units of specific drug delivery systems that are necessary for better clinical translation.

It has been demonstrated that targeted drug development vehicles by self-assembling of pre-functionalized biomaterials simplified optimization and potential systems. The biophysical–chemical properties of the carrier, such as size, charge, surface hydrophilicity, binders nature, and density on its surface, may affect the circulating half-life of the particles as well as their biodistribution (Farokhzad and Langer 2009).

The surface properties of non-targeted drug delivery vehicles, such as ordered splines of functional groups, as well as their shape and size have also been shown to cause increase in particle collection as shown in Fig. 15.3 (Farokhzad and Langer 2009).

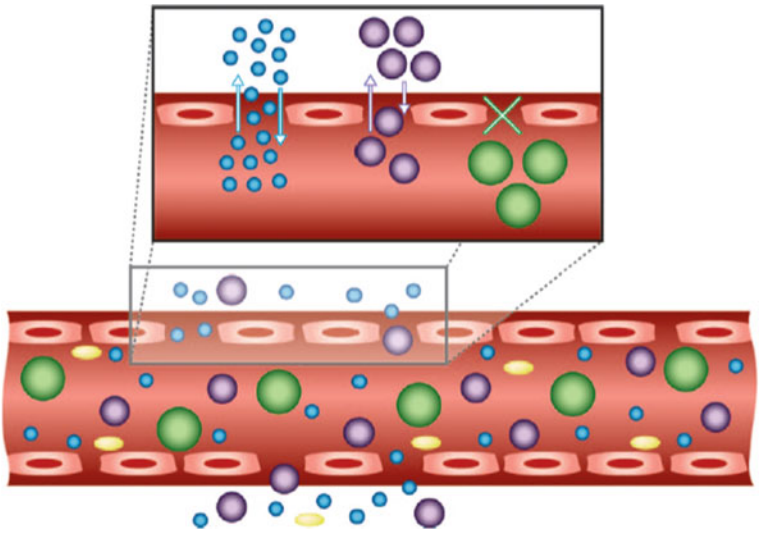

Fig. 15.3 Efficiency of nanoparticles as delivery vehicles is highly dependent on size and shape. The first affects their movement from inside and outside the vasculature; the second affects the marginalization of the particles to the vessel wall due to their shape. With permission from ACSNANO

15.3 Mechanisms of Nanoparticles in Contact with Cells

The peculiar size of nanoparticles is directly related to its ability to penetrate cells. However, the mechanisms involved are still not well understood. The influx of nanoparticles occurs primarily by endocytosis; the particles are inserted and diffused through the lipid bilayer of the cell membrane. It is also found that these nanoparticles are able to enter the cells even after binding with proteins (antibodies) (Doubrovsky et al. 2011).

Several researchers (Renwick et al. 2004; Fang et al. 2006; Unfried et al. 2007) have demonstrated the importance of physicochemical properties of NPs in the toxic and functional effects on macrophages (phagocytosis, release of inflammatory mediators, release of calcium, cytoskeleton function). However, kinetics and specific uptake pathways have not been addressed in most of these studies (Unfried et al. 2007).

Copper oxide (CuO) nanoparticles have been widely used in several applications: as antimicrobial agents, photocatalysts and gas sensors. The expansion of production and widespread use of CuO NPs may pose risks to individual organisms and ecosystems (Hou et al. 2016).

The comprehensive understanding of the adverse effects induced by CuO NPs and their underlying mechanism are of great importance in assessing the environmental risk of these nanoparticles so that their use can be safely expanded. However, the toxic effects of CuO NPs on individual organisms and their

mechanism of action are still poor and have some ambiguities. To ensure the safe use of CuO NPs, more attention should be paid to the chronic and long-term effects of CuO NPs in low concentration (Hou et al. 2016).

According to Hou et al. (2016), the toxic mechanisms of CuO NPs are presented in two ways: (1) the oxidative stress induced by intracellular CuO NPs and (2) by the dissolution of CuO NPs. Extracellular CuO and Cu2 + NPs pass through the cell membrane, and they enter the cytoplasm via endocytosis and through the copper transport proteins, respectively. The schematic synthesis of cellular toxicity induced by CuO NPs can be seen in Fig. 15.4.

Gold nanoparticles of 20 nm were conjugated to various targeting peptides to provide functional nanoparticles that penetrate the biological membrane and target the nucleus. Several nanoparticles have also been applied as targeted biomarkers and drug delivery agents for cancer diagnosis and medical treatment (Daraee et al. 2014).

Physicochemical properties of the nanoparticles, especially size determine their toxicity; therefore, they should be extensively evaluated in the definition of the regulatory guidelines. Accumulation of evidence shows that the toxicity of nanoparticles manufactured from oxides can be influenced by its oxidation state (Park et al. 2016).

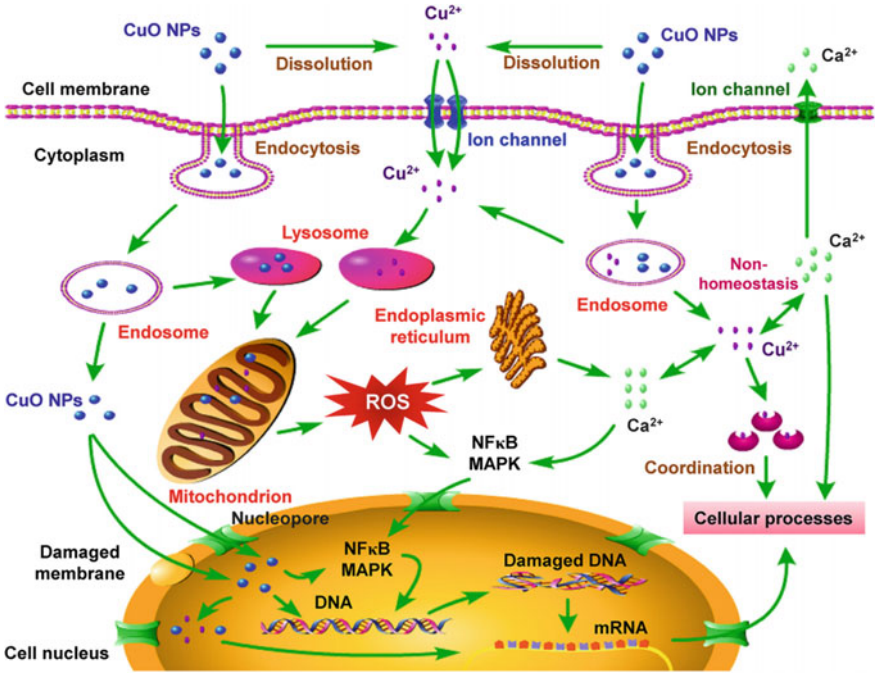

Fig. 15.4 Schematic overview of cellular toxicity induced by CuO nanoparticles (Hou et al. 2016). With permission from Environmental Pollution

Nanoparticles differ in their reactivity and solubility and may interact with various endogenous proteins, lipids, polysaccharides, and cells. Based on the toxicological inhalation experiments, several tests were proposed to evaluate the toxicity of nanoparticles used in drug delivery systems.

Gold nanoparticles (GNPs) can easily enter into cells, and it has been demonstrated that the amine and thiol groups bind strongly to these nanoparticles enabled their surface modification with amino acids and proteins for biomedical applications (Abdelhalim 2011).

Therefore, Abdelhalim (2011) conducted studies in 40 healthy male rats, who received infusions of 50 μl of 10, 20, and 50 nm of GNPs for 3 or 7 days. The animals were randomly divided into groups: six groups of mice treated with gold nanoparticles and a control group that did not receive this treatment. Groups 1, 2, and 3 were infused with 50 μl of nanoparticles of 10 nm size for 3 or 7 days, 20 nm for 3 or 7 days, and 50 nm for 3 or 7 days, respectively. Exposure to doses of GNPs has been shown to produce heart muscle disorder with some dispersed chronic inflammatory cells infiltrated by small lymphocytes, outbreaks of hemorrhage with extravasation of red blood cells, some dispersed cytoplasmic vacuolization, and blood vessels congested and dilated. None of the above changes were seen in the heart muscle of any member of the control group. Changes induced by the intraperitoneal administration of GNPs were size dependent, being the smallest inducers of major affections and also related to the temporal exposure to GNPs. These changes may indicate dispersed cytoplasmic vacuolization, which may induce the effect of toxicity by the inability to cope with the accumulated waste resulting from metabolic and structural disturbances caused by these NPs. These histological changes were more prominent with particles of size 10 nm than with larger ones. The interaction of GNPs with proteins and various cell types was considered as part of the toxicological evaluation.

15.4 Evaluation of Lipid Nanoparticles for Drug Delivery

Lipid nanoparticles are colloidal dispersions that have been used as an alternative to other colloidal carriers, including liposomes, nanoemulsions, and polymer nanoparticles (Wen et al. 2016). Depending on the composition, lipid nanoparticles may exhibit low toxicity while retaining the same advantages as other carriers, such as controlled drug release, drug targeting, protection against degradation, and the ability to increase production (Rostami et al. 2014; Wen et al. 2016).

Lipid nanoparticles will span two generations. The first refers to solid lipid nanoparticles (SLNs) which are composed of a lipid core that remains solid both in the body and at room temperature. The second generation refers to nanostructured lipid carriers (NLCs) corresponding to a mixture of solid and liquid lipids that overcome some of the limitations of SLNs, including poor drug loading capacity and poor long-term stability caused by polymorphic transitions from lipids to more stable forms. The main disadvantage is that the incorporation of drugs into SLNs

and NLCs is strongly governed by the lipophilic character of the drugs, the lipid type, the surfactants used, and the production technique (Wen et al. 2016).

Studies on the use of lipid NPs for the delivery of Alzheimer's disease (AD) drugs have been conducted. Bondi et al. (2009) studied the intravenous administration of SLNs and NLCs prepared by the hot O/W microemulsion method. By encapsulating ferulic acid and leading to a greater protective activity against oxidative stress induced in neurons, suggesting the efficiency of these systems in increasing bioavailability. Lipid nanoparticles have been reported to outgrow the blood–brain barrier (BBB) through the endocytotic mechanism and accumulate in diseases of the central nervous system (CNS), aided by their lipophilic nature. In addition, because of their small size, lipid nanoparticles could be injected intravenously avoiding the uptake of macrophages from the mononuclear phagocytic system (Wen et al. 2016).

Lipid drug conjugates (LDCs) are those especially developed for hydrophilic drug molecules, where in a volume of insoluble drug–lipid conjugate is prepared synthetically either by formation of salt (with a fatty acid) or by covalent attachment (esters or ethers). Mass LDC is then homogenized in the presence of a water stabilizer using high-pressure homogenization (Joshi and Müller 2009).

Some studies already made with lipid nanoparticles and their different types, such as SLN, NLC and LDC, are summarized in Table 15.1, according to the review by Joshi and Müller (2009).

15.5 Safety of Nanotechnology/Safe Handling of Nanomaterials

Nowadays, knowledge of the effects of nanotechnology on human health is complex. Nanomaterials are thought to bring substantial contributions to medical field. In diagnostic medicine, nanoparticles can be used as nanoscale devices, such as nanocantilevers and nanoporous chips, which offer great potential in disease screening (Hu et al. 2011; Hull et al. 2014).

Vanadium has received special and long-term attention in the pharmacological domain, including the regulation of extracellular signaling, as an essential enzyme agent in energy metabolism, or as an analytical therapeutic agent for the treatment of diabetes mellitus, and a preventive chemotherapeutic approach on treatment of a single biological disease (Basu et al. 2014). Vanadium pentoxide (V_2O_5) has also been used for the production of insulin and for the production of sulfuric acid due to its high oxidation (Park et al. 2016). On the other hand, many researchers have suggested that vanadium is not suitable for application in the pharmaceutical market because of the strong biological effects they may have on human health. Some symptoms such as hyperglycemia, hyperphagia, and polydipsia are significantly improved by vanadium treatment, but there are controversies in the use of this compound since side effects such as tissue accumulation, weight gain, and death

Table 15.1 Overview of various actives incorporated in injectable lipid nanoparticles. With permission from European Journal of Pharmaceutics and Biopharmaceutics

Drug	Disease	Type of lipid nanoparticle	Route of administration
3',5'-Dioctanoyl-5-fluoro-2'-deoxyuridine	Cancer	SLN	IV
3-Azido-3-deoxythymidine palmitate/azidothymidine	AntiHIV	SLN	IV
5-FU	Cancer	SLN	IV
99mTc/188Re	Imaging agent	Nanocapsules	IV
Actarit	Rheumatoid Arthritis	SLN	IV
All trans retinoic acid	Cancer	SLN	IV
Beta-element	Cancer	SLN	IV
Bromocriptine	Anti-parkinsonism	SLN	IP
Camptothecin	Cancer	SLN	IV
CdSEe/ZnS	Imaging agent	QDs encapsulated in SLN	IV
Clozapine	Antipsychotic	SLN	ID
Dexamethasone acetate	Pulmonary disease	SLN	IV
Diminazene	Antitrypanosomal	LDC	–
DNA	Cancer	catinoic SLN	–
Doxorubicin	Cancer	Stealth and non-stealth SLN, SLN	IV
Etoposide	Cancer	SLN	IV/SC/IP
Idarubicin	Cancer	SLN	IV or ID
Iron oxide	Imaging agent	SLN	–
Magnetite	Imaging agent	SLN	–
Methotrexate	Cancer	LMBVs	IV
Mitoxantrone	Cancer	SLN	Local injection in breast Cancer tissue
Nitrendipine	Antihypertensive	SLN	IV or ID
Oxymatrine	Antihepatitis	SLN	IV
Paclitaxel	Cancer	SLN/Wax NP/sterically stabilized SLN	IV
Paclitaxel and doxorubicin	Cancer	SLN	–
Paclitaxel and doxorubicin and cholesteryl butyrate	Cancer	SLN	–
Quinine dihydrochloride	Malaria	Transferring conjugated SLN	IV

(continued)

Table 15.1 (continued)

Drug	Disease	Type of lipid nanoparticle	Route of administration
Tamoxifen	Cancer	SLN	IV
Tashione II A	Vasodialator	SLN	IV
Tamoxifen citrate	Cancer	SLN	IV
Temozolomide	Cancer	SLN	IV
Testosterone 125 I radiolabelled	Imaging agent	SLN	IV
Tobramycin	Antibiotic	SLN	IV or ID
Vinorelbine bitartrate	Cancer	PEG-modified SLN	–

IV intravenous; *ID* intrdeodenum; *IP* intraperitoneum; *SC* subcutaneous. Adaptated by Joshi and Müller (2009)

occurred in all mice treated with vanadium (Park et al. 2016). In addition, it has been shown that inhalation of V_2O_5 can impair the immune functions of cells leading to increased risk of cancer development (Park et al. 2016).

When new technologies emerge for human use on the market, there is a great need for attention in relation to assessment of health risk. One must follow a regulation and correct form. Among the most comprehensive regulations in this area is the REACH program (Registration, Evaluation, Authorization and Restriction of Chemical Substances of the European Union). In this program, risk assessment strategies were proposed based on categories of nanomaterials, taking into account their physicochemical properties and modes of action. These categories are carbon (fullerenes and carbon nanotubes), metal-based (quantum dots, nanogold, nanosilver, and metal oxides), dendrimers, and composites (Gulumian et al. 2012).

We must consider health when nanomaterials are used as they cause side effects (Feder 2004). Therefore, the importance of using good laboratory safety practices must be rigorous, such as Personal Protective Equipment (PPE) (gloves to laboratories, safety goggles, face shields, closed shoes, etc.). Skin contact with these nanoparticles should also be avoided. If it is necessary to handle powders of nanoparticles, an exhaust and a laminar flow hood should be used (Vishwakarma et al. 2010).

Workers must at all costs wear appropriate respiratory protection masks. The use of exhaust fans is important to expel smoke from tubular ovens and chemical reactors. Laboratory workers should have periodical and proper training and should be aware of workplace hazards, Material Safety Data Sheets (MSDS), labeling, signage, etc. Proper disposal of nanoparticle wastes should also be considered for the best environmental safety. It must be within the guidelines of hazardous chemical residues (Vishwakarma et al. 2010).

Nano-fibrous materials deserve special attention since these materials can affect the respiratory system in a similar way to asbestos fibers. Both single-walled carbon nanotubes (SWCNT) and multi-walled carbon nanotubes (MWCNTs) are biopersistent in the lungs and cause cell toxicity (Hull et al. 2014). The National Institute for Occupational Safety and Health (NIOSH 2013) estimated a lifetime exposure of 0.2–2 $\mu g/m^3$ of MWCNT to be associated with an excessive risk of 10% effects (Hull et al. 2014).

15.6 Conclusion

Nanotechnology is a science that has come to improve several issues: agricultural systems, food systems, use of medicines, in construction systems, etc. However, as with any new technology, there is need for ethical responsibility to apply this science wisely, recognizing that there are potential unanticipated risks that can come along with its tremendous positive potential. People must be educated through media such as television, Internet, and point-of-sale newsletters, explaining the benefits and application of nanotechnology and its consequences.

In this context, there is a greater need for discussion in the context of convergence, integration, synergy with biotechnology, information technology, and technology knowledge where interdisciplinary collaboration is essential for synergy generation and promising advances in the area.

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