ISSN: 0976-3031

Available Online at http://www.recentscientific.com

CODEN: IJRSFP (USA)

International Journal of Recent Scientific Research
Vol. 8, Issue, 7, pp. 18216-18226, July, 2017

International Journal of Recent Scientific Research

DOI: 10.24327/IJRSR

Review Article

APPLICATIONS OF NANOTECHNOLOGY IN MEDICINE AND HEALTHCARE: A REVIEW

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DOI: http://dx.doi.org/10.24327/ijrsr.2017.0807.0471

ARTICLE INFO

Article History:

Received 17th April, 2017
Received in revised form 21th May, 2017
Accepted 28th June, 2017
Published online 28th July, 2017

Key Words:

Nanotechnology, Medicine, Imaging, diagnostics, cancer, Nanomaterial.

ABSTRACT

Nanotechnology refers to research and technology development at the nanoscale. Objects at this scale, such as "nanoparticles," take on novel properties and functions that differ markedly from those seen in the bulk scale. The small size, improved solubility, large surface to mass ratio and multifunctionality of nanoparticles open many new research vistas for biologists. The novel properties make these materials superior; crucial in many areas of human activity. This rapidly growing field allows cross-disciplinary researchers the opportunity to design and develop multifunctional nanoparticles that can target, diagnose, and treat diseases such as cancer. Current modalities of treatment and diagnosis of various diseases, especially cancer have major limitations such as drug resistance or drug toxicities and poor sensitivity or specificity respectively. Newer and improved methods of cancer detection and treatment based on nanoparticles are being developed. In this review, a brief sketch of various kinds of nanomaterials and their role in molecular diagnosis, drug targeting, and development of nanomedicine is discussed.

INTRODUCTION

Recent years have witnessed that nanotechnology has revolutionized the field of medicine where improved and often physical, chemical, and biological properties of materials at the nanometer scale are used to diagnose and treat major ailments such as cancer (LaRocque *et al*., 2009), heart (Schoenhagen and Conyers, 2008), lung, and blood diseases (Buxton, 2009). Drug delivery (Farokhzad and Langer, 2009), reactive oxygen species (ROS) quenching (Krusrc *et al*., 1991, Lucente-Schultz *et al*., 2009), and targeted imaging (Lucignani, 2009) have been some of the major areas of focus in nanomedicine (Riehemann *et al*., 2009). Nanomedicine, a combinatorial approach using nanotechnology and medicine, has become an increasingly important field of research for diagnostics and theranostics (Medina *et al*., 2007, Allhoff, 2009, Sitharaman *et al*., 2007, Caruthers *et al*., 2007).

Nanotechnology is defined as the "intentional design, characterization, production, and applications of materials, structures, devices, and systems by controlling their size and shape in the nanoscale range (1 to 100 nm)" (British Standards, 2007). Nanomaterials are similar in scale to naturally occurring functional units or components of living organisms and, for this reason, enable more effective interaction with biological systems and can be engineered to perform various functions. Nanomaterials are now being designed to aid the targeted transport of diagnostic or therapeutic agents through biologic barriers; to gain access to molecules; to mediate molecular interactions; and to detect molecular changes in a sensitive, high-throughput manner and to provide other tools in the field of molecular biology.

The reason why these nanoparticles are attractive for medical purpose is based on their important and unique features, such as their size, their surface to mass ratio that is much larger than that of other particles and their quantum properties. Size, of course, is the key. Nanoparticles smaller than 20 nm can transit through blood vessel walls. Magnetic nanoparticles, for instance, can image metastatic lesions in lymph nodes because of their ability to exit the systemic circulation through the permeable vascular epithelium (Bogdanov Jr *et al*., 2005). Nanoparticles also offer the ability to penetrate the blood-brain barrier or the stomach epithelium (Vinogradov *et al*., 2004, Kreuter, 2004, Russell-Jones *et al*., 1999)- barriers that make it difficult for legacy therapeutic and imaging agents to reach their intended targets. Whereas larger drug particles are rapidly filtrated by the spleen, with filaments spaced at roughly 200 nm, which serve as a meshwork for phagocytotic cells (Chen and Weiss, 1973).

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Similarly, to traverse the liver, the particles must be small enough to pass through the organ's 150-200 nm-sized fenestrae and avoid the Kupffer cell-lined sieve plates (Braet *et al*., 1995). Drug-carrying liposomes are believed to have increased life spans, related in part to their ability to extravasate through splenic and liver fenestrae (Moghimi *et al*., 2001).

Nanomaterials have a relatively large ratio of surface area to volume, which may be orders of magnitude greater than that of macroscopic materials, therefore, are more chemically reactive (2008). Cutting a 1-cm cube into 1021 cubes that are each 1 nm on a side will result in the same overall volume and mass, but the surface area will be increased by a factor of 10 million. Thus, the advantage of using nanomaterials as carriers is that their surface can be coated with many molecules.

In addition, unique aspects of metal-containing materials with at least one dimension that is smaller than 100 nm are their electrical and strength properties as the quantum effects dominate the behavior of materials with respect to their optical, electrical, and magnetic properties. This relationship is a direct consequence of the behavior of electrons in the nanomaterial. These properties are being incorporated into new generations of drug-delivery vehicles, contrast agents, and diagnostic devices, some of which are currently undergoing clinical investigation or have been approved by the Food and Drug Administration (FDA) for use in humans.

Biocompatible nanomaterials promising for healthcare applications

In recent times, the focus of nanoscience and nanotechnology research has gradually shifted from the development of high-quality nanomaterials and investigation of their properties to application side. A handful of nanomaterials are being studied in clinical trials or have already been approved by the FDA for use in humans (Peer *et al*., 2007, Davis *et al*., 2010) and many proof-of concept studies of nanomaterials in cell-culture and small-animal models for medical applications are under way (Sperling *et al*., 2008, Resch-Genger *et al*., 2008, Liu *et al*., 2008). Many of these nanomaterials are designed to target tumors in vivo and are intended for use either as drug carriers for therapeutic applications, tissue regeneration, reproductive health or as contrast agents for diagnostic imaging. Nanomaterials infused into the bloodstream can accumulate in tumors owing to the enhanced permeability and retention (EPR) effect when the vasculature of immature tumors has pores smaller than 200 nm, permitting extravasation of nanoparticles from blood into tumor tissue (Hobbs *et al*., 1998). The infusion of antineoplastic drugs with nanomaterials as carriers results in an increased payload of drugs to the tumor, as compared with conventional infusion. Thus, the use of nanomaterials for drug delivery may minimize adverse effects by preventing the nonspecific uptake of therapeutic agents into healthy tissues (Prencipe *et al*., 2009, Alexis *et al*., 2008). More specific tissue targeting ("functionalizing") of nanomaterials can be achieved by the conjugation of the nanoparticle with a ligand, e.g. monoclonal antibodies (Torchilin *et al*., 1994).

With nanomaterials, the high ratio of surface area to volume permits high surface loading of therapeutic agents; in the case of organic nanomaterials, their hollow or porous core allows encapsulation of hundreds of drug molecules within a single carrier particle. When the carrier particle degrades, the drug molecules are released, and the rate of degradation can even be controlled and fine-tuned according to the polymer composition. These nanomaterial delivery vehicles can also be coated with polymers, such as polyethylene glycol, to increase their halflife in the blood circulation, prevent opsonizing proteins from adhering to the nanomaterial surface, and reduce rapid metabolism and clearance

In recent years, studies on nanomaterials for various applications in the field of biomedical sciences have seen a significant increase. Although a plethora of nanomaterials are currently being investigated in the rapidly emerging field of nanomedicine but it is beyond the scope of this review to attempt a detailed discussion of all nanomaterials that are being studied for developing intelligent therapeutic and diagnostic systems. In this review, we attempt to provide an overview of our current knowledge about the key nanomaterials biocompatible for biomedical application, especially their potential in theranostics.

Liposomes

In the last decade or two, liposomes have attracted significant attention as potential drug carriers from researchers interested in the field of nanomedicine. These thermodynamically stable supramolecular structures are formed spontaneously when amphiphilic lipids are brought into contact with an aqueous phase. Once formed, liposomes are typically between 20 nm to 10 mm in size with the phospholipid bilayer membrane being approximately 5 nm in thickness (Jesorka and Orwar, 2008). The unique architecture of liposomes allows for the loading of hydrophobic and hydrophilic therapeutic molecules; their charge and surface properties can be tuned to enable stability during storage, control over the drug-release rate, and to meet specific therapeutic needs (Torchilin, 2005) (Fig.1A). These nanocarriers are also biocompatible, since they are typically made from lipids commonly found in biological systems and biodegradable via the usual metabolic pathways. As such, the high biocompatibility and versatile nature of liposomes have made these nanocolloids key components in biomedical research. The main component of liposome membranes is dipalmitoyl phosphatidyl choline (DPPC). In principle, liposomes can be prepared using PC only (Woodle and Papahadjopoulos, 1989). However, some other compounds are added in order to improve stability or other structural properties. Two compounds are generally added: dipalmitoyl phosphatidyl glycerol (DPPG) and cholesterol. Apparently, cholesterol has the effect of making the membrane less permeable by filling up holes or disruptions.

Liposomal doxorubicin (DaunoXome) was first used as a treatment for Kaposi's sarcoma, a cancer often associated with AIDS (Bergin *et al*., 1995). Doxorubicin had been around as a cancer drug since the 1960s but its encapsulation in a liposome carrier was new. PEGylated liposomal doxorubicin Doxil) has shown better efficacy and safety as compared to conventional preparations in breast cancer treatment both as monotherapy and in combination with other chemotherapeutics (Gregoriadis, 1995). Recently a multicomponent liposome consisting of doxorubicin and antisense oligonucleotide targeted to MRP 1 mRNA and BCL 2 mRNA to suppress pump resistance and non pump resistance have been developed (Gabizon *et al*., 2003).

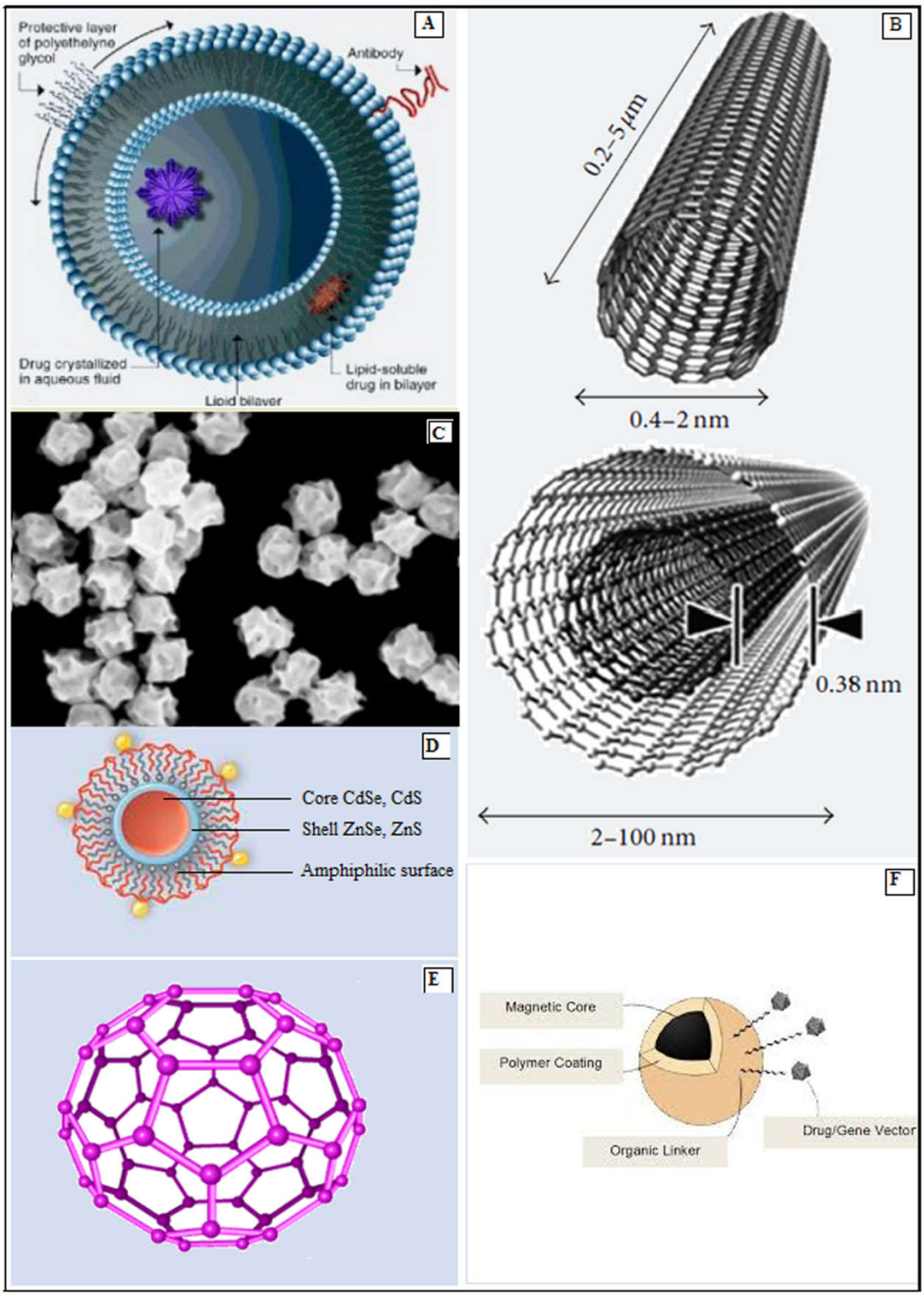

Figure1 Nanomaterials Commonly Used in Medicine. (A) Unilamellar liposomes (B) Conceptual diagrams of single-walled carbon nanotubes (SWCNT) and multi-walled carbon nanotubes (MWCNT) (C) SEM image of gold nanoparticles (AuNPs) (D) Quantum dots consist of a core-and-shell structure (e.g., CdSe [red] coated with zinc and sulfide [blue] with a stabilizing molecule and a polymer layer coated with a protein [yellow structures]). (E) Fullerenes (F) Magnetic naoparticle

Metal nanoparticles

These nanostructures exhibit significantly novel and distinct chemical, physical, and biological properties, and functionality due to their nanoscale size. The preparation of metalic nanoparticles offers several challenges.

There is not a one-fits-all type of production process for nanoparticles and most procedures will differ and depends on the chemical and physical characteristics required in the final product such as size, dispersion, chemical miscibility, optical properties, and so on (Sun and Xia, 2002). The range of procedures to prepare metal NPs and films include chemical

reduction method, electrochemical, hydrothermal, photochemical, sonochemical, chemical vapor deposition, physical vapor deposition, and so on.

Noble metal nanostructures, such as gold and silver, have attracted much attention due to their unique photo-thermal, chemical, and optical properties (Jain *et al*., 2008). Owing to their nanometer size, they exhibit large surface-to-volume ratios that can be leveraged in therapeutic delivery applications. The surface of gold (AuNPs) and silver (AgNPs) nanostructures is also Chemically reactive allowing for facile functionalization with various biological stabilizing agents, biomolecules, and chemotherapeutic agents (Fig.1C).

One of the most promising applications of AuNPs in biotechnology and biomedicine is their use as drug delivery vehicles. The drug delivery properties of AuNPs are a function of their sizes and surface chemistries. The nanometer scale of AuNPs allows these three-dimensional and diffusible self-assembled monolayers to act as substructures for supramolecular assemblies, to extravasate from tumor-supplying endothelia, and to undergo cellular uptake by endocytosis. Aurimmune (CytImmune Sciences), which consists of 27-nm gold nanoparticles coated with recombinant human tumor necrosis factor alpha (TNF-α) and polyethylene glycol, demonstrated safety and tolerability in recent phase I clinical trials and is under investigation in phase 2 clinical trials (ClinicalTrials .gov numbers, NCT00356980 and NCT00436410) for the treatment of patients with a variety of advanced or metastatic cancers who are no longer responsive to conventional treatment. Histopathological studies have shown that these nanoparticles are localized within or around the tumor, with fewer uptakes into healthy organs than is seen with the direct injection of TNF-α. The use of cytokines such as TNF-α is limited by the inflammatory responses they produce, especially when tissues are exposed to high doses. With intravenous injection of Aurimmune, patients are able to tolerate 20 times the usual dose of TNF-α (Libutti *et al*., 2007, Visaria *et al*., 2006).

Particle size is an important parameter when considering designing an effective Drug delivery system as only particles measuring less than 10 nm were observed within nucleus, while the larger particles were aggregated in the cytoplasm (Huang *et al*., 2012). Moreover, ultra-small nanoparticles successfully delivered anticancer drugs such as doxorubicin (Dox) into the nucleus of cancer cells and it was found to be an effective delivery system for treatment of resistant cancer cells (Zhang *et al*., 2010a).

In addition to drug delivery, AuNPs offer promising platforms for non-viral gene delivery and subsequent gene regulation (i.e., gene therapy). AuNPs can potentially help circumvent some of the barriers presented with gene delivery, including cell membrane penetration, avoiding enzymatic degradation, and efficient delivery of the intact gene to the nucleus (Wiethoff and Middaugh, 2003).

Strong light absorbing property of gold nanoparticles makes them suitable as heat-mediating objects; the absorbed light energy is dissipated into the particles' surrounding medium, generating an elevated temperature in their vicinity. The ability for these particles to heat the surrounding medium upon excitation, along with the sensitivity of cancer cells to hyperthermia, is exploited in the cancer treatment method of plasmonic photothermal therapy (PPTT) where the malignant cells are destructed by heating the particle-loaded tissue (Huang *et al*., 2006, NolsÃ¸e *et al*., 1993). For example, gold nanoshells, which comprise a silica core coated with a thin layer of gold, are being used for the treatment of recurrent head and neck tumors. Human pilot studies for the treatment of head and neck tumors were set to be completed by Dec 2013 (NCT00848042), In this application, the nanoshells are injected into the tumor and then illuminated with 700-nm to 800-nm light. Electrons excited by these wavelengths interact with the surrounding water molecules, causing localized heating and subsequent cell death (Hirsch *et al*., 2003). Trials investigating the ablation of atherosclerotic plaques have also been conducted (NCT01436123, NCT01270139). Interestingly, tumor-specific laser exposure has also been used to augment the tissue-specific accumulation of gold nanorods in tumor-bearing mice; this method has yet to be explored in a clinical setting (Shiotani *et al*., 2010). This effect can also be used to open polymer microcapsules, for example, for drug delivery purposes.

Owing to their characteristic Localized surface plasmon resonance (LSPR), Gold Nanoparticles are used in lateral-flow in vitro diagnostic assays (LFA), such as the urine pregnancy test for detecting protein markers (e.g., human chorionic gonadotropin [hCG]) (Posthuma-Trumpie *et al*., 2009). Their optical properties can change upon binding to certain molecules, allowing the detection and quantification of analytes.

Additional applications of AuNP-based lateral flow assays include measuring human immunodeficiency virus (HIV), malaria, and cardiac markers are also available.

Gold nanoparticles are also used in high-throughput genomic detection devices without the need for polymerase-chain-reaction (PCR) amplification but with a sensitivity similar to that of PCR-based assays (Nam *et al*., 2003). This technology uses oligonucleotide-functionalized gold nanoparticles to detect genomic DNA, RNA, or proteins from complex media based on Ag amplification and optical scattering from particles bound to oligonucleotide arrays. This method has been approved to determine drug sensitivity and to detect genetic mutations. One particular application is in screening for single-nucleotide polymorphisms of the factor V and factor II genes and the 5,10-methylenetetrahydrofolate reductase gene, in which the mutations are related to thrombophilia and hyperhomocysteinemia (Lefferts *et al*., 2009).

Like their Au counterparts, Ag nanostructures (AgNPs) have been extensively used in therapeutic applications (Chaloupka *et al*., 2010). One of the most investigated applications is related to their antimicrobial activity. Since Ag compounds have readily been used in antimicrobial applications, many groups have begun investigating the antimicrobial activity of AgNPs (Rai *et al*., 2009, Sharma *et al*., 2009). AgNP have also been used in wound dressings to promote wound healing. Quickened wound healing ability is a result of the AgNPs' antimicrobial activity as well as a reduction in local and systemic inflammation through cytokine modulation, specifically IL-6, TGF-β1, IL-10, VEGF, and IFN-γ. AgNPs have also demonstrated antiviral activity against herpes

simplex virus type 1 (HSV-1), the influenza virus, and the hepatitis B virus (Baram-Pinto *et al*., 2009, Xiang *et al*., 2011, Gaikwad *et al*., 2013) and are under investigation.

Magnetic nanoparticles

Magnetic nanoparticles are a class of nanoparticles which can be manipulated using magnetic field. Such particles commonly consist of magnetic elements such as iron, nickel and cobalt and their chemical compounds. Magnetic nanoparticles are a powerful and versatile diagnostic tool in biology and medicine. It is possible to incorporate sufficient amounts of superparamagnetic iron oxide nanoparticles into cells, enabling their detection in vivo using magnetic resonance imaging (MRI) (Bulte *et al*., 2004).

Magnetic nanoparticles offer some attractive possibilities in biomedicine. Magnetic nanoparticles serve in magnetic drug delivery system which works on the delivery of magnetic nanoparticles loaded with drug to the tumor site under the influence of external magnetic field. MNPs in combination with an external magnetic field and/or magnetizable implants allow the delivery of particles to the desired target area, fix them at the local site while the medication is released, and act locally (magnetic drug targeting) (Kwon *et al*., 2007). Transportation of drugs to a specific site can eliminate side effects and also reduce the dosage required. The surfaces of these particles are generally modified with organic polymers and inorganic metals or oxides to make them biocompatible and suitable for further functionalization by the attachment of various bioactive molecules (Gupta *et al*., 2007) (Fig.1F).

Chen *et al*. developed a magnetic drug delivery system in which doxorubicin (DOX) was chemically bonded to Fe_3O_4 nanoparticles (Chen *et al*., 2010). This complex was then embedded in a polyethylene glycol (PEG) functionalized porous silica shell (Fe_3O_4-DOX/pSiO_2-PEG). The presence of a porous silica shell not only provided a protective layer for drug molecules and magnetite nanoparticles, but also created a thin barrier for the DOX release from the carrier. Hence this composite magnetic drug delivering system exhibited a slower release of DOX than seen in DOX-conjugated Fe_3O_4 nanoparticles alone. In addition, biocompatible polymer PEG, allowed this complex to escape reticuloendothelial system, thus allowing drugs to be administered over prolonged periods of time.

Magnetic nanoparticle technology also offers the potential to achieve selective and efficient delivery of therapeutic genes by using external magnetic fields. As compared to traditional gene delivery strategies, magnetic drug delivery system has been shown to significantly increase gene delivery to human xenograft tumors models. This implies that they therefore have potential to turn the challenge of gene therapy in vivo into a new frontier for cancer treatment (Li *et al*., 2012).

The magnetic nanoparticles can be made to resonantly respond to a time-varying magnetic field, with advantageous results related to the transfer of energy from the exciting field to the nanoparticle. For example, the particle can be made to heat up, which leads to their use as hyperthermia agents, delivering toxic amounts of thermal energy to targeted bodies such as tumors (Bulte *et al*., 2004). In past studies, magnetite cationic liposomal nanoparticles and dextran-coated magnetite (Wang *et al*., 2008) have been shown to effectively increase the temperature of tumor cells for hyperthermia treatment in cell irradiation. This has been proposed to be one of the key approaches to successful cancer therapy in the future (Green, 2005). The advantage of magnetic hyperthermia is that it allows the heating to be restricted to the tumor area. Moreover, the use of subdomain magnetic particles (nanometer-sized) is preferred instead multidomain (micron-sized) particles because nanoparticles absorb much more power at tolerable AC magnetic fields (Jeong *et al*., 2007) which is strongly dependent on the particle size and shape, and thus, having well-defined synthetic routes able to produce uniform particles is essential for a rigorous control in temperature.

Nanoparticles are also attractive as sensitive contrast agents for cancer imaging. On nanoparticle- enhanced MRI, a contrast can be observed between tissues with and those without superparamagnetic iron oxide nanoparticles (SPIONs), owing to a difference in the precession frequency of the protons. In one study, dextran-coated SPIONs were injected into patients with prostate cancer to detect possible lymph-node metastases (Jeong *et al*., 2007). The dextran coating increased the circulation time of the nanoparticles, and because of their small size, these particles could traverse the lymphatic vessels to reach the lymph nodes and be taken up by the resident macrophages. The use of SPIONs with MRI, as compared with conventional MRI, was associated with substantial increases in both diagnostic sensitivity (90.5% vs. 35.4%) and specificity (97.9% vs. 90.4%) in the detection of metastatic tumors.

In another study, SPIONs were injected into patients with solid tumors. The SPIONs remained in the tumors 24 hours after the injection, as compared with 1 hour for gadolinium-chelate contrast agents (Enochs *et al*., 1999). The reason for this difference is that the smaller nanoparticles are more easily taken up by tumor cells and diffuse out of the tumor more slowly (Perrault *et al*., 2009). As a result, the tumor margins can be distinguished on MRI for a longer period.

Quantum dots

QDs are nanometer-scale semiconductor crystals composed of groups II to VI or III to V elements and are defined as particles with physical dimensions smaller than the exciton Bohr radius (Chan *et al*., 2002). QDs exhibit unique luminescence characteristics and electronic properties such as wide and continuous absorption spectra, narrow emission spectra, and high light stability (Bruchez *et al*., 1998). They absorb white light and then reemit a specific color a few nanoseconds later depending on the bandgap of the material (GhoshMitra *et al*., 2011, Dabbousi *et al*., 1997, Bakalova *et al*., 2004). Quantum dots (QDs), often described as 'artificial atoms,' exhibit discrete energy levels, and their bandgap can be precisely modulated by varying the size (Klimov, 2007). QD range is typically between 2 and 10 nm in diameter. QDs consist of a semiconductor core, overcoated by a shell (e.g., ZnS) to improve optical properties, and a cap enabling improved solubility in aqueous buffers (Ghasemi *et al*., 2009) (Fig.1D). Several routes have been used to synthesize QDs (Bera *et al*., 2011) but, generally, techniques for QD synthesis used top-down processing methods and bottom-up approach. Top-down processing methods include molecular beam epitaxy (MBE), ion implantation, e-beam lithography, and X-ray lithography.

Using the alternative bottom-up approach, colloidal QDs are prepared by self-assembly in the solution following a chemical reduction (Bertino *et al*., 2007, Birudavolu *et al*., 2004, Nakata *et al*., 2000). Because QDs have constant and unique optical properties, they are the best candidates for cell labeling, as compared with organic dyes. With the application of QDs, single particle tracking (SPT) has the potential to enter into a new era of high resolution and long timescale imaging (Chang *et al*., 2008, Saxton and Jacobson, 1997). SPT techniques allow scientists to follow single molecules in real time and visualize the actual molecular dynamics in their habitant environment. The employment of satellite cells, which are located between the basement membrane and the plasma membrane in myofibers, is required for myofiber repair after muscle injury or disease. Using QDs conjugated to anti-M-cadherin antibody, Ishido and Kasuga attempted the visualization of satellite cells in both intact and injured skeletal muscle of rat in situ. They demonstrated in situ real-time imaging of satellite cells localized within the skeletal muscle (Ishido and Kasuga, 2011). The detection of cancer biomarkers is important for diagnosis, disease stage forecasting, and clinical management. QDs with intense and stable fluorescent properties could enable the detection of tens to hundreds of cancer biomarkers in blood assays, on cancer tissue biopsies, or as contrast agents for medical imaging. Multicolor and multiplexing potentialities of QDs are used for the detection of four protein biomarkers CD15, CD30, CD45, and Pax5 of Hodgkin's lymphoma from lymphoma tissues. Simultaneous visualization using multiplexed QD staining was advantageous for the selective identification of rare Hodgkin (Reed-Sternberg) cells, a primary diagnostic target for Hodgkin's disease, which was not achievable using traditional immunohistochemistry assays (Liu *et al*., 2010, Ray *et al*., 2011). Similarly, using semiconductor QD-antibody conjugates, Lee *et al*. demonstrated quantitative profiling of biomarkers for pancreatic cancer at the single-cell level. Their results show the possibility of this method for staging and forecasting, such as prostate stem cell antigen claudin-4, and mesothelin, which are expressed in different stages of progression of pancreatic cancer (Lee *et al*., 2012). QDs have also been used as a probe in an anti-malarial drug screening assay. Ku *et al*. showed a simple and efficient method to label P. falciparum-infected RBC using a QD-based probe and its applicability as an efficient probe for antimalarial drug screening (Ku *et al*., 2011).

Quantum dots can also be used for imaging of sentinel node in cancer patients for tumour staging and planning of therapy. This method can be adopted for various malignancies like melanoma, breast, lung and gastrointestinal tumours (Iga *et al*., 2008). Quantum dot probes provide real time imaging of the sentinel node with Near Infra Red (NIR) fluorescence system. The NIR region of the electromagnetic spectrum produces reduced background noise and deeper penetration of rays, of up to 2 to 5 cm into the biological sample. However, the application of quantum dots in a clinical setting is limited owing to different opinions about the toxicity and fate of QDs in vivo. Therefore, more experiments should be done, and much more data should be available, to be sure to do clinical trials on humans.

Carbon nanotubes

Carbon nanotubes (CNTs), discovered by Japanese scientist Iijima in 1991 (Iijima, 1991), are now considered to be a top class subject in academic researches as well as in various industrial areas. These nanomaterials are allotropes of carbon, made of graphite, and have been constructed in cylindrical tubes with nanometer scale in diameter and several micrometers in length (Hirlekar *et al*., 2009, Singh *et al*., 2012). Their impressive structural, mechanical, and electronic properties are due to their small size and mass, their incredible mechanical strength, and their high electrical and thermal conductivity (Usui *et al*., 2012, Zhang *et al*., 2010b). Carbon nanotubes (CNTs) consist exclusively of carbon atoms arranged in a series of condensed benzene rings rolled up into a tubular structure. Based on the number of layers, structures of CNTs are classified into two types: single-walled carbon nanotubes (SWCNTs) and multiwalled carbon nanotubes (MWCNTs). SWCNTs consist of a single graphene cylinder with diameter varying between 0.4 and 2 nm, and usually occur as hexagonal close-packed bundles. MWCNTs consist of two to several coaxial cylinders, each made of a single graphene sheet surrounding a hollow core. The outer diameter of MWCNTs ranges from 2 to 100 nm, while the inner diameter is in the range of 1-3 nm, and their length is 0.2 to several μm (Singh *et al*., 2012, Bekyarova *et al*., 2005) (Fig.1B). Three main techniques generally used for SWCNTs and MWCNTs production are: Arc-Discharge method (using arcvaporization of two carbon rods), Laser Ablation method (using graphite), and Chemical Vapor Deposition (using hydrocarbon sources: CO, methane, ethylene, acetylene).

The main applications of CNTs in pharmacy and medicine include drug, biomolecule, gene delivery to cells or organs, tissue regeneration, and biosensor diagnostics and analysis. CNTs can easily cross the cytoplasmic membrane and nuclear membrane, anticancer drug transported by this vehicle will be liberated in situ with intact concentration and consequently, its action in the tumor cell will be higher than that administered alone by traditional therapy. Thus, the development of efficient delivery systems with the ability to enhance cellular uptake of existing potent drugs is needed. Many anticancer drugs have been conjugated with functionalized CNTs and successfully tested in vitro and in vivo such as epirubicin, doxorubicin, cisplatin, methotrexate, quercetin, and paclitaxel (Chen *et al*., 2011, Xiao *et al*., 2012, Madani *et al*., 2011, Lay *et al*., 2011, Li *et al*., 2010). The problem of their insolubility in aqueous solution has been resolved by studies on protocols for non-covalent polymer coating, which has enabled in-vitro cell viability assays and in vivo studies on biocompatibility. The other development necessary for biomedical use has been the functionalization of CNTs for carrying drugs, genes, and other biomolecules to avoid the harmful effect of anticancer drug on healthy organs and tissues. D. Xiao *et al*., linked epirubicin with a magnetic CNTs complex obtained by fixing a layer of magnetite (Fe_3O_4) nanoparticles on the surface of the nanotubes for lymphatic tumor targeting. Such a system can be guided by an externally placed magnet to target regional lymphatic nodes (Xiao *et al*., 2012). Li and coworkers (Li *et al*., 2010) have shown that SWCNTs can be functionalized with p-glycoprotein antibodies and loaded with the anticancer agent doxorubicin and paclitaxel. Compared with free doxorubicin, this

formulation demonstrated higher cytotoxicity by 2.4-fold against K562R leukemia cells.

The hyperthermia therapy using CNTs has been recently suggested as an efficient strategy for the cancer treatments. SWCNTs exhibit strong absorbance in the near-infrared region (NIR; 700-1100 nm).These nano-materials are considered as potent candidates for hyperthermia therapy since they generate significant amounts of heat upon excitation with NIR light (Madani *et al*., 2011, Lay *et al*., 2011). The photothermal effect can induce the local thermal ablation of tumor cells by excessive heating of SWCNTs shackled in tumor cells such as pancreatic cancer. Some progress in the technique has been achieved in recent years, and it has shown feasibility in clinical application.

Carbon nanotubes may be the best tissue engineering candidate for tissue scaffolds since this nanomaterial is biocompatible, resistant to biodegradation, and can be functionalized with biomolecules for enhancing the organ regeneration. In this field, CNTs can be used as additives to reinforce the mechanical strength of tissue scaffolding and conductivity by incorporating with the host's body (Kateb *et al*., 2010, Usui *et al*., 2012, Bekyarova *et al*., 2005, Liao *et al*., 2011, MacDonald *et al*., 2005). Indeed, MacDonald *et al*., (MacDonald *et al*., 2005) have successfully combined a carboxylated SWCNTs with a polymer or collagen (poly-l-lactide or poly-D,L-lactide-co-glycolide) to form a composite nanomaterial used as scaffold in tissue regeneration.

The use of CNTs in biosensing nanotechnology is recent and represents a most exciting application area for therapeutic monitoring and in vitro and in vivo diagnostics. For example, many searchers have coupled CNTs with glucose-oxidase biosensors for blood sugar control in diabetic patient with higher accuracy and simpler manipulation than biosensors used alone (Bianco *et al*., 2005, Wang, 2005). Other CNT-enzyme biosensors such as CNT based dehydrogenase biosensors or peroxidase and catalase biosensors have also been developed for different therapeutic monitoring and diagnostics (Wang, 2005, Zhu *et al*., 2011).

Fullerenes

Fullerenes, a carbon allotrope, also called as "bucky balls" were discovered in 1985 (Kroto *et al*., 1985). The buckminster fullerene, the most common form of fullerene is a truncated icosahedron containing 60 carbon atoms with C_5–C_5 single bonds forming pentagons and C_5–C_6 double bonds forming hexagons. The diameter of a C_{60}fullerene molecule is 0.7 nm, hence it is an important member of the nanomaterials family. It resembles a soccer ball with 20 hexagons and 12 pentagons and is highly symmetrical (Fig.1E). However, C_{60} has poor solubility in aqueous solvents coupled with a tendency to form aggregates in aqueous solutions, which makes it an unattractive candidate in biological applications (Ruoff *et al*., 1993, Sivaraman *et al*., 1992). This problem has been solved to a great extent by various chemical and supramolecular approaches to functionalize fullerenes (Da Ros and Prato, 1999, Jensen *et al*., 1996). Some of the functionalized fullerenes have excellent solubility in polar solvents and easily overcome the hurdles posed by C_{60}. Since its discovery, fullerenes have captured the imagination of scientists due to their unique physical and chemical properties. Fullerenes are being investigated for drug transport of antiviral drugs, antibiotics and anticancer agents. Paclitaxel-embedded buckysomes (PEBs) are spherical nanostructures in the order of 100-200 nm composed of the amphiphilic fullerene, AF-1 embedding the anti-cancer drug paclitaxel inside its hydrophobic pockets (Partha *et al*., 2008). In vitro studies have demonstrated that PEBs' efficacy toward MCF-7 human breast cancer cells is comparable to that of Abraxane®, the US Food and Drug Administration (FDA)-approved drug for treating diseases such as metastatic breast cancer, and is currently being investigated in preclinical trials using murine models, a necessary step toward clinical testing and ultimate approval of the PEBs for human use.

Ever since Krusic and colleagues documented the potential of fullerenes to scavenge ROS (Krusrc *et al*., 1991) due to presence of high number of conjugated double bonds in the core structure, there has been a great interest in using fullerenes as an antioxidant. These are found to have a protective activity against mitochondrial injury induced by free radicals and iron-induced lipid peroxidation (Cai *et al*., 2008) However, Fullerenes can also generate reactive oxygen species during photosensitization due extended π-conjugation, which allows them to absorb visible light and have a long-lived triplet yield. This property results in the generation of ROS upon illumination with light. This special of ROS generation has resulted in the possible role of fullerenes in photodynamic therapy (PDT) for killing cancer cells.

Endohedral metallofullerenes are another class of functionalized fullerenes that can encapsulate the metal atom inside the fullerene cage. They offer great potential for serving as MRI contrast agents. For example, Gadolinium-encapsulated fullerenes have been proposed as contrast agents to enhance MRI quality (Maeda *et al*., 2008, Bolskar *et al*., 2003, Toth *et al*., 2005, Sitharaman *et al*., 2007). Analogous to a liposome protecting its encapsulated drug, the fullerene cage in a metallofullerene protects the metal inside both against chemical or enzymatic activity within the body and the unwarranted release of the metal. As a result, the tumor margins can be distinguished on MRI for a longer period. Certain functionalized fullerenes may provide great improvements over existing medications and improve the quality of life for patients with severe diseases such as cancer but further toxicity assays before claiming the clinical use of these functionalized fullerenes is needed.

CONCLUSION

Although the expectations from nanotechnology in medicine are high and the potential benefits are endlessly enlisted, the safety of nanomedicine is not yet fully defined. There is growing speculation about possible nanomaterial toxicity on the basis of in vitro cell-culture studies and in vivo animal studies. For example, magnetic nanoparticles used for thermal ablation have been shown to be retained in the urinary tract (in patients with a history of urethral stricture) and to result in treatment-related illness (Johannsen *et al*., 2007). In contrast, numerous studies have shown that certain nanomaterials do not elicit toxic responses in animals, as determined by histopathological studies and analyses of hepatic and renal markers (Schipper *et al*., 2008, Hauck *et al*., 2010). The issue of nanomaterial toxicity remains controversial and requires

more study. Use of nanotechnology in medical therapeutics needs adequate evaluation of its risk and safety factors. However, it is possible that nanomedicine in future would play a crucial role in treatment of human diseases and also in enhancement of normal human physiology but researchers need to optimize the nanomaterials beginning with small-animal models and scaling up to nonhuman primate models-a process that will take some time.

Acknowledgements

The authors are thankful to Dr. Sheikh Tanveer Ahmad for reviewing this paper.

Conflict of interest: All authors have read the journal's policy on authorship agreement and conflict of interest, and declared no conflict of interest.

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How to cite this article:

Asia Asiaf and Mohammad Afzal Zargar.2017, Applications of Nanotechnology In Medicine And Healthcare: A Review. *Int J Recent Sci Res.* 8(7), pp. 18216-18226. DOI: http://dx.doi.org/10.24327/ijrsr.2017.0807.0471

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