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Current Status and Future Perspectives on the Applications of Nanoparticles in Biomedical Field

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ABSTRACT

Nanoparticles are defined as solid colloidal particles ranging in size from 10 to 1000 nm. Nanoparticles offer many benefits to larger particles such as increased surface-to-volume ratio and increased magnetic properties. Over the last few years, there has been a steadily growing interest in using nanoparticles in different biomedical applications such as targeted drug delivery, hyperthermia, photoablation therapy, bioimaging, and biosensors. Iron oxide nanoparticles have dominated applications, such as drug delivery, hyperthermia, bioimaging, cell labeling and gene delivery, because of their excellent properties such as chemical stability, non-toxicity, biocompatibility, high saturation magnetisation and high magnetic susceptibility. In this review, nanoparticles will be classified into four different nanosystems like Metallic nanoparticles, Bimetallic or alloy nanoparticles, Metal oxide nanoparticles and magnetic nanoparticles. This review investigates the use of nanosystems other than iron oxide nanoparticles such as metallic nanoparticles like gold (Au) and silver (Ag), bimetallic nanoparticles like iron-cobalt (Fe-Co) and iron platinum(Fe-Pt) and metal oxides including titanium dioxide (TiO2), cerium dioxide (CeO2), silica (SiO2) and zinc oxide (ZnO) with a focus on the lesser studied nanoparticles such as silver (Ag), iron-platinum (Fe-Pt) and titanium dioxide (TiO2) and how their unique properties allow for their potential use in various biomedical applications.

INTRODUCTION:

Nanomaterials can occur naturally or they can be synthesized chemically, physically, mechanically, or biologically. The most common classification is based on their structure, namely zero-dimensional, one-dimensional, two-dimensional and three-dimensional (Fig. 1), with some substance falling on the borders of these categories. Furthermore, there are several other parameters for the classification of nanomaterials, including their chemical composition (organic and inorganic), their formation (biogenic, geogenic, anthropogenic, and atmospheric), their size and shape, and their application in industry or research [1].

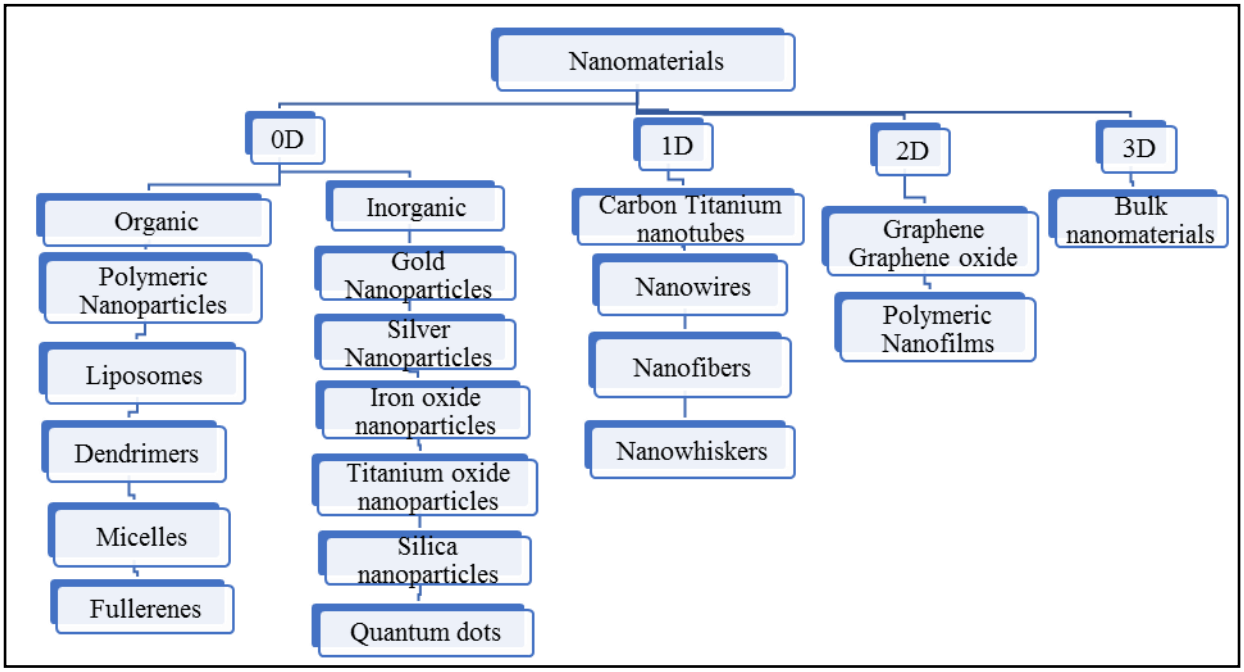

Figure No. 1: Nanomaterials classification based on their dimensionality (0D—zero-dimensional, 1D—one-dimensional, 2D—two-dimensional, 3D—three-dimensional).

Nanomaterials are defined as insoluble or bio-persistent, naturally occurring or intentionally manufactured materials with at least one dimension or an internal structure within the nanoscale regime, specifically within 100 nm [2]. Application of nanomaterials for brain disorders therapy can unintentionally enter the brain through blood circulation from peripheral disorders therapy or after inhalation from the air. Therefore, despite the impressive progress in the field, the application of nanomaterials has brought about a new cause for concern, which is the neurotoxicity of nanomaterials [3,] This science is increasingly inserted in our daily life being used as raw in cosmetics and pharmaceutical materials, in the manufacturing of packaging. As vectors for gene manipulation, diagnosis, and anticancer

treatment. As adjuvants in the formulations of vaccines and antimicrobials, and in the development of tools and analytical instruments [4].

Nanoparticle Research:

Rapid expansion in nanozyme research was possible due to the several advantages that inorganic nanoparticles possess over natural enzymes, such as simple methods of synthesis, low cost, high stability, robust catalytic performance and smooth surface modification. Therefore, nanozymes are being widely explored to establish a wide range of applications in biosensing, immunoassays, disease diagnosis and therapy, theranostics, cell/tissue growth and proliferation, protection from oxidative stress, and removal of pollutants [5,6].

The major goals in designing nanoparticles as a delivery system are to control particle size, surface properties and release of pharmacologically active agents to achieve the site-specific action of the drug at the therapeutically optimal rate and dose regimen. Though liposomes have been used as potential carriers with unique advantages including protecting drugs from degradation, targeting to site of action and reduction in toxicity or side effects, their applications are limited due to inherent problems such as low encapsulation efficiency, rapid leakage of the water-soluble drug in the presence of blood components and poor storage stability. On the other hand, 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 [7,8].

In recent years, biodegradable polymeric nanoparticles, particularly those coated with a hydrophilic polymer such as polyethylene glycol (PEG) known as long-circulating particles, have been used as potential drug delivery devices because of their ability to circulate for a prolonged period, target a particular organ, as carriers of DNA in gene therapy and their ability to deliver proteins, peptides and genes [9].

Biomedical applications

In this section, a brief review of the principles of each application is given and the use of certain nanoparticles in these applications is reviewed. Fig 2 shows a schematic of the biomedical applications that will be discussed in this section.

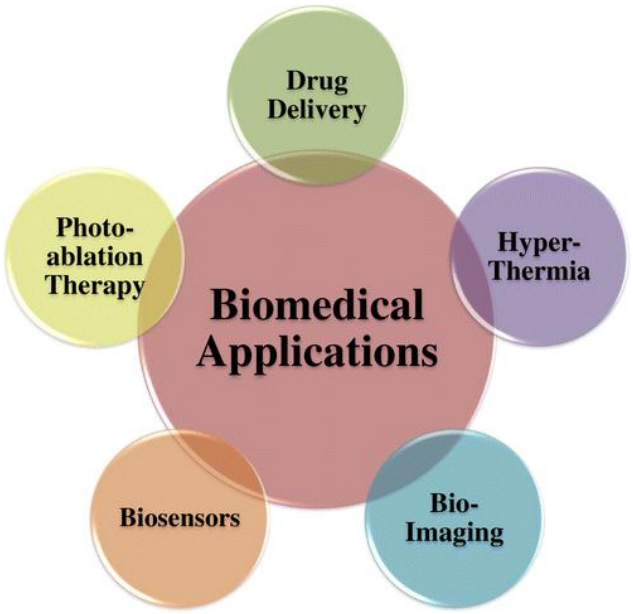

Figure No. 2: Schematic showing some of the biomedical applications of nanoparticles.

Targeted drug delivery is an important biomedical application that aims to deliver anticancer drugs to the specific site of the tumor and avoid damage to surrounding healthy cells. Currently, Iron oxide nanoparticles are used in cancer magnetic nano therapy that is based on the magneto-spin effects in free-radical reactions and semiconductor material ability to generate oxygen radicals, furthermore, control oxidative stress in biological media under inhomogeneous electromagnetic radiation[10,11].

Another important biomedical application of nanoparticles is magnetic hyperthermia treatment. Magnetic hyperthermia treatment treats tumors by heating them to above 42 °C to destroy the cancerous cells. The benefit of this technique over chemotherapy is that it specifically targets the tumor and does not damage the surrounding healthy tissue. Again, iron oxide (Fe_3O_4) nanoparticles are the main material that is currently used for this treatment [10,12,13,14].

1. DRUG DELIVERY

The main problems currently associated with systemic drug administration include even biodistribution of pharmaceuticals throughout the body, the lack of drug specificity towards a pathological site, the necessity of a large dose to achieve high local concentration, non-specific toxicity and other adverse side effects due to high drug doses. Drug targeting aims to resolve many of these problems [15]. A highly publicized example of magnetic drug delivery is as a replacement or augment Chemotherapy/radiotherapy treatments.

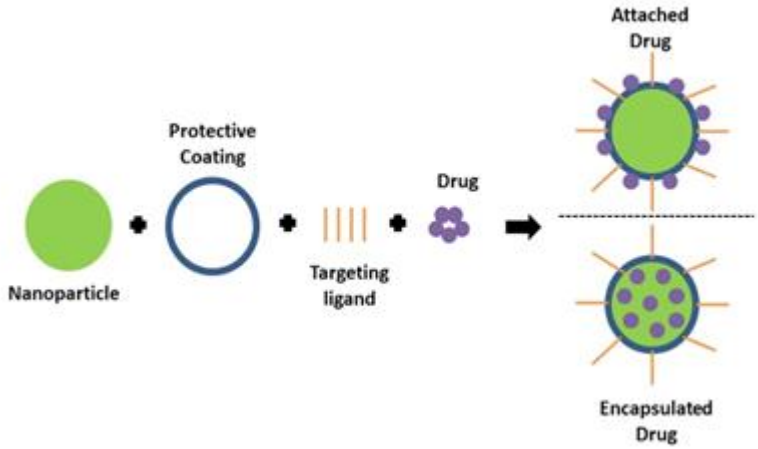

Figure No. 3: Schematic of drug loading options in targeted drug delivery.

The development of techniques that could selectively deliver drug molecules to the diseased site, without a concurrent increase in its level in healthy tissues, is currently one of the most active areas of cancer research. The first clinical trials in humans with a magnetic drug targeting worldwide were reported by Lubbe et al (1997), who used a ferrofluid (particle size 100 nm) to which the drug epirubicin was chemically bound. Epirubicin is a well-known antibiotic anthracycline that has a wide range of applications for the treatment of solid tumours [16]. In targeted drug delivery, magnetic nanoparticles are used to deliver the drug to its specific location. Generally, the magnetic nanoparticles are coated with a biocompatible layer, such as gold or polymers, this is done to functionalised the nanoparticles so that the anticancer drug can either be conjugated to the surface or encapsulated in the nanoparticle as shown in Fig 3. Once the drug/nanoparticle complex is administered, an external magnetic field is used to guide the complex to the specific tumor site. The drug is released by enzyme activity or by changes in pH, temperature or osmolality [10,17].

2. PHOTOABLATION THERAPY

Photoablation therapy is classified into photodynamic therapy (PDT) and photothermal therapy. PDT uses non-toxic light-sensitive compounds called photo-sensitizers and upon exposure to light at a certain wavelength, these compounds become toxic. This therapy is mainly used to target diseased cells such as cancer.

Photothermal therapy mediated by an NIR laser to trigger the surface plasma resonance of gold nanoshells and has been demonstrated to be effective in cancer treatment on several subcutaneous tumour models [18,19].

The photo-catalytic process for TiO_2 has three steps: excitation, diffusion and surface transfer. In the first step, the nanoparticles absorb photons from a light source. This energy is enough to overcome the bandgap and promote the electron into the conduction band. This leaves vacancies or holes in the valance band. The holes and electrons then diffuse to the surface of the photocatalyst. The last step in this photocatalytic reaction is the production of chemical reactions on the surface. The creation of holes and electrons results in these reactions.

Figure No. 4: Schematic showing the photocatalytic process of TiO2 nanoparticles.

The holes can react with absorbed surface water and produce hydroxyl radicals, while the electrons combine with oxygen to form superoxide radical. Fig. 4 depicts the photocatalytic reaction of TiO_2 [20].

3. BIOSENSOR

The increasing demand for sensing a broad range of molecules at low concentrations with high specificity has motivated the development of sophisticated devices that incorporate nanoscale materials, biological elements and advanced materials, which are collectively called nanobiosensors. Many microorganisms, viruses, bacteria and pathogens have similar dimensions to those of nanostructures; therefore, the detection specificity is highly increased by utilizing chemically inert and biocompatible nanomaterials for biomedical approaches.

Various toxic substances in food and environmental pollutants have also been detected and measured using nanomaterial-based biosensors [21].

A biosensor is an analytical device that is used for analyzing biological samples. It converts a chemical, biological or biochemical response into an electrical signal. A biosensor contains three essential components: (1) bio element or bioreceptor, which are generally made up of enzymes, nucleic acids, antibodies, cells or tissues (2) the transducer which can be electrochemical, optical, electronic, piezoelectric, pyroelectric or gravimetric and (3) the electronic unit which contains the amplifier, processor and display [20].

4. BIOIMAGING

Presently, it is the current achievement in the development of new dye-loaded fluorescent silica nanoparticles (SiNPs) for non-invasive fluorescence bioimaging; both in vitro and in vivo. SiNPs are easy to functionalised and demonstrate good biocompatibility, low toxicity, high hydrophilicity and excellent optical transparency. Due to these properties, SiNPs are suitable substrates for the fabrication of fluorescent probes used in the effective imaging of living cells and small animals. The authors also discuss several challenges that limit applications of these nanomaterials, such as leakage of dyes from the fluorescent SiNPs, nonspecific binding and their dispersibility in aqueous media [22]. There are different bioimaging techniques such as MRI, computed tomography (CT), positron emission tomography (PET) and ultrasound that are used for the detection and diagnosis of diseases. These techniques are non-invasive and some can produce high-resolution images of internal organs. Contrast agents are generally used in these bioimaging techniques to identify the organ or tissue of interest as well as identifying healthy tissue from diseased tissue [10].

5. HYPERTHERMIA

Magnetic fluid hyperthermia is based on the principle of converting electromagnetic energy into heat. The magnetic nanoparticles are distributed around the target site and an alternating magnetic field is applied. This alternating magnetic field supplies energy which helps the magnetic moments in the particles to overcome the reorientation energy barrier. Energy is dissipated when the moments in the particles relax to an equilibrium state. This then results in the heating of the particles by Brownian rotation or Neél relaxation [10,23]. Whole-body hyperthermia is achieved by such methods as hot water blankets and thermal chambers. In theory, it should be used for metastatic cancer where focal hyperthermia would be

ineffective. Regional hyperthermia depends on perfusing with heated liquids – the two popular techniques are perfusing the peritoneum with a heated solution of anticancer drugs for peritoneal cancers such as mesothelioma and the perfusion of a part of the patient's blood, taken out and warmed ex vivo, into an artery supplying the limb containing the tumor [24 25].

Many bulk metals, when reduced to a nanoscale, exhibit optical resonances of their surface plasmons, a characteristic wavelength (surface plasmons resonance) at which they strongly absorb and scatter incident light and convert resonant energy to heat. When fabricated in certain geometries, these plasmons resonances of gold can be tuned to near-infrared (NIR) wavelengths, where this light penetrates deepest within human tissues due to minimal absorbance by native tissue chromophores [26].

FACTORS AFFECTING NANOPARTICLES

Biodegradable polymeric nanoparticles (NPs) have been used widely as drug carriers, especially for oral and pulmonary drug delivery. Because of their small size, they can solubilize a concentrated payload of a therapeutic agent, improve drug stability and bioavailability and provide sustained delivery. Moreover, use of biodegradable and biocompatible materials decreases the risk of unwanted toxicities and adverse effects [27,28].

Conventional methods can be used to produce nanoparticles in large quantities with defined sizes and shapes in a shorter period; however, these techniques are complicated, costly, inefficient and outdated. In recent years, there has been growing interest in the synthesis of environment friendly nanoparticles that do not produce toxic waste products during the manufacturing process [29]. The synthesis of nanoparticles using modern techniques has emerged as an important application in the biomedical and human health care field for a broad range of products. In general, nanotechnology can be defined as the manipulation of materials at the atomic level by a combination of engineering, chemical and biological approaches [30].

Methods of Nanoparticles Preparation

For the preparation of nanoparticles, the selection of the appropriate method is based on the drug to be loaded and the physicochemical properties of the polymer.

a. **Emulsion-Solvent Evaporation Method**

The nanoparticles are prepared by two steps in this method. In an aqueous phase, emulsification of the polymer solution is required in the first step. While in the second step, evaporation of polymer solution occurs and nanospheres are formed by inducing the polymer precipitation. Collection of nanoparticles is done by Ultracentrifugation and to remove free drug or residue, it is then washed with distilled water and for Storage, these are lyophilized [30]. This method is also known as the solvent evaporation method and high-pressure emulsification [31]. This technique involves homogenization under high pressure and overall stirring to remove organic solvent [32]. By adjusting the stirring rate, a viscosity of organic and aqueous phases, temperature, type and amount of dispersing agent; the size of the nanoparticle can be controlled [33]. Poor entrapment of hydrophilic drugs is the main drawback of this method.

b. **Double Emulsion and Evaporation Method**

To encapsulate hydrophilic drug, the double emulsion technique is engaged, in which aqueous drug solutions is added to organic polymer solution with vigorous stirring to form w/o emulsions. This w/o emulsion is added into another aqueous phase with continuous stirring to form mixed emulsion (w/o/w). Then by evaporation, the solvent is removed and by centrifugation at high speed, nanoparticles can be isolated. Before lyophilisation, the prepared nanoparticles must be washed [34]. The variables used in this method are- incorporated quantity of hydrophilic drug, amount of polymer, volume of aqueous phase and stabilizer concentration [35].

c. **Salting Out Method**

By using salting-out from aqueous solution, the water-miscible solvent is separated [36]. Initially in a solvent, polymer and drug are dissolved which is consequently containing the salting-out agent (electrolytes like calcium chloride and magnesium chloride or sucrose as non-electrolyte) and polyvinylpyrrolidone(PVP) or hydroxyethyl cellulose as a colloidal stabilizer into an aqueous gel are emulsified. This oil in water emulsion is diluted with water or with an aqueous phase to increase the diffusion of solvent, which indicates the formation of nanospheres. Several parameters such as electrolyte concentration, concentration of polymers in the organic phase, type of stabilizer, stirring rate, internal/external phase ratio

can be varied. This technique leads to high efficiency and easily scaled up in the preparation of Ethylcellulose, PLA and Poly-methacrylic-acids nanospheres [37,38].

d. **Emulsions Diffusion Method**

To prepare nanoparticles, emulsions diffusion method is another method that is commonly used. The encapsulating polymer is dissolved in a solvent which is partially miscible with water such as propylene carbonate, benzyl alcohol and the initial thermodynamic equilibrium of both liquids saturated with water should been sured. Subsequently, the polymer-water saturated solvent phase is emulsified in an aqueous solution containing stabilizer, leading to solvent diffusion to the external phase and according to the oil-to-polymer ratio nanospheres or nanocapsules are formed. Finally, according to boiling point, the solvent is removed by evaporation or filtration. This technique has several advantages such as high reproducibility (batch-to-batch), no requirement of homogenization, high encapsulation efficiencies (generally70%), simplicity, narrow sized tribution and ease of scale-up.

But some drawbacks of this method are the high volumes of water to be eliminated from the suspension and reduced encapsulation efficiency during emulsification because, in the saturated-aqueous external phase, there is leakage of water-soluble drug [39].

Examples: cyclosporine (cy-A-); loaded sodium glycolate nanoparticles33, mesentera (hydroxyphenyl)porphyrin-loaded PLGA(p-THPP) nano particles34 and nanoparticles of doxorubicin-loaded PLGA [40].

e. **Solvent Displacement/Precipitation method**

Solvent displacement includes from an organic solution, the precipitation of a preformed polymer and in the aqueous medium the diffusion of the organic solvent in the presence or absence of surfactant. In a semi-polar water-miscible solvent such as acetone or ethanol, polymers, drug and lipophilic surfactant are dissolved. Then solution is poured or injected using the magnetic stirring, into a stabilizer containing aqueous solution. By the rapid solvent, diffusion nanoparticles get formed. Under reduced pressure, the solvent is removed from the suspension. The particle size is also affected by rate of addition of the organic phase into the aqueous phase. It was observed that by increasing the rate of mixing, both particles size and drug entrapment decreases [41].

f. **Polymerization method**

In this method, polymerization of monomers is done in an aqueous solution and after polymerization completed, drug is incorporated either by adsorption onto the nanoparticles or by being dissolved in the polymerization medium. To remove various stabilizers and surfactants employed for polymerization by ultracentrifugation, the nanoparticle suspension is then purified and in an isotonic surfactant-free medium re-suspending the particles. For making poly butyl cyanoacrylate or poly-alkyl cyanoacrylate nanoparticles, this technique has been reported [42]. Formation of nanocapsule and their particle size affected by the surfactants and stabilizers concentration used [43].

g. **Coacervation or ionic gelation method**

On the preparation of nanoparticles, much research has been focused using biodegradable hydrophilic polymers such as chitosan, sodium alginate and gelatin. A method for preparing hydrophilic chitosan nanoparticles by ionic gelation is developed by Calvo and co-workers. The method contains two aqueous phases, in which one is the polymer chitosan and the other phase is a polyanion i.e., Sodium tripolyphosphate. In this method, the interaction of positively charged amino group of chitosan with negative charged tripolyphosphate occurs which form coacervates with a nanometre size range. Electrostatic interaction between two aqueous phases results in the formation of coacervates, while ionic interaction conditions at room temperature result in transition from liquid to gel due to ionic gelation [44,45].

CURRENT LIMITATION AND PROBLEM OF PROPERTIES OF NANOPARTICLES

In comparison to other available techniques, histology can be used to study the specific accumulation and association of nanoparticles within a cellular context. This technique also does not require exposure to ionizing radiation or contrast agents. However, histology is generally considered a qualitative method when assessing nanoparticle biodistribution and several limitations should be considered when approaching this technique. Light and fluorescence microscopy have generally low resolution compared to other microscopy techniques and are unable to image individual nanoparticles in the lower nanometer range, especially in tissues [46].

Electron microscopy has predominantly been used to determine the cellular association of nanoparticles in vitro [47]. With only limited studies, using this technique to evaluate

nanoparticle biodistribution following in vivo administration [48]. Overall, the main advantage of electron microscopy is the high resolution, which allows visualization of the accumulation of nanoparticles in cells and the localization of nanoparticles in cellular organelles [49]. Although this technique is generally considered a semi-quantitative method, several limitations should be considered when approaching this technique for evaluating nanoparticle biodistribution. Electron microscopy is a more expensive technique and is not capable of evaluating large tissue sections compared to standard histology [50].

One of the advantages of using PLA to make micelles is that its physical and chemical properties, such as size, shape, molecular weight, and liquid-to-gas ratio, can all be easily altered to obtain desirable pharmacokinetic and biodegradable properties [51].

FUTURE PERSPECTIVES

In the area of water and wastewater treatments, advanced oxidation processes (AOPs) are well known for the ultimate removal of organic pollutants as a final cleaning step after conventional physicochemical or biological treatments, since AOPs can mineralize hazardous organic chemicals to carbon dioxide, water and simple mineral acids due to the efficient production of hydroxyl radicals (•OH), a powerful and non-selective oxidant species [52, 53]. The production of conventional products at the nanoscale currently helps and will be continued to the economic progress of numerous countries. Many types of NPs and NSMs have been reported and many other varieties are predicted to appear in the future. Therefore, the need for their classification has ripened. The first idea for NM classification was given by Gleiter et al[54].

CONCLUSION:

The toxicity of nanoparticles is critically important topic for researchers both in material science and biomedical fields. Toxicity assessment so far has been informative but it could not catch up the development of technology especially in the biological application of nanoparticles. Even in a in vitro assay, results were often challenged by their inconsistencies. For in vivo application it is even more important to have well defined, consistent assay protocol and techniques so that one can try to discover the key to the unknown, “black box” of particle toxicity in vivo. The immediate need in this regard will be the standardization of assessment protocols for nanoparticle toxicity. Government, academics and worldwide cooperation are desirable to facilitate this process for standardization of assays. In

vitro findings should be carefully integrated into the *in-vivo* behavior of nanoparticles since it is a fairly different environment that nanoparticles will experience. For in vivo applications, therefore, extra care should be taken in the prediction of the potential toxicity of nanoparticles before their actual implementation. Catalyzing ROS generation forms one of the most potent contributors to nanoparticles toxicological components and sparks cascades of oxidative stress and inflammatory signals that ultimately lead to necrosis, expedited apoptosis or carcinogenesis.

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