Chapter 21

Overview of Nanoparticles and their Biomedical Applications

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ABSTRACT

The development and implications of nanoparticles synthesis is an emerging field that covers a wide range of applications. It plays a major role in the development of innovative methods to produce new products to suitable existing production equipment and to reformulate new material and chemicals. The nanoparticles are classified usually into organic, inorganic and carbon based on their nature. They can also be classified on the basis of dimension into zero, one, two and three-dimensional nanoparticles. Nanotechnology has been efficiently and successfully used in the field of biomedical sciences. Currently, hundreds of nanoparticles are known and have found their applications in cancer therapy, gene delivery, treatment of cardiovascular diseases, dentistry, drug delivery, molecular imaging, biosensors, orthopedic infection regenerative medicine and infectious diseases, etc. The following chapter deliberates on nanoparticles, their classification, their applications in the biomedical science, and future perspectives are also briefed.

KEYWORDS		
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INTRODUCTION

The current progression in the biomedical field is the result of the progress of the synthesis and application of nanoparticles. Nanoparticles also refer to as “zero-dimensional” nanomaterials, can be easily synthesized and modified so that they have new electronic, optical, magnetic, medical, catalytic, and mechanical properties. Such a powerful modification results in a high surface-to-volume ratio and quantum size effect, which depend greatly on their structure, size and shape (Khursheed et al., 2022). Nanoparticles are referred to as solid particles having a size within in the range of 10-100 nm. The nanocapsules and nanoparticles can be produced by using different preparation methods. The drugs are usually encapsulated, dissolved, entrapped, or attached to a nanoparticle matrix (Langer, 2000). Nanotechnology referred to the technology that is involved in the development and study of nanoscale-level matter their function and organization (Boulaiz et al., 2011; Jeevanandam et al., 2018). This chapter’s purpose is to highlight the major contributions of nanoparticles to modern medical science.

Background History

It is quite difficult to exactly date back to the era when nanosized substances were first utilized by humans. However, the history of utilization of nanomaterial is not new. It is evident that approximately 4500 years ago nanofibers had been used to stiffen a mixture of ceramics (Heiligtag and Niederberger, 2013). In 1959 during the annual meeting of the American Physical Society, the concept of nanotechnology was introduced by Richard Feynman an American Nobel Prize physicist in his speech. This was the first time when nanotechnology was discussed at the academic level (Langer, 2000). About 4000 years ago, lead sulphide (PbS) nanoparticles were used in hair-dyeing formula by ancient Egyptians (Walter et al., 2006; Jeevanandam et al., 2018). In the fourth century, Romans were producing the “Lycurgus Cup” which is a dichroic cup. In direct light, it looks like a jade (green gemstone) while under transmitted light it gives a luminous ruby color. The variations of color were due to the presence of silver and gold nanoparticles and incident light (Freestone et al., 2007). Nanotechnology is considered the most promising technology of the 21st century (Emerich and Thanos, 2003).

Need for Nanotechnology in Biomedical Science

The discoveries in the field of nanotechnology and nanomedicine are massive and widespread. Nano drugs have undergone remarkable modifications, pushing the creativeness of the drug to a novel level with noteworthy healthcare results. Still there is a significant need to study the substantial capabilities of nanotechnology in the healthcare sector. In medicine, wide-range research is conducted to find best practices and methods to be used in cancer therapy, nephrology, gene therapy and cardiovascular disease. Remarkable development and improvement in the traditional treatment, along with the improvement in the quality of nanotechnology and nanoparticles leads to stirring results (Vishwakarma et al., 2013; Keskinbora and Jameel, 2018).

Classification of Nanoparticles

The nanomaterials are classified on the basis of (a) nature and (b) dimension (Fig. 1).

Classification of Nanoparticles based on Nature

Based on nature, the nanoparticles typically fall into three categories which are the following

Organic Nanoparticles

Organic nanoparticles include liposomes, dendrimers ferritin and micelles etc. Organic nanoparticles have some unique characteristics such as they are nontoxic, biodegradable and some organic nanoparticles have a hollow core i.e. liposomes and micelles are which recognized as nanocapsules and are sensitive to heat and light (Tiwari et al., 2008). These unique properties make them a perfect choice for drug delivery systems. Organic nanoparticles are extensively used in the field of biomedical sciences for example in drug delivery system as well as in targeted drug delivery.

Inorganic Nanoparticles

Nanoparticles not made up of carbon are commonly known as inorganic nanoparticles. The inorganic nanoparticles are further categorized into metal based and metal oxide based inorganic nanoparticles.

Metal based

The synthesis of nano-sized particles from metals is known as metal based inorganic nanoparticles. Either constructive or destructive methods are used in the production of metal-based nanoparticles. Nearly the nanoparticles of all the metals can be synthesized (Salavati-niasari et al., 2008). Silver (Au), gold (Au), aluminium (Al), copper (Cu), lead (Pb), cadmium (Cd), zinc (Zn), iron (Fe) and cobalt (Co) are the most commonly used metals for the synthesis of the nanoparticle.

Metal Oxides based

The synthesis of nano sized particles from metal oxides is known as metal oxide based inorganic nanoparticles. Their synthesis modifies the properties of their particular metal-based nanoparticles. Iron oxide (Fe_2O_3) is one good example where under aerobic conditions, the iron (Fe) nanoparticles are instantaneously oxidized into iron oxide nanoparticles at room temperature. This conversion increases the reactivity of Fe_2O_3 nanoparticles compared to the Fe nanoparticles. Mainly due to high efficiency and increased reactivity metal oxide-based nanoparticles are synthesized (Tai et al., 2007). Iron oxide (Fe_2O_3), Zinc oxide (ZnO), Silicon dioxide (SiO_2), Aluminium oxide (Al_2O_3), Titanium oxide (TiO_2), Cerium oxide (CeO_2) and Magnetite (Fe_3O_4) commonly used metal oxides for the synthesis of nanoparticle

Carbon based

Entirely, carbon-made nanoparticles are recognized as carbon-based nanoparticles (Bhaviripudi et al., 2007). Carbon nano-tubes (CNT), carbon black, fullerenes, carbon nanofibers, graphene, carbon nanofibers and occasionally activated nano-sized carbon are included in carbon-based nanoparticles.

Classification of Nanoparticles based on Dimension

Nanoparticles have numerous dimensions. Siegel also classified nanoparticles on the basis of dimension into four types such as zero-dimensional, one-dimensional, two-dimensional and three-dimensional nanoparticles. (Jeevanandam et al., 2018).

Zero-Dimensional Nanoparticles

The nanoparticles that with no dimension larger than 100 nm (nanoscale) are known as zero-dimensional nanoparticles. They are the most common type of nanoparticles. These are small point-like particles. The most common examples include Quantum dots, nano lenses and hollow spheres (Jeevanandam et al., 2018).

One-Dimensional Nanoparticles

The nanoparticles having at least one dimension that is larger than 100 nm (nanoscales) while other dimensions are within nano scale range are known as one-dimensional nanoparticles. The most common examples include nanotubes, nanofibers and nanorods (Jeevanandam et al., 2018).

Two-Dimension Nanoparticles

The nanoparticles having two dimensions that are larger than 100 nm (nanoscales) while other dimensions are within nano scale range are known as two-dimensional nanoparticles. The most common examples include nanocoating, nanofilms and nanolayers (Jeevanandam et al., 2018).

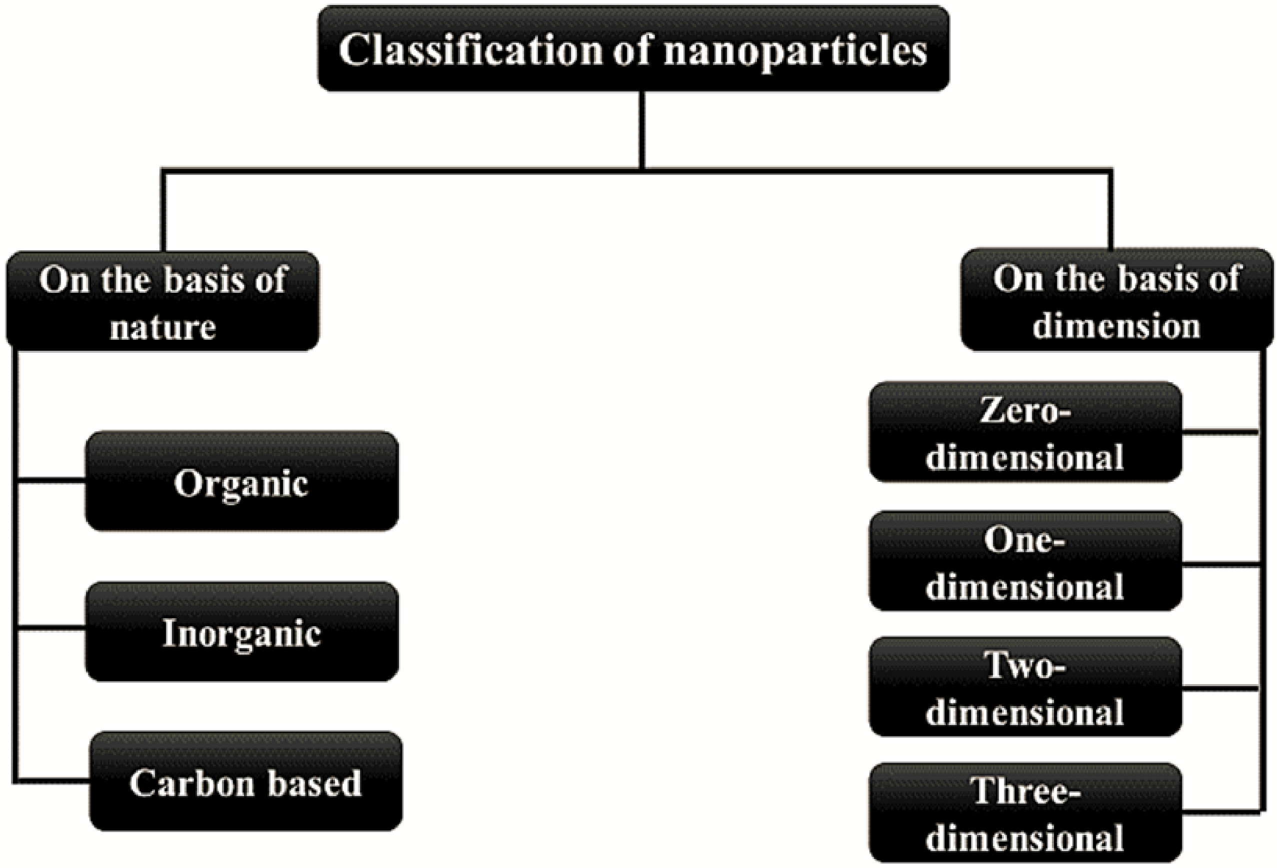

Fig: 1: Classification of nanoparticles

Three-Dimensional Nanoparticles

The nanoparticles having three dimensions that are larger than 100 nm (nanoscales) while other dimensions are within nano scale range are known as two-dimensional nanoparticles. These particles have numerous applications and are usually nonporous. The most common examples include multi nano-layer type structure, nanocomposites and bundles of nanofibers (Jeevanandam et al., 2018).

Applications of Nanotechnology in Biomedical Science

Nanoparticles have a large number of applications in the biomedical field (Table. 1). Some of these applications are discussed here.

Nanoparticles used in Cancer Therapy

In clinical trials, the nanomedicines used for the cancer treatment are considered to be the most important application (therapeutic) of nanoparticles among others. Many different formulations of nanoparticles are clinically approved to be used in the treatment of various cancers at different stages.

Remarkably, all of these systems but one such as Abraxane are liposomal systems that encapsulate an ant cancerous drug. The first cancer nanomedicine approved by FDA, in 1995 was Doxil. It was a PEG (polyethylene glycol) liposomal doxorubicin formulation (Barenholz, 2012). Soon after this, other formulations of liposomes were approved by the Food and Drug Administration (FDA) such as liposomal vincristine (Marqibo), liposomal daunorubicin (DaunoXome), and most new liposomal irinotecan (Onivyde) (Fox, 1995; Silverman and Deitcher, 2013; Carnevale and Ko, 2016). While non-PEGylated liposomal mifamurtide (MEPACT) and liposomal doxorubicin (Myocet) were approved by the European Medicines Agency (EMA) (Leonard et al., 2009; Ando et al., 2011). Abraxane, a paclitaxel albumin-bound nanoparticle is recently approved lone nonliposomal nanoparticle system for the treatment of cancer nanoparticles (Miele et al., 2009). Except, for Doxil and Onivyde most of these drugs formulations are not PEGylated (Chang et al., 2015; Otsuka et al., 2003; Suk et al., 2016; Gref et al., 1994). Furthermore, despite preclinically proven advantages of active targeting, all of these drug formulations are passively targeted, having no chemical or active based targeting moieties; (Wang et al., 2012; Byrne et al., 2008; Peer et al., 2020). It is expected that the other advantages, especially their reduced toxicity restricting their ability to specially accumulate at the site of the tumor and limit side effects on non-target area through the enhanced permeation and retention (EPR) effect (Maeda, 2012).

Nanoparticles in Gene Delivery

In the case of polynucleotide-based vaccines, the relevant genes are delivered, encode a specific antigen to the host cells, expressed and produce antigenic protein within the locality of original antigen presenting cells to trigger immunological response (Gurunathan et al., 2000). However, the applications of polynucleotides have been limited due to numerous issues associated with their delivery. Plasmid DNA-loaded nanoparticles could also serve as an effective sustained release gene delivery system because of their speedy escape to the cytoplasmic potion from the degradative endo-lysosomal portion (Panyam et al., 2002). This strategy of gene delivery could be applied to enable bone healing by using poly (lactic-co-glycolic acid) (PLGA) nanoparticles comprising therapeutic genes i.e. bone morphogenic protein (Hadley et al., 1998).

Nanoparticles used in the Treatment of Cardiovascular Diseases

Several kinds of nanoparticles are broadly utilized in the site-specific delivery of cardioprotective drugs for the treatment of cardiovascular diseases (CVDs). Gold (Au) nanoparticles are one among them. They have extensively used nanocarriers for the delivery of drugs (cardioprotective) to treat CVDs (Zhang et al., 2018). Clinical drugs are reported to have high efficacy and accuracy in combined form. One such example is combine cardioprotective effect of gold nanoparticles and simdax are far superior to their effect (Spivak et al., 2013). Liposomes, spherical nanoparticles have a bilayer structure composed of natural lipids or synthetic cholesterol. Biological benefits and delivery systems can be improved by using them in conjugated form with peptides or proteins (Mufamadi et al., 2011; Maurer et al., 2001). The first FDA-approved liposomal therapeutic drug prescribed to patients is Doxil (Liposomal doxorubicin). It is used in the treatment of different types of cancers (Hamilton et al., 2002). A study conducted by Basu (2018) reported that in cardiac grafting starburst dendrimers can be used for genes transfer (DNA or RNA).

Nanoparticles in Dentistry

Teeth are present inside the buccal cavity and consist of different parts like enamel, pulp, dentin, cementum, and periodontal ligament. The teeth are used to cut and crush food thus, aiding the process of swallowing and digestion (Tortora and Derrickson, 2018). In dentistry, nanotechnology using nanoparticles acts as a promising approach that can help in the prevention, shortening of treatment duration and in the eradication of oral related problems i.e. dental caries, periodontal disease, oral candidiasis, and hyposalivation (Ghafar et al., 2020). Typically, the fluoride level in the buccal cavity is greatly increased by using nanoparticles of calcium fluoride (CaF_2NPs). According to Kulshrestha et al. (2016) CaF_2NPs inhibit exopolysaccharide production by *Streptococcus mutans*. Nanotechnology is capable of overcomig such complications (Niemirowicz et al., 2017). Periodontal is an infectious disease that occurs due to the imbalancement between the colonization of pathogenic bacteria and the immune response of the host toward infection (Bao, 2018). Azithromycin and clarithromycin conjugated with silver nanoparticles are reported to have an efficient synergistic effect against microorganisms that cause periodontal infection (Emmanuel et al., 2015).

Nanoparticles in Drug Delivery

Nanoparticles and nanomaterials are progressively being sightseen for their possible applications in the field of medicine. Drug delivery is one such promising application. Nanoparticles are used as carriers in delivering of drugs to precise cells or tissues in the body. Nanoparticles can be engineered, having particular surface properties, enabling them to target diseased cells selectively and avoid healthy cells. Thus, increasing their efficiency and decreasing the side effects of drugs (Huang et al., 2010). In the research field, the widely used nanoparticles for therapeutic purposes comprise encapsulated mRNA (siRNA) or DNA (in gene therapy), metal complexes and inorganic metal, or chemotherapeutic agents with pharmacological capabilities (Khurana et al., 2019; Sharma et al., 2022).

Nanoparticles in Molecular Imaging

In molecular imaging, nanoparticles have great potential and formed a new set of diagnostic tools (Jokerst et al., 2011). There are different molecular imaging (MI) techniques, comprising of magnetic resonance imaging, ultrasound imaging, optical imaging, computed tomography and nuclear imaging and imaging with theranostics nanoparticles. The efficacy of ultrasound therapy can be enhanced by using distinct sound-active materials such as nanoparticles (Janib et al., 2010). From a clinical view, magnetic resonance imaging (MRI) is one of the most significant and non-invasive diagnostic tools for monitoring of disease (Shubayev et al., 2009). Currently, a multipurpose liposome incorporated with gadolinium-DOTA (MRI distinct agent) functionalizing with anticancer drugs such as $\alpha v\beta 3$ integrin (targeted peptide) and paclitaxel was developed by the Xin Zhou group (Ren et al., 2015). Computed tomography (CT) is a documented and widely used technique that permits spatial imaging of tissues, providing comprehensive visualization of anatomy. Korean researchers designed gold nanoparticles (GNP) designed for the immediate therapy and imaging of prostate cancer (Kim et al., 2010).

Nanoparticles as Biosensors

Various types of nanoparticles are used as biosensors components. Mostly they work as probes identifying, and discriminating an analytical interest for screening and diagnostic purposes. Such approaches involve the attachment of nanoparticles with biological molecular species through an exclusive modification process. The probes are used to bind with the sample and also signal the target's presence on the basis of their mass, color and other physical properties. Quantum dots, metallic nanobeads, nanobarcodes, carbon nanotubes, magnetic beads and silica nanoparticles-based biosensors are capable of to be skilled to the nanoprobe's group. Some other biosensors use nanoparticles in a different way (Kubik et al., 2005).

Table 1: Applications of nanoparticles in biomedical sciences

Nanoparticle	Application	Reference
Silver nanoparticles	Reduce orthopaedic infections	Jeyaraman et al., 2023
	High potential for use in the treatment of anticancer, antidiabetic	Stasyuk et al., 2016
	Antifungal activity against *Puccinia graminis tritci, Aspergillus flavus, Aspergillus niger* and *Candida albicans*	Terentyuk et al., 2014
	Antibacterial activity against *Escherichia coli*	Seo et al., 2014
	Used to treat urinary tract infections (UTI)	Jacob et al., 2011
	Antibacterial activity against Gram-negative and Gram-positive bacteria	Thakkar et al., 2010
Gold nanoparticles	Used in prostate cancer's therapy and imaging	Kim et al., 2010
Poly(butylcyanoacrylate)	Enable drug delivery to brain by crossing Blood-brain barrier (BBB)	Kreuter, 2004
Liposome	Deliver siRNA to the tumor tissues	Ozpolatet al., 2014
	Used to treat hepatitis B and hepatic fibrosis	Bobbin and Rossi, 2016
	Enable drug delivery to brain by crossing Blood-brain barrier (BBB)	Sato et al., 2008 Pardridge, 2005
Silver nanoparticles in glass ionomer cements (NanoAg-GIC)	Antibacterial properties Inhibit growth of *E. coli* and *S. mutans*	Paiva et al., 2018
Silver and zinc oxide nanoparticles	Inhibit growth of *Mycobacterium tuberculosis*	Jafari et l., 2016
Zinc oxide	Used to treat a respiratory infection caused by *Klebsiella pneumonia*	Reddy et al., 2014
Aptamers and Au nanoparticle modified Morin pH-sensitive liposome (AptAu@MSL)	Used in targeted drug delivery for cancer treatment	Ding et al., 2020
Gold nanoparticle (Au NPs) conjugated Gentamicin	Used to treat of serious kind of microbial infection	Yeluri et al., 2015
Gold nanoparticle (Au NP) conjugated everolimus	Used in Bronchiolitis obliterans syndrome to inhibit proliferation and increasing mesenchymal cell's apoptosis	Meloni et al., 2014
Abraxane (albumin-based nanoparticle)	Used in the treatment of breast cancer	Kadri et al., 2024 Miele et al., 2009
Abraxane in combination with narmafotinib and gemcitabine	Used in pancreatic cancer therapy	Cock et al., 2024
Pegylated Liposomal Doxorubicin (Doxil®)	Used in the treatment of ovarian and breast cancer	Perez et al., 2002 Barenholz, 2012
Simdax, conjugated on Au nanoparticles	Cardioprotective effect against doxorubicin-induced heart failure in rats	Spivak et al., 2013
Liposomal vincristine (Marqibo), liposomal daunorubicin (DaunoXome), liposomal irinotecan (Onivyde)	Used in cancer treatment	Silverman and Deitcher, 2013 Carnevale and Ko, 2016
Plasmid DNA loaded nanoparticles	Used in gene delivery	Panyam et al., 2002
Dendrimers	Used to transfer in cardiac grafting	Basu, 2018
Quercetin loaded PLGA nanoparticles	Used to prevent CVDs	Zhang et al., 2018
Calcium fluoride nanoparticles	Inhibit exopolysaccharide production by *Streptococcus mutans*	Kulshrestha et al., 2016

Nanoparticles in Orthopedic Infection

In orthopaedic infections, unreasonable and continued use of antibiotics is a major threat that leads to the development of antimicrobial resistance. In the field of orthopaedics, implant infections can be reduced by silver nanoparticles (AgNP) (Jeyaraman et al., 2023). The orthopaedic implants have been modified by using silver nanoparticles that increases antimicrobial effects through various processes i.e. plasma electrolytic oxidation, plasma immersion ion implantation (PIII), 3DP-Ag-containing scaffolds and magnetron sputtering (Qing et al., 2018).

Nanoparticles in Infectious Diseases

The diseases caused by bacteria, viruses, fungi and parasites are known as infectious diseases. Globlly, many deaths occurred due to these infectious diseases. The treatment and control of these infectious diseases are difficult as they undergo drug resistance (Fauci and Morens, 2012; Morens and Fauci, 2013; Parrish et al., 2008). Metal-based nanoparticles, have been utilized to treat infectious diseases. Metal-based nanoparticles are usually small-sized ranges between 10–100 nm enabling their efficient interaction with biomolecules on the surface of cell or inside the cell (Mody et al., 2010).

Mycobacterium tuberculosis, a bacterium causes an infectious disease of lungs known as Tuberculosis. The use of antibiotics against tuberculosis for extended period of time leads to drug resistance thus, hindering treatment. The growth rate of *Mycobacterium tuberculosis* can be inhibited by using mixture of silver and zinc oxide nanoparticles (Reddy et al., 2014).

Conclusion

The future potential of nanotechnology in the sector of medicine and healthcare is very vast. This technology has revolutionized our mode of diagnosis, treatment and disease preventions. In nanotechnology the materials are manipulated at a very small scale substantially varying the properties of materials from their bulk complements, enabling specific control of their biological, physical and chemical properties. Thus, opening new ways for the development of innovative therapies, highly sensitive diagnostic tools and targeted drug delivery systems. Moreover, nanoparticles can also be used to increase the efficiency of current drugs by enhancing their stability, bioavailability and solubility, stability. Furthermore, devices and sensors that are nanotechnology-based can be used in monitoring the health of patient in real-time, allowing early detection and improved personalized treatment plans. In the future, nanotechnology may even develop nanorobots that can move through the bloodstream, navigate the target and cause the destruction of cancer cells or deliver a precise load of drugs at a specific tissue.

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