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Biomedical Applications and Toxicological Effects of Nanomaterials: A General Approach

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ABSTRACT
Nanomaterials are a new class of smart materials having the ability to tune their functionality with particle size. Advancements in the field of nanotechnology have made possible to manufacture engineered nanomaterials for various biomedical applications. Recent research outcomes showed that the nanoparticles (NPs) interact successfully within biological environments for the treatment of various diseases. The surface modified biocompatible NPs can act as an artificial receptor on biomolecular surface and can be used for various biological applications. Nanomaterials are also being incorporated to deliver conventional drugs directly to the targeted cell or molecules. The controlled release of a drug prevents side effect of damaging healthy tissues or cells. But with all these benefits, the toxicity of nanomaterials is one of the major concerns which limits its use in commercial applications. The scientific literature available is not sufficient to identify and measure the hazards originated by nanomaterials due to their variable physical and chemical properties. This review article main objective is to study and understand the applicability of nanomaterials in biomedical applications along with their toxicological effects. It is expected to broaden the understanding in development of nanomaterial-based diagnostics, sensors and other pharmaceutical nanotechnology-based systems with safety evaluation procedures.
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Introduction

Nanotechnology has turned out to be as one of the most prominent technological revolutions of the 20th century, which deals with the manipulation of matter on atomic and molecular levels [1]. It is a multidisciplinary field covering basic sciences along with various interdisciplinary subjects like molecular biology, biophysics, bioengineering, etc.[1-3]. Scientists have precisely manipulated atoms for the fabrication of nanoscale products covering a wide range of applications [4-5]. These products are called engineered nanomaterials and have a variety of applications in important technological platforms, especially in pharmacology, therapeutics and biomedical fields [6-9]. A new field of study with high potential applications has been evolved with the intersection of molecular biology and nanotechnology, termed as nanobiotechnology. It can be referred as a discipline in which tools (probe, sensors, or drug delivery system) developed by nanotechnology are applied to study the biological phenomenon. The materials developed by this technology are termed as nanobiomaterials.

Various inorganic and organic materials were used in the past but the former one was found to be more promising entity in these platforms because of their high drug loading capacity, ease of surface functionalization and higher stability in biological environments [10-11]. Metallic NPs encompass both optical and magnetic properties, therefore can be used for variety of applications [12-14]. Incident light on the metallic NPs surface produces surface plasmon resonance (SPR) due to the motion of all the valence electrons. Therefore, these NPs can absorb or emit much higher values of electromagnetic radiations than any quantum dot or molecule. There are enormous biomedical applications of magnetic nanomaterials. The ease of size tunability in these nanomaterials further increases their applicability. Due to small size, they can easily be inserted inside the tumour/cancerous cell by oral drug delivery or can be injected to a specific place. Their properties can further be tuned by providing an external magnetic field from distance [15].

Synthesis of nanomaterials

Two different methodologies generally adopted for preparation of nanomaterials are top-down and bottom-up. The top-down approach refers to cutting, breaking or slicing of a bulk macrostructure into smaller pieces using lithography, mechanical attrition, gas condensation, etc., to obtain nanostructure in desired dimensions. Bottom-up approach starts with self-assembling of atoms or molecules. The physical forces functional at nanoscale combine basic units into larger stable structures. It can further be classified into three major categories *viz.* physical, chemical and biological [16-17]. Some of the techniques commonly used for the synthesis of nanomaterials are listed in Fig. 1. The type of method, experimental conditions, and encapsulating agent determines the shape, size and stability of NPs. The widely used physical methods are atomic layer deposition (ALD), pulsed laser deposition (PLD), physical vapour deposition, etc. Generally, chemical methods are preferred over other methods as they are cost-effective, energy savvy and provide an easy way to synthesize NPs in solution [16-18]. Some of the extensively used chemical synthesis methodologies adopted in the synthesis of NPs are colloidal route, sol-gel technique, solvothermal method, hydrothermal method, electrodeposition, etc. Biological methods are also used to prepare NPs with desired shape and size. NPs prepared using microorganisms (bacteria, yeast, fungi, etc.), plant extracts, templates of DNA/viruses, etc., are found to have very small size [17-19].

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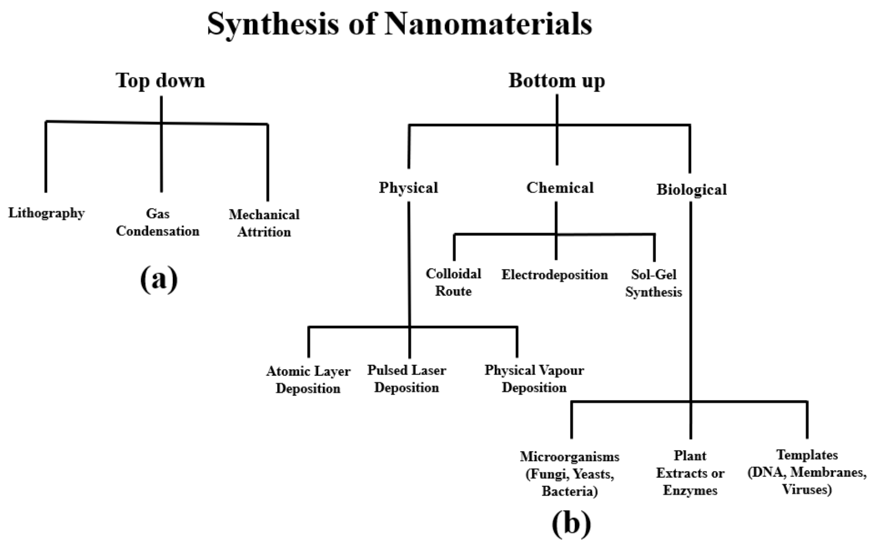

Figure 1: Various techniques for the synthesis of nanomaterials

Characterization of nanomaterials

Several experimental techniques are available for the characterization of nanomaterials. Some of the techniques are listed in Fig. 2.

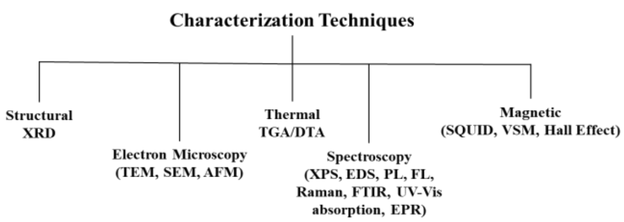

Figure 2: Different techniques for the characterization of nanomaterials

The structural and morphological studies of the NPs are performed using X-ray diffraction (XRD) and high-resolution transmission electron microscopy (HR-TEM). Average particle size, the presence of different crystalline phases and various other parameters are obtained by these techniques [20]. The surface studies are performed using field emission scanning electron microscopy (FE-SEM), scanning tunneling microscopy (STM) and atomic force microscopy (AFM). The elemental composition present in the nanomaterials can be estimated using Energy-dispersive X-ray spectroscopy (EDS), X-ray fluorescence and X-ray photoelectron spectroscopy (XPS). There are several other spectroscopic techniques *viz.* Raman spectroscopy, Fourier transform infrared spectroscopy (FTIR), Uv-visible absorption and photoluminescence (PL) spectroscopy, etc., by which qualitative and quantitative analysis, detection of functional groups, impurities, a relation between various functional groups and detections of conjugation of compounds can be evaluated [21-22]. The measurements of magnetic properties can be performed using superconducting quantum interference device (SQUID), vibrating sample magnetometer (VSM) and Hall effect at low and high temperatures [23-24]. The thermal decomposition behaviour of the nanomaterials can be studied by thermogravimetric (TGA) and differential scanning calorimetry (DSC) at ambient as well as inert conditions [25-26]. The average-size distribution of the synthesized NPs can be studied using dynamic light scattering (DLS) [27]. The zeta potential analysis calculates the surface charges present at the NPs surface when they are dispersed in a colloidal solution. It measures the dispersion stability of a nanoparticle in a solution [28]. Nanobiomaterials developed from NPs are extensively studied and are being used in variety of pharmaceutical products, including drug delivery, programmable drugs release system, sensors and medical equipment's [13, 29].

Biomedical applications of nano-materials

Nanomedicine is an emerging area of research in the biomedical field that can transform the traditional use of drugs to an advanced level. This new approach has the ability of early level disease diagnosis, targeted drug delivery, treatments of tumour/cancer cells without cutting or slicing body parts and faster recovery system. Nanomaterials are synthesized and engineered in such a way as to make them suitable for various biomedical applications such as, tissue engineering, nanobots, nano-pharmaceutics, therapeutics, bio-imaging, drug delivery, biosensors, biomarkers, biocatalysts, nanocarriers, bio-electronics, bone/nerve/tissue regeneration, etc. [30-34]. Since last decade, a huge amount of work has been carried out in this field of study. Nanomaterials were repetitively examined and tested for their biocompatibility, biodegradability and toxicology. Multifunctional ability present in these nanomaterials can also be used to enhance the therapeutic effect of a drug. Liposomes are the well-known example of nanocarriers in drug delivery [35]. In addition, nanomaterials are also used for antimicrobial activities [36], cancer diagnosis and therapy [37-38], detecting and treating tumours [37], tuberculosis [39] and dental implants [40].

In this review article, the potential biomedical applications of metallic nanobiomaterials are discussed. Some of the metallic NPs most widely used for biomedical applications are, gold (Au), silver (Ag), copper (Cu), iron oxide (Fe_2O_3), zinc oxide (ZnO), titanium dioxide (TiO_2), iron-platinum (Fe-Pt), selenium (Se), gadolinium (Gd) and palladium (Pd). These nanomaterials are chemically stable and have shown good biocompatibility. Biomedical applications of some metallic nanobiomaterials are as follows:

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Au NPs

Au NPs are one of the most important NPs in the biomedical fields and plays a very significant role within the field of nanomedicine, due to their excellent compatibility with human cells and tissues, low toxicity, size tunability, small dimensions, and their ability to interact with a variety of substances. The prominent application includes, cancer treatment using radio waves to heat and destroy tumour or cancer cells, targeted drug delivery, bio markers, anti-cancer therapy, contrast agent in medical imaging, molecular imaging in living cells, etc. [39, 41-44].

Ag NPs

Ag NPs are incorporated in various products that range from photovoltaics, photonics to biological and chemical sensor industries. They are highly conducting in nature with good physical and chemical stability. Due to their simplicity in synthesizing and holding a variety of biomedical applications, Ag NPs have been found in many therapeutic and medicinal applications. The biomedical applications of Ag NPs are: catalysis, bio-sensors, wound dressing, tissue engineering, anti-microbial activities, anti-bacterial activities, antifungal treatments, wound healing, implanted material, etc. [13, 36, 40-41, 45-47].

Gd NPs

Gd NPs are attractive positive contrast agent materials for magnetic resonance imaging (MRI) scanning. Doping Gd based NPs by luminescent lanthanides (Eu^{3+}, Tb^{3+}, etc.) led to fluorescent and paramagnetic NPs which can then be detected by both MRI and fluorescence imaging. They can act as effective radio sensitizers under different types of irradiation for radiotherapy, neutron therapy, etc. Liposomal-based Gd NPs have induced significant interest for use as blood pool and molecular MRI contrast agents. They are also used in Neutron Capture Therapy for treating tumorous tissues, anti-cancer treatments, imaging-guided drug delivery and monitoring the treatment[31, 48-51].

Fe_2O_3 NPs

Fe_2O_3 NPs also classified as Super Paramagnetic Iron Oxides NPs, finds numerous applications in biology, medicine and diagnostics. These NPs are easily functionalized and can be made biocompatible by conjugating ligands/proteins to their surface. Due to magnetic characteristics and very less bio-degradability, they are considered as a safe drug delivery system. These NPs find applications in contrast agent in medical imaging, ultra-sensitive molecular imaging, cancer treatment by hyperthermia, photothermal cancer therapy, targeted drug delivery, etc.[31, 41, 49-50, 52-53].

Cu NPs

Cu NPs are found to be used mainly in medical diagnosis, dental implants, detection of biomolecules, theranostics, anti-fungal activities, cancer imaging & therapy, photothermal ablation of tumour cells, molecular imaging, etc.[47, 54-55].

ZnO NPs

ZnO NPs exhibits unique semiconducting, optical, piezoelectric properties and are extensively used in a wide variety of applications. They possess low toxicity, biodegradability and are used to treat a range of different skin conditions. They have anticancer properties and can be used as an antibacterial agent in nanoscale formulation. In addition, ZnO NPs are found suitable in various applications *viz.* targeted drug delivery, biosensing, tumour detection, bioimaging, biomarkers, etc.[40, 47, 56-59].

Fe-Pt NPs

Fe-Pt NPs possess unique magnetic and chemical properties such as superparamagnetism, high coercivity, oxidation resistance, chemical stability, biocompatibility and are therefore gaining attention for biomedical applications. The prominent applications of Fe–Pt NPs in biomedical applications are found to be in, magnetic hyperthermia, contrast agents for MRI, anti-oxidant, drug delivery, cancer therapy, biosensors, etc.[60-62].

Se NPs

Se provides a wide range of applications in photovoltaics, electronics, electrical, biology and medicine. It is an essential micronutrient for animals and humans but with all the benefits, the toxicity of Se is always a crucial concern. Se NPs have emerged as a novel selenium source with the advantage of reduced risk of selenium toxicity with same bioavailability and efficacy. Biomedical applications of Se NPs include, drug delivery vehicles, intracellular analysis, anti-cancer therapy, etc. [63-65].

Pd NPs

Pd NPs are found to be an effective catalyst in a variety of chemical reactions. These NPs are used in various applications *viz.* chemical/biological sensing, environmental protection, biocatalysts, anti-microbial activities, targeted drug delivery, biosensors, etc. [66-69].

Toxicological effects

The novel properties exhibited by nanomaterials due to their size, geometry and chemical composition can also lead to precarious hazards to human health if not properly handled. It has been found that the cytotoxicity of quantum dots varies with their size and concentration. As the size of the quantum dots reduces, the cytotoxicity increases with the increase in concentration[70]. Some of the adverse effects to human health are reported as, mitochondrial damage, cell membrane and lysosome damage, a transition in mitochondrial permeability, uptake through the olfactory epithelium, platelet aggregation and cardiovascular effects [70-72]. A different methodology needed to be developed to handle their toxicology[73].

The environmental toxicity of gold NPs affecting humans, plants and animals, has always been one of the prime topics under investigation. It is assumed that Au NPs are generally inert as their bulk counterparts above 5 nm size [74]. But as the size is further reduced, the cytotoxicity of the Au NPs drastically increases. Pan et al. [75] prepared water soluble Au NPs stabilized by triphenylphosphine derivatives ranging in size from 0.8 to 15 nm. It was found that the cytotoxicity of surface-modified Au NPs depended primarily on their size and not on ligand chemistry. Particles having 1–2 nm sizes were found to be highly toxic and bigger (~15-nm) colloids were comparatively nontoxic, irrespective of the cell type tested. Recent studies have investigated the cytotoxic effects of Ag NPs on the human body, specifically on the respiratory and cardiovascular systems, osteoblasts and osteoclasts, DNA and embryo development malformations [76-77]. Beer et al. [78] found that the toxicity of Ag NPs depends on the silver ion fraction in the Ag NPs suspension. At high silver

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ion fraction, the toxicity levels in Ag NPs are least. However, at low silver ion fraction, the Ag NP suspension is more toxic than its supernatant. The iron oxide NPs though having tremendous biomedical applications, are not free from cellular damage associated with these NPs [79]. Dhakshinamoorthy et al. [80] studied the neuro-behavioural toxicity of Fe_2O_3 NPs in Mice. Due to redox potential, its exposure to living systems can cause deleterious effects. When adult male mice were treated with Fe_2O_3 NPs, a significant change in locomotor behaviour and spatial memory was observed. The damages to blood–brain barrier permeability by Fe_2O_3 NPs and their accumulation in brain regions were also recorded. The accumulated NPs when interact with biomolecules, causes deleterious effects on neuronal physiology resulting in behavioural changes. The study indirectly indicates the occurrence of neurodegeneration and behavioural changes in humans from exposure to Fe_2O_3 NPs. The increased use of ZnO NPs raises safety concerns about the toxicity of ZnO NPs when they interact with the biological environment. Reshma et. al. [81] studied the interaction of ZnO NPs with human embryonic kidney 293 (HEK 293) cells in vitro. As kidney plays a decisive role in NPs excretion, it was found that the cellular viability was much affected by ZnO NPs in a dose and time-dependent manner. When ZnO NPs interacts with HEK 293 cells, they produced reactive oxygen species, which affects both mitochondrial and lysosomal activity, leading to autophagy-type 2 programmed cell death.

Conclusions

The application of nanomaterials in the biomedical field and its toxicological effects have been reported in this review. NPs of desired dimensions are prepared using different physical, chemical and biological synthesis methodologies. The characterization techniques available provide an in-depth knowledge of the physical properties and chemical composition of the nanomaterials. The surface treatment of NPs makes them biocompatible and useful for several biomedical applications. On the other hand, these applications also raise the concerns about health and safety of the employees manufacturing nanomaterials, as well as of consumers. It was found that even the inert elements like Au showed a certain level of toxicity at very low dimensions. Though having risks and uncertainties, many nanomaterial-based products are available in the market and are growing day by day. The impact of nanomaterials on living organisms and environment must be broadly understood to explore its biomedical applications with minimizing detrimental effects.

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