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Research Article

HYDROXYAPATITE NANOPARTICLES AS DELIVERY SYSTEM IN COMBATING VARIOUS DISEASES

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A B S T R A C T

Many people suffer from bone-related diseases such as osteoporosis, osteosarcoma, microbial infections and cancer throughout the world each year resulting in their deaths. Recently, hydroxyapatite nanoparticles have been emerged as a potent nanotechnology-based delivery system to treat several diseases. Owing to their nanosizes (<100 nm), high surface to volume ratio, easy of surface functionalization and suitable physico-chemical features such as bioactivity, biocompatibility, osteoinductivity and osteoconductivity, they are highly potent and favorable to generate cytotoxicity to kill the cells especially by the high uptake of calcium concentration within the cells. Moreover, their appropriate surface-modifications with ligands and other biomolecules may make them highly efficient carrier to deliver potent loaded-cargos to specific site of interest with a controllable and sustained manner leading to cellular destructions. The review demonstrates their synthesis, surface-functionalizations, mechanism of actions, immune responses and biomedical applications against various diseases to consider them as future nanotechnological delivery system.

INTRODUCTION

Osteoporosis, a growing bony disease, is distinguished by reduced bone mass and micro-architectural bone tissue deterioration accompanied with increased bone fragility and subsequent susceptibility to fracture, and diagnosed when bone mineral density of a patient becomes 2.5 standard deviations or more below the average bone mass value for young healthy adults [Kanis and Kanis, 1994]. In adults, remodeling of bones is performed through a coordinated mechanism by which bone-resorbing osteoclasts remove old bones and bone-forming osteoblasts mineralize and synthesize new bone matrix, while their disturbances in the physiological metabolic process cause reduced bone mass named as degenerative osteoporotic disorder [Beck *et al*., 2012; Riggs and Melton, 2015; Mackey and Whitaker, 2015]. Another neoplastic disorder is osteosarcoma characterized by malignant tumor of the skeleton [Abate *et al*., 2010; Pakos *et al*., 2009]. In this context, the growth of solid neoplasm is accompanied by neo-vascularization i.e. angiogenesis in tumor growth and progression and subsequent metastases supported by the over-expressions of vascular endothelial growth factor (VEGF) and matrix metalloproteinases [Carmeliet and Jain, 2000; Ferrare and Kerbel, 2005; Fukumura and Jain, 2007; Hao *et al*., 2015; Li *et al*., 2015; Ouyang *et al*., 2015; Shojaei, 2012; Holash *et al*., 1999; Vu *et al*., 1998].

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In another concern, mitochondrial dysfunction causes the generation of superoxide anion free radicals due to electron transport chain leakage resulting oxidative stress induction through reactive oxygen species (ROS) over-production [Turrens, 2003]. This ROS-production, inturn, causes several harmful consequences such as protein and lipid oxidations, mitochondrial RNA / DNA damages, Ca^{2+}-dependent mitochondrial permeability transition pore activation and cytochrome c liberation following cellular apoptosis [Orrenius *et al*., 2007]. Both the mutations of mitochondrial proteins and oxidative stress trigger the cell death signaling cascade leading to organ damage, failure and disease development reflected on diabetes, cancer, neurodegenerative Alzheimer's and Parkinson's diseases, ischemia-reperfusion injury and heart failure [Taylor and Turnbull, 2005; Butterfield, 2002; Bayeva *et al*., 2013; Moreira *et al*., 2010; Weissig *et al*., 2007]. Furthermore, other criterion is the microbial infections associated with multidrug resistance and biofilm-development [Mandal, 2018]. These diseases generally develop when antioxidant defense system and innate and acquired immune system of the body become failure to overcome the inductive origin of disease development [Mandal, 2018].

In the past decades, global investigators have attempted to discover new solutions for improving treatments utilized for various bone related disorders, injuries, cancer and microbial infections. Their attention has been concentrated to the biomaterial field to create and develop new and improved ceramic biomaterials for tissue engineering where nanotechnology has restructured the conventional method of

ceramic-usage in medical sciences. In general, patients suffer from drug resistance, insolubility, toxicity, bioavailability, enzymatic degradation, physiological barriers and specific target efficacy. In this concern, hydroxyapatite nanoparticles (HAp NPs, $Ca(PO_4)_6(OH)_2$), the main component of the hard tissue such as bone and teeth, have attracted more attention in the field of biomedical applications owing to their exceptional characteristics such as favorable bioactivity, bioresorbablity, biocompatibility, biodegradability, osteoinductivity and osteoconductivity in treating bone related diseases, infective diseases, cancer and repair of hard tissue injury [Zhou and Lee, 2011; Danoux *et al*., 2014; Kobayashi and Murakoshi, 2014; Sooksaen *et al*., 2010; Zyman *et al*., 2013]. HAp NPs can exhibit significant cytotoxicity to diseased cells or organisms through mitochondria-dependent apoptotic induction emerging from oxidative stress and retardation of protein synthesis owing to their profuse nuclear and endoplasmic reticulum localizations as well as high intracellular concentrations of calcium ions (Ca^{2+}) [Yuan *et al*., 2010; Meena *et al*., 2012; Qing *et al*., 2012; Chen *et al*., 2007; Xu *et al*., 2012; Han *et al*., 2014; Tang *et al*., 2014]. Moreover, HAp NPs may also be utilized as a carrier for protein, gene and drug delivery [Tada *et al*., 2010; Matsumoto *et al*., 2004; Uskokovic and Uskokovic, 2011]. These NPs can adsorb various chemicals onto their surfaces through electrostatic interactions, and owing to their soluble capability, the cargos may be liberated at specific targeted sites, while their solubility may be regulated by different substituted ions such as chloride, fluoride or carbonate, and low pH medium located in cancerous areas [Gomi *et al*., 1993]. Utilizing surfactants as the structure directing agent based on different synthesis techniques, pores were introduced into the diverse structure of HAp at the nano level to achieve desired loading and release profile of cargos [Al-Sokanee *et al*., 2009; Palazzo *et al*., 2005; Sadat-Shojaj *et al*., 2013]. In order to modulate HAp NPs-surface, they may be coated with three layers of poly (allylamine), alginate and alendronate where outer alendronate layer is used as a targeting moiety to bind bone tissue and also as anti-resorptive drug to induce osteoconduction leading to increment of bone density in bone matrix for the treatment of osteolysis [Allen and Cullis, 2013]. HAp NPs loaded with appropriate active biomolecules may also be surface-functionalized with various ligands such as monoclonal antibody, sugar, protein, genes, lipids, poly ethylene glycol, poly (lactide-co-glycolide), poly (glycolide)-poly (ethylene glycol) and doped with rare-earth ions and metals to treat bone related diseases, cancer, metastases and infections [Dougall *et al*., 1999; Kim *et al*., 2016; Tokatlian and Segura, 2010; Giger *et al*., 2013; Hwang *et al*., 2016; Khajuria *et al*., 2016; Coelho *et al*., 2013; Han *et al*., 2008; Turner *et al*., 1989; Turner and Claringbold, 1991; Shi *et al*., 2009; Tai *et al*., 2013; Perry *et al*., 2012; Huang *et al*., 2008; Singh *et al*., 2015; Puljula *et al*., 2015].

This review demonstrates a survey of latest investigations regarding hydroxyapatite nanocomposites dealed with active ingredients-loaded preparatory methods, surface-modifications / encapsulations and doping with biomarkers accompanied with their targeting to specific diseased sites of interest crossing biological barriers for considering them as a highly promising delivery system against various diseases.

Synthesis of hydroxyapatite nanocomposites

HAp NPs are generally prepared by utilizing chemical precipitation, emulsion, hydrothermal and sol-gel methods. The most commonly used chemical precipitation methods are followed by any of the chemical reactions:

1. $10\ Ca(OH)_2 + 6\ H_3PO_4 \rightarrow Ca_{10}(PO_4)_6(OH)_2 + 18\ H_2O$
2. $10\ Ca(NO_3)_2 + 6\ (NH_4)_2HPO_4 + 2\ H_2O \rightarrow Ca_{10}(PO_4)_6(OH)_2 + 12\ NH_4NO_3 + 8\ HNO_3$

The basic common synthesis process involves the drop by drop addition of one phosphate reagent to the calcium reagent under continuous stirring, while the molar ratio of Ca/P maintained at HAp NPs is 1.67. In general, 5M aqueous Ca^{2+} ion solution is made by liquefying 0.03M $Ca(NO_3)_2.4H_2O$ in 6 mL distilled water. An aqueous 1500 µg / mL drug solution is separately prepared by dissolving drug into DMSO / Tween 20 and finally in distilled water. Afterthat, the solutions are stirred until a clear suspension is found. NH_4OH is adjoined drop by drop to maintain the pH of Ca^{2+} solution at 9 followed by the slow-addition of drug solution into this solution with continuous stirring. For maintaining the molar ratio of Ca to P at 1.67:1 in the reaction mixture, 0.018M $(NH_4)_2HPO_4$ is adjoined to Ca^{2+}-drug solution following the re-adjustment of the pH of the reaction-mixture to 9 by drop by drop NH_4OH-addition. The dissolution is kept for 24 h at room temperature and spun to void supernatant out. The precipitate is then cleansed with phosphate-buffered saline (PBS, pH 7.0) and de-ionized water three times for the removal of NO_3^- ions and loosely bound other components. 2M% Zn^{2+} and Mg^{2+}-doped HAp -drug NPs may be prepared by the adjoining of the needed amount of $Zn(NO_3)_3.6H_2O$ and $Mg(NO_3)_3.6H_2O$ respectively in the Ca^{2+} aqueous solution. After cleansing, NPs are dried at room temperature. Porous HAp NPs may be prepared by various methods such as double emulsion [Shum *et al*., 2009], self-assembly [Saha *et al*., 2009; Xia *et al*., 2009; Ye *et al*., 2010; Huang *et al*., 2011], solvo-thermal [Ma and Zhu, 2009], hydrothermal [Wang *et al*., 2008; Ng *et al*., 2010; Guo *et al*., 2011; Guo *et al*., 2012], sol-gel [Dou *et al*., 2012] and spray drying [Sun *et al*., 2009]. During preparation of HAp NPs, an extensive regulated over size and morphology may be attained by modifications of experimental conditions [Zhang *et al*., 2009; Wuthier *et al*., 1985; Ren *et al*., 2013], the inclusion of surfactants [Cao *et al*., 2004] such as saccharides, cetyltrimethylammonium bromide (CTAB) and stearic acid, and chelating agents [Lopez *et al*., 1998; Ma, 2012] such as potassium sodium tartrate and trisodium citrate. Utilizing pore expander and cationic co-surfactant such as 1-dodecanethiol and CTAB respectively, large pore HAp NPs may also be synthesized [Bakhtiari *et al*., 2016].

Nanocrystalline hydroxyapatite doped with rare-earth samarium (Sm) element may be produced by adjusting the atomic ratio of Sm / [Sm+Ca] from 0% to 10% and [Ca+Sm] / P as 1.67. Samarium (III) nitrate hexahydrate and calcium nitrate tetrahydrate are liquefied in deionised water to get 300 mL Ca+Sm solution, while ammonium dihydrogen phosphate is liquefied in deionised water to form 300 mL P-containing solution. Then Ca+Sm solution is stirred at 100°C for 30 minutes, while pH of P-containing solution is set to 10 with NH_3 followed by stirring for 30 minutes. Then the P-containing solution is adjoined drop-wise into the Ca+Sm solution followed by stirring for 2 h, while the pH is adjusted

to 10. Afterthat, the precipitate (Sm:HAp NPs) is cleansed several times with deionised water and dried at 100°C.

Grafting or coating of HAp NPs with polymers suited with the copolymer / polymer matrix is also performed by several methods. For PGA-PEG coating of HAp NPs, 40 mg of this nanoparticles and 464 mg (4 mmol) of glycolide are dried overnight under 32 in Hg vacuum. Then HAp NPs and glycolide are dissoluted in 3 mL dimethylformamide (DMF), while glycolide, phosphazene base P_2-t-Bu at 2M in THF is added to it. The reaction vessel is purged under N_2 continuing 24 h reaction, while PGA coating-thickness is regulated by altering the ratio of glycolide and HAp NPs. Afterthat, 100 mg (0.02 mmol) of methoxy-poly (ethylene glycol)-isocyanate is adjoined directly into the reaction-mixture and kept on with for an additional 6 h under N_2 atmosphere. The yield is cleansed twice with DMF, and probable free polymer / monomer once with double distilled water through spinning at 5000 rpm for 5 min and lyophilized. The surface of HAp NPs may also be grafted through the reaction with their surface hydroxyls with poly (L-lactide-co-glycolide) (PLGA) to improve characteristics, dispersability and tensile strength [Song *et al*., 2013]. Furthermore, chitosan and carboxymethylated-chitosan may also be coated on the surface of HAp NPs to get higher solubility, viability and narrower size distribution [Muzzarelli *et al*., 2012; Berger *et al*., 2004; Kaya *et al*., 2015; Kaya *et al*., 2014; De Souza *et al*., 2009; Liang *et al*., 2004; Dumont *et al*., 2016; Barna *et al*., 2015]. In addition, to overcome microbial infection, biofilm and drug resistance, silver ions have been incorporated into HAp NPs-surface following co-precipitation method [Rameshbabu *et al*., 2007; Kim *et al*., 1998; Lim *et al*., 2015].

Characterizations of hydroxyapatite nanocomposites

The size and morphology of HAp nanocomposites may be monitored and determined by using transmission electron microscope, while their phase composition may be determined by X-ray diffraction analysis. The composition of nanocomposites may be analyzed by Fourier transform infrared (FT-IR) spectroscopy, while the zeta potential, hydrodynamic size and surface charge of particles in suspension may be measured by utilizing Zetasizer Nano ZS dynamic light scattering device.

Mechanism of action of hydroxyapatite nanoparticles

HAp NPs may be interiorized by cells via pinocytosis, phagocytosis, caveolae / clathrin –independent endocytosis and nonendocytosis pathways, while elevation of Ca^{2+} within cells and around endoplasmic reticulum hampers cellular Ca^{2+} homeostasis causing oxidative stress mediated cytotoxicity leading to caspases- 9 and 3 -activated cellular apoptosis via the mitochondrial-dependent pathway, inhibition of protein synthesis by reducing the mRNA binding to its proper ribosomal binding site owing to their high adsorption capability for ribosome, and the cell cycle arrest in G0/G1 phase causing inhibition of cell proliferation, accompanied with necrosis and autophagic cell death [Zhao *et al*., 2011; Rothen *et al*., 2006; Monteith *et al*., 2007; Zhivotovsky and Orrenius, 2011; Meena *et al*., 2012; Xu *et al*., 2012; Han *et al*., 2014; Beland *et al*., 1979]. The overload of Ca^{2+} by the exposure of HAp NPs is caused by their quick decadence in acidic cancer cells throughout intracellular translocation in phagolysosomal compartment containing hydrolases, while exorbitant extracellular Ca^{2+} influx, Ca^{2+} liberation from intracellular storage or decreased Ca^{2+} efflux may also cause in raised Ca^{2+} level to produce cytotoxicity [Zhao *et al*., 2011; Bloebaum *et al*., 1998; Tang *et al*., 2014; Orrenius *et al*., 2003; Zhivotovsky and Orrenius, 2011].

Hydroxyapatite nanoparticles as delivery vehicle

HAp NPs have been applied as a carrier to deliver varieties of therapeutics such as drugs, proteins, enzymes, antigens and genes [Thomas *et al*., 2015; Thomas *et al*., 2016]. HAp NPs-coated liposomes have been utilized as efficacious drug delivery vectors for hydrophobic compounds such as indomethacin, a non-steroidal anti-inflammatory drug [Xu *et al*., 2007]. The osteoconductive HAp NPs loaded with bisphosphonate alendronate have been coated with layer-by-layer pH-responsive biopolymers poly (allylamine) and sodium alginate to treat osteoporosis for targeted drug delivery by providing superb biocompatibility and surface functionality via their COOH groups [Leu *et al*., 2006; Liang *et al*., 2012]. Based upon the surface functionalization of nanoparticles, especially by positively charged polymer chitosan coating, celecoxib has been encapsulated in the HAp NPs coated system for the treatment of colon cancer as well as tumor growth inhibition as an efficient vehicle for targeted drug delivery as positively charged HAp nanocomposites become highly accumulated into negatively charged cancer cells through electrostatic interactions [Yang and Hon, 2009; Li *et al*., 2009; Venkatesan *et al*., 2011]. As hydrophilic and negatively charged hyaluronic acid (HA) is a rising polymer to target the CD44 glycoprotein, expressed in tumor cells, some investigators have designed doxorubicin-loaded HAp NPs coated with HA to get efficient tumor targeting delivery [Zollen, 2011; Xiong *et al*., 2016]. Cancer may be dealt with cytotoxic free radicals and ROS through photodynamic therapy, but this technique has limitation owing to the low tissue piercing capability of visible light [Robertson *et al*., 2009; Klein *et al*., 2013]. In this context, researchers have reported metal-doped HAp NPs to utilize for cell apoptosis and *in vivo* tumor growth inhibition after irradiation with γ-rays as radiosensitizer metal ions give rise to significant ROS generation in cells for their damages [Kwatra *et al*., 2013; Matusiewicz, 2014; Chen *et al*., 2016]. Porous HAp NPs loaded with different antibiotics such as norflaxacin, ibuprofen, vancomycin exhibited high drug loading capacity and sustained liberation characteristics to the target site against infections [Melde and Stein, 2002; Tang *et al*., 2011; Ye *et al*., 2010]. Some researchers investigated in vitro desorption and adsorption of few anticancer drugs such as di (ethylenediamineplatinum) medronate, cisplatin and alendronate towards plate-shaped and needle-shaped porous HAp NPs, while the specific characteristics of the drugs and the morphology of the HAp NPs affected the desorption and adsorption kinetics of the drugs [Palazzo *et al*., 2007]. The other group of researcher prepared porous HAp NPs-surface functionalized and modified by using polyethylene glycol and folic acid with the attachment of anticancer paclitaxel drug, while the drug liberation profile exhibited an initial burst due to easily detachment from the NPs-surface, followed by a sustained release [Venkatasubbu *et al*., 2013].

Biodistribution and elimination of hydroxyapatite nanoparticles

The biodistribution pattern of HAp NPs differs on their morphology, size, surface charge and surface chemistry along

with the modes of administration such as oral, intravenous, intraperitoneal, subcutaneous and intramuscular. HAp NPs may be decomposed to their consisting ions i.e. Ca^{2+}, PO_4^{3-} and OH^- into the body after administration in an acidic environment due to the exchange of phosphate ions by hydrogen ions catalyzation from the NPs-surface into solution and recycled in bone construction [LeGeros, 1993; Christoffersen and Christoffersen, 1982]. Some particles may be endocytosed or phagocytosed by macrophages to accumulate into reticuloendothelial cells and become decomposed by lysosomal hydrolytic enzymes [Huang *et al*., 2004]. Smaller (<5 nm in size) HAp NPs are generally eliminated through urine, whereas larger NPs phagocytosed by macrophages undergo hepatobiliary excretion through feces [Mandal, 2018a]. Few researchers demonstrated that the intravenous administration of HAp NPs (40 nm and 200 nm in size) showed their major accumulation in liver and minor in spleen [Li and Huang, 2008; Ong *et al*., 2008]. Another group of investigators demonstrated that the HAp NPs (50-100 nm in size) conjugated to quantum dots showed their accumulation mainly in liver followed by spleen and other tissues elsewhere in the body [Guo *et al*., 2008]. Other group focused that rod-like HAp NPs (40-60 nm in size) loaded with plasmid DNA showed their accumulations in liver, kidney and brain tissue after intravenous administration [Zhu *et al*., 2004]. Few researchers also showed PEG-coated nanoparticles to accumulate in tumor cells through their leaky vascular endothelium due to enhanced permeation retention effect for longer blood circulation [Maeda, 2001].

Immune responses of hydroxyapatite nanoparticles

The administration of HAp NPs affects the rate of polymer matrix degradation causing inflammatory cell-mediated immune responses associated with antigen recognition by T-lymphocytes with consequent activations of the innate immune factors, mainly humoral macrophages and their derivatives, while the mature dendritic cells can activate the adaptive immune responses. The interactions with HAp NPs may cause death of macrophages implying their cytotoxic damage-effect by the suppression of the cellular immune responses. The immune responses occur primarily by the activation of inflammation and tissue damage accompanied by increased pro-inflammatory cytokines -secretions, secondly by the regulation of the secreted inflammatory cytokines governed by the macrophages, and thirdly by the induction of suppressive activity on the monocytes-differentiative energy to produce cytokines [Popova *et al*., 2011]. Some investigators studied *in vitro* cytokine levels while the exposure of HAp NPs with human monocytes THP-1 cells for 24 h exhibited increased levels of TNF-α and IL-1β, and increased IL-6 production in the co-cultures of THP-1cells and human umbilical vein endothelial cells (HUVECs) [Liu and Sun, 2014]. Few other researchers demonstrated the immunostimulatory potentials of HAp NPs in bone-marrow derived macrophages (BMDMs) and bone-marrow derived dendritic cells (BMDCs) and *in vivo* on their shape and size -dependent activations of the NLRP3 inflammosome and IL-1β secretion, while the smaller and needle -shaped HAp NPs significantly increased cytokines-secretion but not larger nanoparticles [Lebre *et al*., 2017].

CONCLUSIONS AND FUTURE PERSPECTIVES

HAp NPs are reported to be a suitable candidate for biomedical usages due to their good biodegradability, biocompatibility and bioactivity features, though their targeting and controlled contents-release to specific sites depends on the particles' synthesis, shape, size, compositions and surface modifications. Use of surfactants and ligands for the synthesis of HAp NPs to overcome aggregation or agglomeration, make them nano or meso -porous utilized for cargos- loading and release for specific targeting to cells owing to the NPs' high surface area and pore volume. Moreover, their doping with active compounds, rare-earth ions or metals makes them multifunctional not only for the treatments of low-bone density pathologies but also for the microbial, biofilm or cancer related diseases. The previous studies demonstrated that medium lethal dose (160 mg/kg) of HAp NPs to Wistar rats caused their deaths due to acute capillary blockage for the accumulation of NPs-aggregates [Aoki *et al*., 2000]. Therefore, the synthesis of the particles should be nano or meso -porous coated with cargos, ligands or doping with other materials to overcome the biological barriers, drug resistance, biofilm and toxic side effects and to deliver the specific active ingredients to the diseased site with sustained release manner. However, it is needed a thorough systematic study to synthesize HAp NPs with appropriate size, shape and functionalization with their biodistribution, pharmacokinetics, elimination, immune responses and efficacies to overcome systemic toxicity before going to clinics for consideration as delivery system for biomedical applications against different diseases.

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