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Biomedical Applications of Manganese and Cobalt Nanocomposites: a Review

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ABSTRACT

In this review, the synthesis, characterization and biomedical applications of the manganese and cobalt nanocomposites were discussed. Nanocomposites and biomedical applications are the recent developments in the field of science and medicinal science. The age-old chaos pertaining to causality determination, complexities in diagnosis of the disease and the causality level have decreased due to these recent innovations. Generally, manganese and cobalt nanocomposites are synthesized by variety of methods like hydrothermal, sol-gel, co-precipitation, thermal decomposition, laser and micro-emulsion with suitable precursor and reagents. The synthesized manganese and cobalt nanocomposites can be characterized by AFM, XRD, FTIR, UV-Vis., DSC, TGA, NMR, SEM, TEM, EDS, CCD and VSM. In all the results, these nanocomposites have shown excellent fluorescence and magnetic properties. They are widely employed in the biomedical applications such as bio-imaging, drug delivery and diagnostics, owing to their low toxic effect and high fluorescent property to emit the state of the affected area of the organ in a precise manner.

Keywords: Biomedical applications; Cobalt; Cancer theranostics; Diagnostics; Manganese; Nanocomposites.

1. INTRODUCTION

Nanotechnology is a relatively recent development in the field of science and technology. Typically, the size of particles less than 100 nm is considered as nanomaterial (Lai and Shafi, 2003; Vestal and Zhang, 2003). The nano-structured materials are widely utilized in various fields of science and engineering. In chemistry, nano-scale drugs are routinely used to control proteins, signaling complexes and medical theranostics. In status, more nanocomposites having been synthesized and these composites are applied in bio-medical field in the treatment of anti-diabetic treatment, anticancer and antibacterial fields. In this process of synthesis of nanocomposites, the initial step involves preparation of quantum dots, these are widely used in chemical industry for making paint and other synthetic products (Weddemann *et al.*2010; Daniel and Astruc, 2004). The semiconductor quantum dots are fluorescent; they emit colored light when exposed through ultraviolet excitation. These are also used to predict images which are used for computers and mobile phones. Today, nanocomposites have biomedical applications like drug carriers, labeling agents, tracking agents, gene therapy, hyperthermia, MRI contrast agents, *in-vitro* applications such as conventional agents having minimum cytotoxicity and *in-vivo* conditions of having good target efficiency (Kumar *et al.* 2011).

Recently, nanocomposites are being the promising materials for biomedical applications. Biomedical science is one of the important filed in science and medicinal sciences. The determination and treatment diagnosis pattern of the disease has become open and the causality level has been decreased due to the recent innovations of nanocomposites in biomedical science. Hence, the present review was aimed at the study of synthesis, characterization and the recent bio-medical applications of manganese and cobalt nanocomposites (Bhattacharyya *et al.* 2011; Karrina Mc Namara and Syed, 2017).

Manganese is found in quite a lot of minerals and as a free element in nature. It seems hard and brittle, tarnishes slowly in air, and rusts in water containing dissolved oxygen. It is chiefly used as industrial metal alloy, particularly in the production of stainless steels. The molar mass of manganese nanoparticles is 54.94 g/mol and the melting point of 1244 ºC, and the boiling point of 1962 ºC (Deborah *et al.* 2014).

The current potential applications of cobalt nanoparticles are in electronic and optical fields and they have unexpected optical properties due to their nano-size and are capable of producing quantum effects. Nanoparticles research is a rapidly developing area with immense potential in the field of chemistry and other sciences. The morphology of cobalt nanoparticles is spherical, grey or black color powder. Cobalt nanoparticles possess admirable magnetic properties, which leads to the applications of imaging, sensors, and many other areas in medical principles. The density of cobalt nanoparticle is 8.86 g/cm and its molar mass is 58.93 g/mol. Its melting point and boiling point are 1495 ºC and 2870 ºC, respectively.

2. EXPERIMENTAL METHODS

2.1 Magnetic Properties

Magnetism are of five types; these five types are separated into two categories. The first category includes paramagnetism, ferromagnetism and ferrimagnetism which are present in materials that are attracted to the applied magnetic field. These materials have unpaired electrons in their valence atomic shell. The unpaired electrons align in the same direction as the applied field resulting in a net magnetic moment leading to a positive susceptibility. The second category contains the remaining types of magnetism like diamagnetism and anti-ferromagnetism and they are present in materials that repel the magnetic field (Mathew *et al.* 2007). Manganese have two oxidation states: +2 and +3 (MnO, Mn_2O_3, Mn_3O_4). At room temperature, Mn_3O_4 is paramagnetic. But below 41-43 K the Mn_3O_4 is ferromagnetic; these are reported by nanocrystalline sample. Co_3O_4 has antiferromagnetic nature.

Super-paramagnetic properties of nanoparticles find them in many applications and specifically in the biomedical field due to their compatibility with the physiological conditions. The main applications of super-paramagnetic nanoparticles like bio-imaging, MRI contrast agents, targeted drug delivery and treatment of hyperthermia. Magnetic iron oxide nanoparticles are commonly used in biomedical applications. As compared, manganese nanoparticles have super-paramagnetic elements, these have high magnetism than iron oxide nanoparticles (Chen *et al.*1994; Bettini *et al.* 2015).

2.2 Synthesis of Nanocomposites

Nano - structures are basically synthesized by two methods namely Bottom-up and Top-down. These methods are done by growing or assembling of atoms or molecules by building blocks; the building blocks are manipulated by controlled chemical reactions in self-assemble to make nanostructures or quantum dots. Chemical / Electrochemical, Precipitation, Vapor Deposition, Sol-gel, Laser and Aerosol Pyrolysis are some of the bottom-up methods, which are toxic. Green synthesis such as plant extract, bacteria and fungus are non-toxic. In Top-down Methods, Bulk materials are reduced by breaking, cutting, or engraving to form nanostructure materials (Yin *et al.* 2010; Rajib Ghosh *et al.* 2012; Respaud *et al.*1998).

In general, Hydrothermal method is the best and simple method for all nanocomposites (Deyang and Meng, 2017). Manganese nanoparticles are produced using n-butyl lithium as a reducing agent in hydrothermal method. Manganese oxide was prepared by the reduction of potassium permanganate under atmospheric pressure in a closed vessel at 170 ºC (Cui *et al.* 2013). Cobalt nanoparticles are produced by a simple one-step hydrothermal method with the capping of oleic acid. Cobalt nanoparticles $Co(CH_3COO)_2 \cdot 4H_2O$ are prepared by $K_2C_4H_4O_6.0.5H_2O$ and $NaC_4H_4O_6 \cdot 4H_2O$ through the activation of mild hydrolysis (Ovanovi *et al.* 2014). The nanoparticles of cobalt can be produced using Laser evaporation process. In this process high purity cobalt is used as a raw material for producing high purity, small particle, and large quantities at a very reasonable cost. Variety of organic and inorganic polymers enhances mechanical, electronic, catalytic and optical properties. For example, PDDA polymer intercalated with manganese oxide forms thin film of electrode to improve catalytic and electrochemical properties (Li and Han, 2015; Michele Karoline *et al.* 2018). Mn_3O_4 nanoparticles are produced by using two different manganese precursors from Co-precipitation method (Bama Krishnan and Sundrarajan Mahalingam, 2016). $MnCl_2$-SWNT and $MnBr_2$-SWNT nanocomposites obtained by Capillary filling of single wall nano-tube with manganese halogenides (Kharlamova and Eliseev, 2012). The MnO_2-MWCNT nanocomposites are synthesized by Redox titration method at room temperature (Chung and Jeng, 2011) MnO_2NT are synthesized by a simple single-step hydrothermal method in acidic $KMnO_4$ in the absence of surfactants (Mahmoudian and Alias, 2014). Co-NiO nanocomposites are synthesized by Sol-gel method using $NiCl_2$ and $CoCl_2$ (Harish *et al.* 2018). Porous Co_3O_4 nanowires are produced by hydrothermal methods using nitrilotriacetic acid (Hua-Jun Qiu *et al.* 2014). Mesoporous Co_3O_4 nano-belts and nano-needles are prepared by calcinations of α-$Co(OH)_2$ (Lou *et al.* 2008). Cobalt oxide nanoparticles are synthesized by Sol-gel method using Poly-vinyl alcohol (PVA) (Tian *et al.* 2010; Zhang *et al.* 2008).

2.3 Characterization

Nanocomposites are characterized by various techniques and with the aid of equipment like Atomic Force Microscopy (AFM), which is a scanning probe magnifier. Fourier Transformed Infrared Spectroscopy (FTIR) throws light upon the purity of the sample. Infrared spectroscopic studies confirm the single-phase cobalt nanoparticles with a high structural quality. Using X-ray Diffraction (XRD) the average crystallite size of the nanocomposites can be calculated by using the Debye–Scherrer equation (Meysam Soleymani and Mohammad Edrissi, 2006; Pugazhradivy *et al.* 2013). The lattice constants and crystal structure of nanocomposites are also estimated. The structural, physio-chemical and magnetic properties of cobalt nanoparticles are investigated and verified for their applicability in biomedicine, using X-ray diffraction method (Cuizhu *et al.* 2012). Differential Scanning Calorimetric (DSC), TGA and DSC curves detect the thermal stability of MnO_x-MWCNT nanocomposites (Chung and Jeng, 2011). Scanning and Transmission Electron Microscopy (SEM/TEM) are employed to identify the morphology of nanocomposites. Magnetic behavior and chemical constancy of MnO nanoparticles are explained by SEM/TEM (Michele Karoline *et al.* 2018).

In the Electron Microscopy imaging analyses, the cobalt nanoparticles demonstrate a ferromagnetic character over a wide range of temperature 20-300 K. The temperature dependence of the magnetic parameters namely, saturation magnetization, remnant magnetization and reduced remnant magnetization were finalized with the structure of the cobalt nanoparticles using Electron Microscopy imaging. The Energy Dispersive Spectroscopy (EDS) were used to study the surface morphology of the nanoparticles. Cytotoxicity studies demonstrate that these nanoparticles show mild anti-proliferative characteristics against the cancer cells and safeguard the normal cells (Ansari *et al.* 2016; Gornati *et al.* 2016). The scattered light of nanocomposites is analyzed by using Charge Coupled Device (CCD). Finally, the magnetic properties are measured using Vibrating sample magnetometer (VSM).

3. APPLICATIONS OF NANOCOMPOSITES

The nanocomposites are used in information and computing sensors, electronic and optical devices, quality measurement of soil, water, plant, food, energy storage and data storage, waterproof fabrics, electronics, ceramics, paints, drug delivery, vehicles, catalysis and environmental remediation. The key applications of manganese nanoparticles are in the recent fields of magnetic data storage, MRI, biosensors, textiles, coatings, nanowires, plastics and nanofibers. Manganese nanocomposites are majorly used in electrochemical applications. Cobalt oxide nanoparticles can also be used in several applications like high performance materials for gripping particularly high frequency, millimeter wave, visible light and infrared. Currently, researchers are concentrating more in new nano-field applications like electric, magnetic and optical imaging, catalytic, biomedical and bioscience (Li *et al.* 2010; Howes *et al.* 2014; Huang and Davis, 2011).

4. BIO-MEDICAL APPLICATIONS OF MANGANESE AND COBALT NANOPARTICLES

Some nanocomposites are toxic, but manganese and cobalt nanocomposites have low cytotoxicity. They are used for biosensor, biomimetic, human health monitoring, diagnosis of disease, drug and gene therapy, molecular imaging and drug delivery and in reproduction of damaged tissues. Nanoparticles are used to transitional species in the protein functional processes such as antibody-antigen interaction, receptor-substrate interaction and biotin-avidin interaction. Binding of protein with nanoparticles is to reduce cytotoxicity. Peptide ligand stabilizes the nanoparticles. Phospholipids are allowed to dole out nano-composites with possible drug delivery, hyperthermia applications and to reduce non-specific interactions (Doaga *et al.* 2013; Mayank Bhushan *et al.* 2017).

In the modern technological advancement, the use of manganese-based nanoparticles in the biomedical field has been focused in their application as positive contrast agents for Magnetic Resonance Imaging (MRI). The MRI contrast agents are basically in the form of paramagnetic complexes or magnetic nanoparticles. For instance, manganese-enhanced MRI, which uses manganese ion Mn^{2+} as a contrast agent is applicable to animals only owing to the toxicity of Mn^{2+} in neuroscience research (Allison *et al.* 2012; Jain *et al.* 2011).

The crystalline MnO nanoparticles are expected to become positive contrast agents for MRI scanning. It is commonly recognized that the manganese to the surface only contributes the major contrast effect, which could be in close contact with the proton of water molecules. The as-synthesized MnO nanoparticles are generally hydrophobic; one of the Mn-based MRI contrast agent namely *Mangafodipir trisodium* has clinical use. On the other hand, Mn-based complexes are very easy to dissociate after administration to yield free Mn^{2+} for the conversion between the six- and seven-coordinated states. Due to the physiological function, the exposure to excess Mn can provoke harmful effects on the central nervous system and cause Parkinsonism syndrome in patients with liver failure (Colognato *et al.* 2008; Ling and Hyeon, 2013).

The *in vivo* volatility of Mn-DPDP has raised special concerns about its latent toxicity from the Mn^{2+} ions, which ultimately led to its gradual withdrawing. Hence, it was suggested that it is necessary to find biocompatible and thermodynamically stable Mn compounds to activate. The advances in nanotechnology have developed some types of Mn-NP-based MRI contrast agent with well-defined morphology and high solubility. They exhibit positive behaviors in exposure, localization, classification and assessment of hepatic lesions and offer clinical advantages over the accessible Mn-based MRI contrast agent, Mn-DPDP in medical field. It is noticed that some of them have offered an improved biocompatible profile. In the selective imaging of exact biomarkers in brain pathologies, MnO nanoparticles can be functionalized in conjugation with the antibody for a selective target towards the epidermal growth factor receptors, which are over expressed on the exterior of brain cancer cells. Nowadays, recent studies have reported the primary biocompatible and nano structured contrast agent for MRI applicable to different organs and body tissues, allowing to obtain clear images of the brain, liver, kidney and bone marrow from 5 days to 3 weeks after the administration of MnO nanoparticles. Their distribution, accumulation in organs, tissues and its low cellular toxicity open a new way for the growth of contrast agents for molecular therapy and cellular imaging in medicine (Lagendijk *et al.* 2014; Limaye *et al.* 2009; Fang and Zhang, 2009; Keall *et al.* 2014; Tse *et al.* 2015).

The cobalt nanoparticles have been used for a hundred periods as a dye and it is an important human nutrient as part of the vitamin B_{12}. It is used in medical sensors for contrast enhancement agent in magnetic resonance imaging and it is used as drug delivery agents for cancer therapies. One of the objectives of the discussion is to investigate the effect of as-synthesized Co NPs on the cancer cell and normal cell for Cisplatin-resistant ovarian cancer among women. Ovarian cancer is the leading cause of death in women worldwide. According to the information of National Cancer Institute, USA ovarian cancer has the highest mortality rate among all the reproductive type of cancers in women. The advanced stage diagnosis and chemo-resistance is a major barrier in treating advanced stages of ovarian cancer. Commonly, the most chemotherapeutic drug for ovarian cancer treatment is Cisplatin. Many patients ultimately become resistant to Cisplatin. The usefulness of current treatments may be enhanced by increasing the sensitivity of cancer cells. It was clear that, the increase of Cisplatin-resistant ovarian cancer cells are reduced in a dose dependent manner. Notably, cell viability of NPs was observed above 86% for all the different Cobalt nanoparticles concentrations in the process. The higher concentration of NP (300 μg/mL) viability was found to be 87.36% and the lowest viability was observed 87% (at 250 μg/mL) in many of the past researches. Nearly, the cytotoxicity against the Cisplatin-resistant ovarian cancer cells was observed to be 5–13% (viability: 87 - 95%) for 10-300 μg/mL concentration of Co nanoparticles. However, in clinical settings, 30% response of patient to anti-cancer drugs is taken as a good index. Co NPs are mildly cytotoxic against human cisplatin resistant ovarian cancer cells (Ansari *et al.* 2016; Gornati *et al.* 2016).

The presence of magnetic nanoparticles on the cell surface affects the plasma membrane and it causes cell death as compared to control. The cytotoxicity data of these nano-materials has been difficult to compare since the toxic effects of magnetic nanoparticles are influenced by many parameters such as size distribution, surface coating, magnetic properties, etc. in biomedical applications. It has been reported that the surface coating can modify the surface properties of nanoparticles. The studies tell that oleic acid plays an important role in the control of the size and shape of the magnetic nanoparticles. The magnetization was found to be lower than the bulk Co with the size of individual particles. Oleic acid is used as capping agent during the synthesis but not after the synthesis. Hence, capped NPs are less toxic than the bulk NPs (Dong *et al.* 2015; Wolfe *et al.* 2015; Chatterjee *et al.* 2008; Nelson *et al.* 2009).

Malvindi *et al.* examined that the NPs' surface passivation reduces the oxidative stress and alteration of iron homeostasis. Consequently, the overall toxicity, despite bare and passivated nanoparticles, shows similar cell internalization efficiency. The researchers also found that the higher toxicity of these nanoparticles is due to their stronger *in-situ* degradation with larger intracellular release of iron ions when compared to surface passivated nanomaterials. Their results indicate that surface engineering of magnetic nanoparticles plays a vital role in improving particle stability in biological environments, plummeting both cytotoxic and genotoxic effects (Papisa *et al.* 2009; Sabbioni *et al.* 2013; 2014; Puntes *et al.* 2001).

From the cytotoxicity analyses of Co nanoparticles against the cancer cell and normal cell, the concentrations range of 10-300 μg/mL can be used for biomedical applications as it shows the viability more than 81% against the normal cell and cancer cell. As a result, the present review suggests that, as-synthesized NPs are mildly anti-proliferative against Cisplatin-resistant human cancer cells. It is evident that the nanoparticles did not show adverse effect on normal cell as compared to its control; these NPs can be tested for anticancer agents with existing drugs in biomedical applications. Moreover, it can also be used for treatment for drug delivery in the affected area of body (Lin *et al.*1998; Montiel *et al.* 2011; Peng *et al.* 2014; Pankhurst *et al.* 2009; Shouheng and Murray *et al.* 1999; Thanha, 2015; Warner *et al.* 2012).

5. CONCLUSION

Today, there are several biomedical applications of nanoparticles like drug carriers, labelling agents, tracking agents, gene therapy, hyperthermia, MRI contrast agents, *in-vitro* application such as conventional agents having minimum cytotoxicity and in-vivo conditions of having good target efficiency. The Mn and Co nanoparticles play a vital role in the biomedical methods. They are found in minerals or as free elements. The nanoparticles are currently a subject of intense research owing to their potential applications in medical, electronic and optical fields. Chemical constancy of MnO nanoparticles and cobalt nanoparticles are investigated. Cytotoxicity studies demonstrate that these nanoparticles show positive characteristics against the cancer cells and safeguard the normal cells. In biomedical applications, manganese and cobalt nanocomposites are available and have low cytotoxicity. The distribution, accumulation in organs and tissues, its tolerable low cellular toxicity may surely open a new way for the growth of contrast agents for molecular therapy and cellular imaging in medicine in the near future. They can be utilized for cancer theranostics. In site-specific areas, it may be used as drug delivery agent for cancer therapy. As a result, the present review suggests that the Mn and Co NPs are useful in the treatment of human cancer cells. Consequently, it is suggested that these NPs can be tested as the particles of anticancer agents either alone or with existing drugs in biomedical applications.

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CONFLICTS OF INTEREST

The authors declare that there is no conflict of interest.

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