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Current Nanoscience, **2013,** *9,* **000-000** **1**

Nanoceria: Synthesis and Biomedical Applications

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Abstract: Cerium oxide or ceria is an inorganic compound of Cerium, a rare earth element of lanthanide series. Due to the unique ability of cerium to switch oxidation states between +3 and +4 it has various applications as ultraviolet light absorbers, catalytic converters for automobile exhaust systems, solar cells, optics, oxygen sensors and other commercial and biomedical applications. Cerium oxide nanoparticles popularly known as nanoceria are efficient free radical scavengers and are considered as a potent therapeutic option for the treatment of ROS mediated disorders like neurodegenerative disorders, retinal disorders, cancer and can also act as a potent drug delivery agent. Engineered nanoparticles have the potential to revolutionize diagnosis and treatment of many diseases which require the synthesis of nanoceria with biocompatibility so as to enhance its therapeutic potential without inducing any cytotoxicity. Here we review the various methods for synthesis of nanoceria for biomedical applications and we discuss the challenges to realize the potential of nanoceria in therapeutics.

Keywords: Antioxidants, biocompatibility, cytotoxicity, drug delivery, nanoceria, nanoparticle, therapeutics.

INTRODUCTION

Cerium Oxide (CeO_2) commonly called as ceria is a rare earth metal oxide. Nanoceria is currently being used as a catalyst for car exhaust fumes. Due to the unique arrangement of 4f electrons, it possesses many unique physical and chemical properties, such as high conductivity, large magnetic moment and very high complexation reactivity [1, 2]. The face-centered cubic fluorite-type crystal structure of ceria [3] is highly stable [4] unlike other rare earth oxides such as Zirconia (ZrO_2), Thorium dioxide (ThO_2) and Bismuth oxide (Bi_2O_3) [5, 6] thus making it appropriate for many industrial applications including solid oxide fuel cells, solar cells [7], optics [8], catalytic agents and as oxygen sensors [9,10].

Cerium can exist in two oxidation states (Ce^{4+} and Ce^{3+}). High Resolution Transmission Electron Microscopic (HRTEM) studies, show that bulk ceria particles contain mainly Ce^{4+}, whereas cerium oxide nanoparticles (nanoceria) contain a large fraction of Ce^{3+} [11] and the interconversion of oxidation states gives rise to large number of oxygen vacancies on the surface of nanoceria [12-14]. Computer simulation studies of the surfaces of ceria reveal presence of three low energy surfaces of nanoceria viz. (111), (110) and (310) surface planes but (111) is the most stable one [15]. High-resolution scanning tunneling microscopy and density functional calculations of (111) surface plane show that the electrons left behind by released oxygen, localize on cerium ions [16] thereby imparting free radical scavenging activity to it. Recent investigations show that the decrease in the particle size of nanoceria and the introduction of oxygen vacancies leads to large lattice expansion [17] due to increased surface to volume ratio [18] in contrast to other metal nanoparticles which show decrease in lattice parameter with decreasing size [18-20]. Presence of these oxygen vacancies makes nanoceria a potent antioxidant for therapeutic applications like antioxidant, drug delivery agent and biosensors. The unique physical and chemical properties of nanoceria making it highly bioactive material and can react with cells, micro- and macro-organisms [21]. Their application in the field of biomedicine is still under investigation.

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SYNTHESIS OF NANOCERIA FOR BIOMEDICAL APPLICATIONS

Nanoceria due to its unique free radical scavenging properties is considered as one of the potent candidates for treatment of disorders induced as a result of oxidative stress. This demands synthesis of biocompatible cerium oxide nanoparticles for therapeutic applications without inducing any toxic responses. The synthesis of the nanoparticles can be done through many pathways of which some are reviewed below.

- **Precipitation Method**

Precipitation method is one of the simplest processes for the synthesis and scale up of nanoceria.

Aqueous precipitation: Aqueous solutions of organic stabilizer like Poly ethylene glycol (PEG) or Poly acrylic acid (PAA) and cerium nitrate ($Ce(NO_3)_3{\cdot}6H_2O$) with 50% hydrogen peroxide (H_2O_2) solution when mixed with high speed shearing at elevated temperature leads to the formation of nanoceria via $Ce(OH)_3$ intermediate phase. Stabilizer combination of ethylene diamine tetra acetic acid (EDTA) and lactic acid, leads to formation of 1.1 nm particles, whereas 2 nm particles are stabilized by methoxyethoxy ethoxy acetic acid [22].

Homogenous precipitation method for nanoceria (3-12nm) synthesis involves mixing equal volumes of solutions of $Ce(NO_3)_3$ and hexamethylenetetramine at room temperature [20, 23]. Pure nanoceria suitable for biomedical applications can also be synthesized by the homogeneous precipitation of cerium nitrate in ethylene glycol [24] or ammonia [25-27].

Crystalline nanoceria can be synthesized by surfactant (ionic surfactant Tween) [28] mediated precipitation technique in acetone/water mixed solvent system [29]. The cerium nitrate hexahydrate subjected to different vacuum/thermal treatments leads to the production of nanoceria having different extents of water of crystallization [30].

Synthesis of copper promoted ceria catalysts can be done using the urea co-precipitation method which involves aging of solutions containing urea, $Ce(NO_3)_3$, and $Cu(NO_3)_2$ at 363 K for 5 h. The precursors, after moderate thermal treatment, evolve into Cu(II)-promoted nanoceria catalysts [31] which are suitable for the catalysis of water gas shift reactions [32].

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- **Hydrothermal Crystallization**

Hydrothermal synthesis utilizes single or heterogeneous phase reactions in aqueous media at elevated temperature and pressure to crystallize the metal oxide directly from solution [33]. Nanoceria can be synthesized from aqueous cerium nitrate solution in hydrothermal conditions [34-36] using a mixture of hydrogen peroxide (H2O2) as oxidizer and ammonium hydroxide (NH4OH) as mineralizer [37]. Nanoceria (9nm) can be synthesized by microwave thermal decomposition method using cerium nitrate, propylene glycol and ammonia as a precursors [38]. Cerous nitrate and zirconium nitrate and hydrazine hydrate used as precursor to prepare catalytic Ce0.6Zr0.4O2. nanoparticle of less than 50 nm under high temperature[39].

- **Microemulsion**

Microemulsions are colloidal '*nano-dispersions*' of water in oil (or oil in water) stabilized by a surfactant film which can be used to carry out synthesis of nanoparticles [40]. Pure and doped nanoceria (3nm) with narrow size distribution can be prepared under soft conditions [41] with AOT as a surfactant [42].

- **Spray pyrolysis**

Flame spray pyrolysis (FSP) helps in the single step preparation of multi-component nanomaterials like the CeO^{2}-TiO_2 photocatalysts [43]. Hydrated cerium nitrate precursor dissolved in an ethanol/diethylene glycol butyl ether mixture injected into a methane/air premixed flame using an electrospray method leads to the synthesis of nanoceria [44].

- **Surface functionalization and stabilization**

Nanoceria suitable for biomedical applications should remain stable in solutions containing high concentrations of proteins and salts and in cell culture media [45]. Stabilization of nanoceria with low molecular weight molecules called dispersants or ligands modifies their interaction due to steric or electrostatic barriers [46] whereas surface functionalization with high molecular weight polymeric species like dextran, glucose, polyethylene glycol (PEG), polyacrylic acids, polyvinyl alcohol (PVA), methanol [47-52] and phosphonated-PEG oligomers [46] changes the zeta potential of the system thereby extending its stability over a wide pH range suitable for various applications such as catalysis of synthesis of polyhydroquinoline derivatives [53]. Moreover PEG functionalized nanoceria has additional advantages in tuning the regeneration of Ce^{3+} state of nanoceria [54].

CELLULAR UPTAKE MECHANISM OF NANOCERIA

The cellular uptake mechanism study of fluorophore (carboxyfluorescein) associated nanoceria in keratinocyte model system reveals endocytosis as the underlying mechanism [55-57] whereas cellular uptake of citric acid coated and PAA coated nanoceria depends on the surface charge [48]. Apoferritin encapsulated nanoceria promotes the cellular internalization process mediated via specific ferritin receptors and prevent the adverse interactions between the nanoceria and biomolecules in the cytoplasm [58]. Current investigations are aimed towards studying the cellular uptake mechanisms of nanoceria and the toxic responses induced depending on the charge and cellular localization [59].

BIOMEDICAL APPLICATIONS

Nanoceria due to its unique redox chemistry are currently investigated for their possible applications in biomedicine.

- **Free Radical Scavenger**

Hydroxyl radical is one of the strongest oxidants and can induce oxidative stress mediated DNA damage, protein damage and lipid peroxidation and these conditions may lead to induction of cancer, tissue injury, renal failure and aging [60-63]. Because of ceria's ability to cycle between the +3 and +4 oxidation states, cerium metal can catalyze Fenton-like reaction with hydrogen peroxide [64]. The Ce^{3+}/Ce^{4+} ions concentration ratio in nanoceria is important to determine the number of oxygen vacancies at the surface and the capability to react with superoxides and hydrogen peroxide [12]. By virtue of this ability nanoceria prepared by hydrothermal synthesis are capable of reduction of hydroxyl radical concentration and their ability to do so, increases with decreasing size [65]. Superoxide dismutase and catalase are the first line of defense against oxidative stress under physiological and pathological conditions. Thus therapeutics mimicking their antioxidant activity is highly sought for the treatment of diseases which progress though oxidative stress [66]. Nanoceria show catalase and SOD mimetic cytoprotective activity [67] in preparations with higher levels of Ce^{+4} as opposed to Ce^{+3} [68]. Apart from the reactive oxygen species, the formation of reactive nitrogen species stimulate mitochondrial production of superoxide, hydrogen peroxide, and peroxynitrite thereby causing DNA damage and finally stimulating the apoptotic pathway [69]. Recent studies reveal that nanoceria pretreatment of cardiomycetes as well as cardiac progenitor cells cause significant inhibition of H2O2 and cigarette smoke-induced ROS production, depletion of antioxidant enzymes and intracellular glutathione content along with a significant down-regulation of NF-κB-regulated inflammatory genes tumor necrosis factor-α, interleukin (IL)-1β, IL-6, and inducible nitric-oxide synthase thus making it a potent therapeutic option for the treatment of smoking related diseases [70, 71] and ischemic cardiomyopathy in mice by decreasing serum levels of monocyte chemo attractant protein-1, C-reactive protein, and total nitrated proteins [72]. Nanoceria administration in monocrotaline induced hepatotoxicity rat models results in significant increases in hepatic catalase and superoxide dismutase (SOD) activities and thus serves as an effective hepatoprotective agent [73]. Administration of a combination of nanoceria and sodium selenite to streptozotocin-induced diabetic rats show significant improvement in biomarkers of diabetes including oxidative stress, energy compensation (ADP/ATP) and lipid profile [74]. Macrophage and epithelial cells treated with nanoceria particles exert a cytoprotective effect due to its antioxidant properties as shown by oxidant injury paradigm [75]**.**

- **Neuroprotective activity**

Nanoceria plays a protective role against production of ROS and Amyloid-beta 1–42 (Ab) which are considered as major etiological and pathological factor in the promotion of neurodegenerative diseases like Alzheimer's Disease (AD) [76-80]. PEG conjugated nanoceria (3-5nm) functionalized with an amine group followed by anti Ab antibodies treatment significantly reduce the ratio of apoptotic nuclei and helps in the treatment of AD [81]. Likewise one of the factors for induction of Parkinson's disease is the reduction of dopamine due to degradation of dopaminergic neurons which can be treated by grafting of dopamine generating neurons generated from embryonic stem cells [82] during which monitoring the level of dopamine in *in vitro* cultures of embryonic cells can be done efficiently using multilayer thin film electrode prepared by using PAA coated nanoceria and poly-diallyl dimethyl ammonium chloride [83]. Nanoceria prevents ischemic insult in adult rat spinal cord neurons as suggested by oxidative injury assay [84, 85]. Thus further studies should be done regarding the application of nanoceria as a therapeutic strategy for ROS mediated disorders.

- **Retinopathy**

Retinal photoreceptor cells possess the highest rate of oxygen metabolism as they are constantly bombarded with photons of light which increases their risk of oxidative damage mediated diseases including diabetic retinopathy, macular degeneration and glaucoma [86-90]. *In vivo* tests and electroretinography wave amplitude studies followed by treatment with nanoceria show functional improvement of retinas in albino rat eyes [91, 92], Tubby mice by the

upregulation of neuroprotection-associated genes and down-regulation of apoptosis signaling pathways [93] and Vldlr knockout mice by inhibition of ROS in the retina, increase in vascular endothelial growth factor (VEGF) in the photoreceptor layer [94, 95].

Carboxybenzenesulfonamide, an inhibitor of the enzyme human carbonic anhydrase (hCAII) which is associated with glaucoma when attached to nanoceria particles using epichlorohydrin bind to the active site of hCAII thereby preventing progression of the disease [96]. Thus the use of nanoceria as a direct therapy for neurodegenerative diseases represents a novel strategy for protection of the eye against the generation of reactive oxygen species [97].

- **Cancer Therapy**

Scientific advances enabling a detailed exploration at the level of DNA, RNA, proteins and metabolites which are in nanoscale [98]. Current investigations of nanoceria aim towards application of nanoceria in providing a cure for cancer indicate that nanoceria is nontoxic towards normal cell lines (L929) but cytotoxic towards prostate cancer cell lines (PC-3) as analyzed by MTT assay. This selectivity of the nanoceria can be harnessed for finding more reliable options for cancer treatment [99]. Unlike other nanoparticles used to deliver DNA, RNA, protein, or drugs, nanoceria themselves act as therapy, as they directly scavenge the reactive oxygen species. Studies demonstrate that drug delivery by nanoceria depends on the differential surface-charge-dependent cellular localization. When nanoceria are localized in the lysosomes (acidic) of cancer cells, they exhibit significant cellular toxicity, but they show minimal toxicity when localized in the cytoplasm (neutral pH) of normal cells [100]. This property of nanoceria can be utilized for selective drug delivery options. Further tuning the surface charges of nanoceria improves the adhesion of ligands and enhances the adhesion of a ligand conjugated nanoceria with the cell surface thereby enhancing the receptor mediated cellular uptake [101]. Current investigations show that nanoceria confers radioprotection to normal human breast line by scavenging the free radicals generated due to the radiation exposure as opposed to human breast tumor line, MCF-7 [102] which indicates that treatment of nanoceria prior to the radiotherapy can protect the normal cells from radiation induced damage. The reliable and sensitive detection of cancer-specific biomarkers is important for the diagnosis and treatment of cancer. Nanoceria is able to oxidize various colorimertic dyes at acidic pH, such as TMB and AzBTS, and using this ability of nanoceria designing diagnostic assays for screening the folate receptors(over expressed in tumours) by immobilizing anti-folate-receptor antibody on the Protein G-nanoceria conjugate is under study [103]. Furthermore the oxidase-like activity of nanoceria can be tuned by changing the pH of the solution, facilitating the mild oxidation of substrate to yield a product with enhanced fluorescent properties like the selective nanoceria mediated oxidation of ampliflu which can be used to develop sensitive cell-based ELISA for detection of folate receptors. The use of antibody-immobilized nanoceria based ELISA is expected in the clinic and field as a robust nanoprobe for efficient and sensitive cellular assays [104, 105].

- **Diagnostic Imaging**

Application of nanoceria (7nm) for imaging of macroglial brain cells does not show any cytotoxic response as opposed to imaging with quantum dots and iron oxide nanoparticles [106, 47]. Cyto-compatible, co-doped nanoceria due to its strong upconversion properties, kills lung cancer cells by inducing apoptosis thereby demonstrating the potential to be used as clinical contrast agents for imaging and as therapeutic agents for treatment of cancer [107].

- **Biosensors**

Sol-gel derived nanoceria films deposited on gold electrode, platinum coated glass plate and even filter paper followed by immobilization with glucose oxidase (GOx) are efficient glucose sensors without the need for any mediator [108-111]. Likewise Cholesterol oxidase (ChOx) immobilized sol–gel derived nanoceria film can be used as cholesterol biosensor to measure cholesterol concentration in serum samples [112].

Rabbit-immunoglobulin antibodies (r-IgGs) and bovine serum albumin (BSA) immobilized nanoceria film fabricated onto an indium–tin-oxide coated glass plate can detect neurotoxin (ochratoxin-A) [113, 114]. Praseodymium associated ceria shows efficient oxygen sensor activity [115]. Nanoceria and chitosan composite matrix developed for the single-stranded DNA probe immobilization can be used as DNA biosensor for the colorectal cancer gene [116].

TOXICITY

Nanoceria acts as an antioxidant but studies indicate that it may induce oxidative stress in cells depending on the ambient pH [105, 117]. Inefficient synthesis methodology can also contribute towards nanoparticle toxicity due to the incorporation of additives, detergents, and solvent chemicals which may not be completely removed [118]. Genotoxicity studies of nanoceria in murine neuronal cells reveal that nanoceria uniquely alter genes related to neurological disease, cell cycle control, and growth [119]. Nanoceria (7nm) particles induce strong DNA lesions and chromosome damage related to oxidative stress in human dermal fibroblasts [120]. Nanoceria can also activate mast cells contributing to pulmonary inflammation, impairment of vascular relaxation and exacerbation of myocardial ischemia/reperfusion injury [121]. Though nanoceria was found to be neurotoxic in rats [122] but studies of mRNA levels of intercellular adhesion molecule 1 (ICAM-1), interleukin (IL)-8, and monocyte chemotactic protein (MCP-1) in aortic endothelial cells show very little inflammatory response [123]. Ceria exposure enhances the rate of fibrillation of the amyloidogenic protein β-2-microglobulin [124].

FUTURE PROSPECTS

Cerium oxide nanoparticles show promising therapeutic results for antioxidant therapy of various neurodegenerative diseases, drug delivery and diagnostics. Thus they induce an array of biological responses which range from cytotoxic to cytoprotective. Recent studies show their application in glucose and cholesterol biosensors. The potential of nanoceria as a therapeutic treatment of chronic neurodegenerative diseases like Alzheimer's and Parkinson's disease needs to be studied in depth and extensively. Further studies are essential for the development of better nanoceria based imaging and diagnostic tools. There is a cause of optimism that many new applications for nanoceria could emerge in the near future and this would lead to a substantial growth and demand for these nanoparticles.

CONFLICT OF INTEREST

The authors confirm that the article content has no conflict of interest.

ACKNOWLEDGEMENTS

The authors are grateful to DST INSPIRE, Delhi, India; Mizoram University, Aizawl, Mizoram ,India and Head, Department of Biotechnology, Goa University, Goa, India for the funding and the facilities provided.

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Received: January 29, 2013 **Revised: May 21, 2013** **Accepted: June 21, 2013**