WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 8.074
Volume 7, Issue 16, 1745-1759. Review Article ISSN 2277– 7105

REVIEW ON NANOPARTICLES

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Article Received on
18 July 2018,

Revised on 08 August 2018,
Accepted on 29 August 2018

DOI: 10.20959/wjpr201816-13310

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ABSTRACT

Nanotechnology refers to the creation and utilization of materials whose constituents exist at the nanoscal and by convention by up to 100nm in size. NMs are categorized depending on their size, composition, shape and origin. Due to increased growth of production of NMs and their industrial application, issues relating to toxicity are inevitable. Additionally, the types of toxicity reaction associated with NPs and NSMs are also discussed. Several techniques are used for the preparation of nanoparticles like Dispersion of performed polymers, Polymerization of monomers and Ionic geleation or coacervation of hydrophilic polymers. Through nanotechnology we can achieve better therapeutic action, better bioavailability and better patient compliance. This review focuses on classification, method of preparation, application, advantages of nanoparticles and health perspectives and toxicity of nanoparticles.

KEYWODS: Nanotechnology, NPs and NSMs.

INTRODUCTION

Nanoparticles (NPs) and nanostructured materials (NSMs) represent an active area of research and a techno-economic sector with full expansion in many application domains. NPs and NSMs have gained prominence in technological advancements due to their tunable physicochemical characteristics such as melting point, wet ability, electrical and thermal conductivity, catalytic activity, light absorption and scattering resulting in enhanced performance over their bulk counterparts. A nanometer (nm) is an International System of Units (Système international d'unités, SI) unit that represents 10−9 meter in length. In principle, NMs are described as materials with length of 1–1000 nm in at least one dimension; however, they are commonly defined to be of diameter in the range of 1 to 100

nm. Today, there are several pieces of legislation in the European Union (EU) and USA with specific references to NMs. However, a single internationally accepted definition for NMs does not exist. Different organizations have a difference in opinion in defining NMs. According to the Environmental Protection Agency (EPA), "NMs can exhibit unique properties dissimilar than the equivalent chemical compound in a larger dimension". The US Food and Drug Administration (USFDA) also refers to NMs as "materials that have at least one dimension in the range of approximately 1 to 100 nm and exhibit dimension dependent phenomena". Similarly, The International Organization for Standardization (ISO) has described NMs as a "material with any external nanoscale dimension or having internal nanoscale surface structure". Nanofibers, nanoplates, nanowires, quantum dots and other related terms have been defined based on this ISO definition. Likewise, the term nanomaterial is described as "a manufactured or natural material that possesses unbound, aggregated or agglomerated particles where external dimensions are between 1–100 nm size range", according to the EU Commission.[1] The prefix "nano" is resulting from the Greek word "nanos" meaning "dwarf".[2] Nanoparticles have relatively higher intracellular uptake compared to microparticles. In the last decade, significant effort has been made to develop nanoparticles for drug delivery. Considerable research has been directed towards developing safe and efficient chitosan based particulate drug delivery systems such as nanoparticles. Various polymeric nanoparticles have been studied for intracellular delivery of different classes of therapeutic agents. Nanoparticles are thought to enter cells via an endocytic pathway through either specific or nonspecific interaction with cell membrane.[3]

HISTORY AND DEVELOPMENT OF NANOMATERIALS

Humans already exploited the reinforcement of ceramic matrixes by including natural asbestos nanofibers more than 4,500 years ago. The Ancient Egyptians were also using NMs more than 4000 years ago based on a synthetic chemical process to synthesize ≈5 nm diameter PbS NPs for hair dye. Similarly, "Egyptian blue" was the first synthetic pigment which was prepared and used by Egyptians using a sintered mixture nanometer-sized glass and quartz around 3rd century BC. Egyptian blue represents a multifaceted mixture of $CaCuSi_4O_{10}$ and SiO_2 (both glass and quartz). In ancient geographical regions of the Roman Empire, including countries such as Egypt, Mesopotamia, and Greece, the extensive use of Egyptian blue for decorative purposes has been observed during archaeological explorations. The synthesis of metallic NPs via chemical methods dates back to the 14th and 13th century BC when Egyptians and Mesopotamians started making glass using metals, which can be

cited as the beginning of the metallic nanoparticle era. These materials may be the earliest examples of synthetic NMs in a practical application. From the late Bronze Age (1200–1000 BC), red glass has been found in Frattesina di Rovigo (Italy) that is colored by surface plasmon excitation of Cu NPs. Similarly, the Celtic red enamels originating from the 400–100 BC period have been reported to contain Cu NPs and cuprous oxide (cuprite Cu2O). Nevertheless, a Roman glass workpiece is the most famous example of ancient metallic NPs usage. The Lycurgus Cups are a 4th-century Roman glass cup, made of a dichroic glass that displays different colors: red when a light passes from behind and green when a light passes from the front. Recent studies found that the Lycurgus Cups contain Ag–Au alloy NPs, with a ratio of 7:3 in addition to about 10% Cu. Later, red and yellow colored stained glass found in medieval period churches was produced by incorporating colloidal Au and Ag NPs, respectively. During the 9th century, Mesopotamians started using glazed ceramics for metallic luster decorations. These decorations showed amazing optical properties due to the existence of distinct Ag and/or Cu NPs isolated within the outermost glaze layers. These decorations are an example of metal nanoparticles that display iridescent bright green and blue colors under particular reflection conditions. TEM analysis of these ceramics revealed a double layer of Ag NPs (5–10 nm) in the outer layer and larger ones (5–20 nm) in the inner layer. The distance was observed to be constant at about 430 nm in between two layers, giving rise to interference effects. The scattered light from the second layer leads to the phase shift due to the scattering of light by the first layer. This incoming light wavelength dependent phase shift leads to a different wavelength while scattering. Later, the red glass was manufactured using this process all over the world. In the mid-19th century, a similar technique was used to produce the famous Satsuma glass in Japan. The absorption properties of Cu NPs were helpful in brightening the Satsuma glass with ruby color. Furthermore, clay minerals with a thickness of a few nanometers are the best examples of natural NM usage since antiquity. It was reported that even in 5000 BC, clay was used to bleach wools and clothes in Cyprus. In 1857, Michael Faraday reported the synthesis of a colloidal Au NP solution, which is the first scientific description to report NP preparation and initiated the history of NMs in the scientific arena. He also revealed that the optical characteristics of Au colloids are dissimilar compared to their respective bulk counterpart. This was probably one of the earlier reports where quantum size effects were observed and described. Later, Mie (1908) explained the reason behind the specific colors of metal colloids. In the 1940s, SiO2 NPs were being manufactured as substitutes to carbon black for rubber reinforcement. Today manufactured NMs can significantly improve the characteristics of bulk materials, in terms of

strength, conductivity, durability, and lightness, and they can provide useful properties (e.g., self-healing, self-cleaning, anti-freezing, and antibacterial) and can function as reinforcing materials for construction or sensing components for safety. Notwithstanding the other possible benefits, simply taking advantage of the beneficial size and shape effects to improve the appearance of materials is still a major application of NPs. Moreover, the commercial use of NMs is often limited to the bulk use of passive NMs embedded in an inert (polymer or cement) matrix, forming a nanocomposite. In 2003, Samsung introduced an antibacterial technology with the trade name Silver Nano™ in their washing machines, air conditioners, refrigerators, air purifiers and vacuum cleaners, which use ionic Ag NPs. NPs and NSMs are extensively used in auto production: as fillers in tires to improve adhesion to the road, fillers in the car body to improve the stiffness, and as transparent layers used for heated, mist and ice-free, window panes. By the end of 2003, Mercedes-Benz brought a NP-based clear coat into series production for both metallic and nonmetallic paint finishes. The coating increases the scratch resistance and enhances the gloss. Liquid magnets, so-called ferrofluids, are ultra stable suspensions of small magnetic NPs with super paramagnetic properties. Upon applying a magnetic field, the liquid will macroscopically magnetize, which leads to the alignment of NPs along the magnetic field direction. Recent research has focused on creating enhanced Earth-based astronomical telescopes with adaptive optics and magnetic mirrors with the shape-shifting capability made up of ferrofluids. TiO2 NPs are commercially used in solar cells with dye-sensitization ability. In summer 2012, Logitech brought an external iPad keyboard powered by light on the market, representing the first major commercial use of dye-sensitized solar cells. In 2005, Abraxane, which is a human serum albumin NP material containing paclitaxel, was manufactured, commercialized and released in the pharmaceutical market. In 2014, there were about 1814 nanotechnology- based consumer products that are commercially available in over 20 countries.[1]

NEED FOR DEVELOPING NANOPARTICLES

The major goals in designing nanoparticles as a delivery system are to control particle size, surface properties and release of pharmacologically active agents so as to achieve the site specific action of the drug at the rationale rate and dose. Polymeric nanoparticles offer some specific advantages over liposomes. For instance, they help to increase the stability of drugs/proteins and possess useful controlled release properties.[4]

CLASSIFICATION OF NANOPARTICLES

Nanoparticles are broadly classified in to three classifications.

ONE DIMENSION NANOPARTICLES

One dimensional system (thin fine lm or manufactured surfaces) has been used for decades. Thin films (sizes 1–100 nm) or monolayer is now common place in the field of solar cells offering, different technological applications, such as chemical and biological sensors, information storage systems, magneto-optic and optical device, fiber-optic systems.[5]

TWO DIMENSION NANOPARTICLES

Carbon nanotubes (CNTs): Carbon nanotubes are hexagonal network of carbon atoms, 1 nm in diameter and 100 nm in length, as a layer of graphite rolled up into cylinder. CNTs are of two types, single walled carbon nanotubes (SWCNTs) and multi-walled carbon nanotubes (MWCNTs). The small dimensions of carbon nanotubes, combined with their remarkable physical, mechanical and electrical properties make them unique materials. They display metallic or semi conductive properties, depending on how the carbon leaf is wound on itself. The current density that nanotubes can carry is extremely high and can reach one billion amperes per square meter making it a superconductor. The mechanical strength of carbon nanotubes is sixty times greater than the best steels. Carbon nanotubes have a great capacity for molecular absorption and offering a three dimensional configuration. Moreover they are chemically and chemically very stable.[6]

THREE DIMENSION NANOPARTICLES

Fullerenes (Carbon 60): Fullerenes are spherical cages containing from 28 to more than 100 carbon atoms, contain C60. This is a hollow ball composed of interconnected carbon pentagons and hexagons, resembling a soccer ball. Fullerenes are class of materials displaying unique physical properties. They can be subjected to extreme pressure and regain their original shape when the pressure is released. These molecules do not combine with each other, thus giving them major potential for application as lubricants. They have interesting electrical properties and it has been suggested to use them in the electronic field, ranging from data storage to production of solar cells. Fullerenes are offering potential application in the rich area of nanoelectronics. Since fullerenes are empty structures with dimensions similar to several biological active molecules, they can be filled with different substances and find potential medical application.[7]

NANOPARTICLES: TYPES

SILVER: Silver nanoparticles have proved to be most effective because of its good antimicrobial efficacy against bacteria, viruses and other eukaryotic micro-organisms. They are undoubtedly the most widely used nanomaterials among all, thereby being used as antimicrobial agents, in textile industries, for water treatment, sunscreen lotions etc.Studies have already reported the successful biosynthesis of silver nanoparticles by plants such as Azadirachta indica, Capsicum annuum and Carica papaya.[8]

GOLD: Gold nanoparticles (AuNPs) are used in immunochemical studies for identification of protein interactions. They are used as lab tracer in DNA fingerprinting to detect presence of DNA in a sample. They are also used for detection of amino glycoside antibiotics like streptomycin, gentamycin and neomycin. Gold nanorods are being used to detect cancer stem cells, beneficial for cancer diagnosis and for identification of different classes of Bacteria.[8]

ALLOY: Alloy nanoparticles exhibit structural properties that are different from their bulk samples. Since Ag has the highest electrical conductivity among metal fillers and, unlike many other metals, their oxides have relatively better conductivity, Ag flakes are most widely used. Bimetallic alloy nanoparticles properties are influenced by both metals and show more advantages over ordinary metallic NPs.[8]

MAGNETIC: Magnetic nanoparticles like Fe3O4 (magnetite) and Fe2O3 (maghemite) are known to be biocompatible. They have been actively investigated for targeted cancer treatment (magnetic hyperthermia), stem cell sorting and manipulation, guided drug delivery, gene therapy, DNA analysis, and magnetic resonance imaging (MRI).[8]

NANOPARTICLES PREPARATION

Nanoparticles are aimed to be prepared from a variety of materials such as proteins, polysaccharides and synthetic polymers. The selection criteria of matrix materials depends on many factors such as: (a) Size of nanoparticles required; (b) Inherent properties of the drug, e.g., aqueous solubility and stability; (c) Surface characteristics such as Charge and Permeability; (d) Degree of biodegradability, biocompatibility and toxicity; (e) Drug release profile desired; and (f)Antigenicity of the final product. Nanoparticles preparation is most frequently by three methods: (1) Dispersion of preformed polymers; (2) Polymerization of monomers; and (3) Ionic gelation or coacervation of hydrophilic polymers. However, other methods such as supercritical fluid technology 8 and particle replication in non-wetting

templates have also been described in the literature for production of nanoparticles. The latter was claimed to have absolute control of particle size, shape and composition, which could set an example for the future mass production of nanoparticles in industry.[9]

DISPERSION OF PREFORMED POLYMERS

Dispersion of preformed polymers is a common technique used to prepare biodegradable nanoparticle from poly (lactic acid) (PLA); poly (D,L-glycolide),PLG; poly (D,Llactide-coglycolide) (PLGA) and poly(cyanoacrylate) (PCA), This technique can be used in various ways as described further:[9]

SOLVENT EVAPORATION METHOD

In this method, the polymer is dissolved in an organic solvent such as dichloromethane, chloroform or ethyl acetate, which is also used as the solvent for dissolving the hydrophobic drug. The mixture of polymer and drug solution is then emulsified in an aqueous solution containing a surfactant or emulsifying agent to form oil in water (o/w) emulsion. After the formation of stable emulsion, the organic solvent is evaporated either by reducing the pressure or by continuous stirring. Particle size was found to be influenced by the type and concentrations of stabilizer, homogenizer speed and polymer concentration. In order to produce small particle size, often a high-speed homogenization or ultrasonication may be employed.[9]

SPONTANEOUS EMULSIFICATION OR SOLVENT DIFFUSION METHOD

This is a modified version of solvent evaporation method. In this method, the water miscible solvent along with a small amount of the water immiscible organic solvent is used as an oil phase. Due to the spontaneous diffusion of solvents an interfacial turbulence is created between the two phases leading to the formation of small particles. As the concentration of water miscible solvent increases, a decrease in the size of particle can be achieved. Both solvent evaporation and solvent diffusion methods can be used for hydrophobic or hydrophilic drugs. In the case of hydrophilic drug, a multiple w/o/w emulsion needs to be formed with the drug dissolved in the internal aqueous phase.[9]

POLYMERIZATION METHOD

In this method, monomers are polymerized to form nanoparticle in an aqueous solution. Drug is incorporated either by being dissolved in the polymerization medium or by adsorption onto the nanoparticles after polymerization completed. The nanoparticle suspension is then

purified to remove various stabilizers and surfactants employed for polymerization by ultracentrifugation and re-suspending the particles in an isotonic surfactant-free medium. This technique has been reported for making polybutylcyanoacrylate or poly (alkylcyanoacrylate) nanoparticles.[9]

COACERVATION OR IONIC GELATION METHOD

The nanoparticles preparation is carried by using biodegradable hydrophilic polymers such as chitosan, gelatin and sodium alginate. Developing a method for preparing hydrophilic chitosan nanoparticles by ionic gelation. In this method, positively charged amino-group of chitosan interacts with negative charged tripolyphosphate to form coacervates with a size in the range of nanometer.[9]

ADVANTAGES OF NANOPARTICLES

A nanoparticle offers numerous advantages in drug delivery system. These advantages include, but are not limited.[10]

- Nanoparticles have many significant advantages over conventional and traditional drug delivery system.
- Nanoparticles are control and sustain release form at the site of localization; they alter organ distribution of drug compound. They enhance drug circulation in blood, bioavailability, therapeutic efficacy and reduce side effects
- Nanoparticles can be administered by various routes including oral, nasal, parenteral, intra-ocular etc.
- In the tiny areas of body nanoparticles shows better drug delivery as compare to other dosage form and target to a particular cell type or receptor.
- Due to small particle size nanoparticles overcome resistance by physiological barriers in the body and
- Easily penetrates to cell walls, blood vessels, stomach epithelium and blood–brain barrier.
- Nanoparticles enhance the aqueous solubility of poorly soluble drug, which improves bioavailability of drug.
- As a targeted drug carrier nanoparticle reduce drug toxicity and enhance efficient drug distribution.
- By using polymers drug release form nanoparticles can be modified which makes polymeric nanoparticle an ideal drug delivery system for cancer therapy, vaccines, contraceptives and antibiotics.

- Useful to diagnose various diseases
- Enhanced stability of ingredients
- Prolonged shelf life
- Used in dental surgery also as filling the tiny holes in teeth.
- Change the method of drug delivery to improve customer acceptance or reduce manufacturing costs.[10]

STABILITY OF NANOPARTICLES

Stability studies of prepared nanoparticles determined by storing optimized formulation at 4°C ±1°C and 30°C ± 2°C in stability chamber for 90 days. The samples were analyzed after a time period like at 0, 1, 2, and 3 months for their drug content, drug release rate (t50%) as well as any changes in their physical appearance.[11]

TOXICITY OF NANOPARTICLES

Despite the gaining popularity of nanotechnology in the field of medicine, their applications have been restricted due to their potential toxicity and long-term secondary adverse effects. Nanotoxicology includes the study of the toxicity of nanomaterials to better understand and assess the health risks involved in the use of nanoparticles. The physicochemical properties of nanoparticles, such as small size, large surface area and flexible chemical composition/structure that favor their use in nanomedicine, have also been found to contribute to their enhanced toxicological side effects. Specifically, particle size and surface area are considered important factors that contribute directly and significantly to toxicity of nanoparticles, with smaller sized nanoparticles exhibiting higher toxic effects due to increased surface area. Apart from size, structure and shape of the nanoparticle also contribute to nanotoxicity. For example, studies with carbon nanofibers, single-wall nanotubes (SWCNTs) and multi-wall nanotubes (MWCNTs), have revealed that the toxicity of carbon material with high-aspect ratio is determined by particle form and dimensions. Moreover, the nanoparticle surface dictates the adsorption of ions and bimolecular, thus influencing the cellular responses elicited, and thereby contributing to nanoparticle induced toxicity. Humans can be exposed to nanomaterials via several routes such as inhalation, injection, oral ingestion and the dermal route. Specifically, the respiratory system, gastrointestinal tract, the circulatory system as well as the central nervous system are known to be adversely affected by nanoparticles. In vivo experiments have revealed that carbon nanotubes are found to cause dose-dependent epithelioid granulomatous lesions in the lung

and persistent interstitial inflammation on chronic exposure. Furthermore, ceramic nanoparticles, commonly used for drug delivery, have been reported to exhibit oxidative stress/cytotoxic activity in the lungs, liver, heart, and brain, as well as have teratogenic/carcinogenic effects. In addition to causing detrimental respiratory effects, nanoparticles administered via injection have been shown to enter the systemic circulation, causing secondary complications in the circulatory system and further gain access to the central nervous system. Engineered carbon nanoparticles and nanotubes were found to induce the aggregation of platelets in vitro, and thus enhance vascular thrombosis in rat carotid artery. Furthermore, the effect of SWCNTs was studied in cellular models of human kidney and bronchi, where they were observed to induce cell apoptosis and decrease cell adhesion via either up regulating genes involved in cell death or down regulating genes associated with cell proliferation and survival. Wistar rats injected intraperitoneally with 20 mg/kg titanium dioxide nanoparticles (TiO2NPs) every two days for 20 days, revealed an accumulation of TiO2NPs in the liver, lung and brain, and an increase in aspartate aminotransferase/alanine aminotransferase ratio (AST/ALT ratio), indicating sub acute toxicity. In the injected rats, pathological changes were found in the liver and abnormal neurobehavioral performance, as evidenced by the increased anxious index was observed, suggesting that TiO2NPs are able to translocate and biodistribute to various organs leading to toxicity effect. Oral ingestion of a single dose of 500 mg/kg titanium dioxide (TiO2), zinc oxide (ZnO) and aluminum oxide (Al2O3) nanoparticles were shown to result in nanoparticle translocation to the central nervous system. These nanoparticles accumulated in the brain and caused auxiliary toxicity, disrupting normal metabolism of neurotransmitters and ultimately leading to brain damage. The effect of different sized TiO2 nanoparticles were studied in rat astrocytes, in which these nanoparticles were found to inhibit cell survival rates in a dose-dependent manner, with pathological effects such as blood-brain barrier destruction, cellular oedema and brain tissue necrosis. Furthermore, nano-manganese dioxide (MnO2) was also found to cause dopaminergic neuronal dysfunction and astrocyte activation, thus affecting the learning abilities of rats. Dermal exposure of nanoparticles is often mediated through the use of nonmaterial containing cosmetic products or wound dressings. For instance, sunscreens containing TiO2 were found to pass through the stratum corneum and in the deeper parts of hair follicles. In addition, Acticoat, a nanocrystalline silver-coated wound dressing, is now being used for treatment in burn patients. Despite various studies reporting about the safety of Acticoat for the use on burn patients, silver toxicity was reported in a patient with 30% burns who had received the silver-coated dressing for treatment. The accumulation of nanoparticles

in various organs and adverse side effects have hindered their use in the field of nanomedicine, and have deterred full exploitation of their potential in molecular diagnostics and as drug delivery systems.[12]

MECHANISMS OF NP TOXICITY

Many studies have attempted to elucidate the mechanisms of NP toxicity and distinguish between their bulk counterparts. Nanomaterials differ from their bulk counterparts in several ways, including high surface/volume ratio. Other factors such as dissolution, size, shape, aggregation state, surface coatings, and solution chemistry also influence the toxicity of NPs. The toxicity of various NMs AgNP, CuO NP, TiO2 NP, and Ni NP has been studied in various aquatic species, such as Daphnia magna, fish, algae, and marine and freshwater crabs. Silver, carbon, and titanium NMs are among the most widely used types NMs used as additives in cosmetics and pharmaceuticals. Also, different NMs exhibit different properties had hence have different toxicity potencies. For example, Heinlaan et al. compared the toxicities of three nanometal oxides: ZnO NPs, CuO NPs, and TiO2 NPs. ZnO NPs was determined to be the most toxic; whereas Zhu et al. reported CuO NP the most potent to cytotoxicity and genotoxicity. The assessment of NP toxicity has largely been assessed *in* vitro, reporting inducing various negative effects at different levels of cellular organization. Typical end points measured include end points examined which include mortality, as well as sub lethal effects such as development, growth, respiration, malformation, oxidative stress, and gene expression. Generation of reactive oxygen species (ROS) and free radicals causes oxidative stress (activation or inhibition of the antioxidant defense system), lipid per oxidation, and DNA damage. Toxicity of NPs will be discussed further in the following sections.[13] Most advanced effort to date has recommended that ROS generation which can be moreover protecting or destructive throughout biological interactions and subsequent oxidative stress are persistently detected with nanoparticle toxicity.[14]

OXIDATIVE STRESS

Oxidative stress is referred to as an imbalance between the production of reactive oxygen species (ROS) and the cells' ability to reduce ROS, which may be as a result an increased ROS production, a decrease in the cell's defense mechanisms, or a combination of both. An Overproduction of ROS may induce oxidative stress, resulting in cells failing to maintain Normal physiological redox-regulated functions further resulting in oxidative modification of Proteins to generate protein radicals, initiation of lipid per oxidation, DNA strand breaks and

modification to nucleic acids, modulation of gene expression, thereby leading to cell death and genotoxic effects. To minimize the effects of ROS-oxidative damage to cellular components, biological systems have developed a complex antioxidant system, comprised of both enzymatic and non-enzymatic defense mechanisms. The antioxidant defense system has evolved to provide a balance between the production and removal of ROS. These are catalyzed by a number of different enzymes including Phase I and Phase II enzymes. Phase I enzymes, such as cytochrome P450, initiate the detoxification process by introducing a polar moiety which renders a lipophilic contaminant more hydrophilic. Activity of Phase I enzymes typically leads to an increase in ROS production. Phase II enzymes are involved in conjugating metabolized xenobiotics to endogenous molecules. Phase III involves further modification and excretion.[13]

ECOTOXICITY

The potential ecotoxicity of NPs has currently provoked public and scientific dialogues due to debates around the risks and benefits of these materials. As such, studies on the ecotoxicological fate and effects of NMs have increased in recent years. There has been extensive research investigating the toxicity of NPs to aquatic organisms with several recent reviews reporting on ecotoxicology of NPs. Data on the biological effects of NPs indicate that NPs can be toxic to bacteria, algae, invertebrates, fish, and mammals. Nonetheless, nano-ecotoxicology studies remain poorly and unevenly distributed as most research undertaken has largely been restricted to a narrow range of test species. Most of the current ecotoxicological data pertaining to NMs have been done on Daphnia magna. These crustaceans represent the food and energy link between algae and fish; therefore, these studies are particularly relevant. Park and Choi studied the ecotoxicity effects of AgNPs to D. magna and reported increased mortality. Asghari et al. reported abnormal swimming in D. magna following exposure to AgNPs, while Heinlaan et al.reported ultra structural changes in the midgut of D. magna upon exposure to CuO NPs.[13]

GENOTOXICITY

An important issue relating to the toxicity of NPs in biological media is the ability to cause damage to the genetic material, particularly since NPs have the capacity to cross cell membranes. In the section below, evidence of NP-induced genotoxicity is reviewed. DNA is a significant cellular component highly susceptible to oxidative damage. As such, there has been increasing interest in the analysis of the potential nanoparticle genotoxicity to aquatic

organisms. Genotoxic assessments of various NPs have largely been reported on in *vitro* studies. Reported abilities of NPs include chromosomal fragmentation, DNA strand breakages, point mutations, oxidative DNA adducts, and alterations in gene expression profiles and consequently may initiate and promote mutagenesis and carcinogenesis. Primary genotoxicity stemming from the direct interactions of NP with DNA following NP internalization has been reported. Genotoxicity mediated by the generation of excess ROS, referred to as secondary genotoxicity, has been reported. Oberholster et al., using DNA strand breakage as an indicator of genotoxicity, reported concentration-dependent effects to several NPs (α-alumina, β-alumina, precipitated silica; silica fume, calcined silica fume, colloidal antimony pentoxide, and superfine amorphous ferric oxide). DNA cleavage, an indicator of irreversible completion of apoptosis, occurred in organisms exposed to 5000 μg/kg of precipitated silica, amorphous ferric oxide, and colloidal antimony pentoxide NMs. The inter-nucleosomal DNA ladder bands occurred at 500 μg/kg of γ-alumina and α-alumina.

As with NP toxicity, NPs are also known to have more adverse genotoxic effects than their bulk counterparts. For example, Park and Choi studied the genotoxicity of AgNPs on the freshwater crustacean Daphnia magna. Their results reported a higher degree of DNA damage in the form of DNA strand breaks in AgNPs when compared to Ag ions. Similarly, NP size is also known to affect its genotoxicity potential, inducing significant DNA and chromosomal damages compared to the larger NPs. This size effect was confirmed: the authors showed that smaller sized TiO2 NPs (10 nm) have significant chromosomal damage when compared to the larger TiO2NP (>200 nm). As such, there is a general consensus that smaller sized NPs produce higher reactivity and thus higher genotoxicity. However, particle size is not the only factor that determines particle (geno-) toxicity. Nanoparticle surface coating has also been reported to promote genotoxicity. Surface coating modifies the particle surface, and therefore, they may also alter the particle's genotoxicity. For instance, Hong et al. reported positively charged coatings of iron oxide NPs which consequently resulted in increased DNA strand breaks, while the impact of genotoxicity of negatively charged coatings was insignificant. Similarly, Lui et al. reported various genotoxic responses of iron oxide NPs depending on the type of coating.[13]

CONCLUSION

Because of their incredible properties, nanoparticles have become significant in many fields in recent years such as energy, health care, environment, agriculture etc. The toxicity

profiling of NMs is a highly demanded research area worldwide in recent times. However, research advancement have found some acute toxic effect of nanosized particles in living system. Extensive research in the field of nanotoxicology and strict laws by government agencies are essential to identify and avoid toxic NPs.

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