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REVIEW ARTICLE

An Overview of Synthesis Based Biomedical Applications of Hydroxyapatite Nanomaterials

Netra Lal Bhandari[*1], Sunita Bista[1], Tika Ram Gautam[1], Kabita Bist[1], Ganesh Bhandari[1], Sumita Subedi[2], Kedar Nath Dhakal[3]

[1]*Department of Chemistry, Tri-Chandra Multiple Campus, Tribhuvan University, Kathmandu, Nepal*
[2]*Department of Chemistry and Chemical Engineering, Inha University, Incheon, South Korea*
[3]*Central Department of Chemistry, Tribhuvan University, Kirtipur, Kathmandu, Nepal*
Corresponding E-mail: netra.tu.edu@gmail.com

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Abstract
Hydroxyapatite (HAp) is the mineral phase of animal bones embedded in the collagen-containing organic matrix of the bones. It is a naturally optimized material that provides physical support to the bones. Hydroxyapatite-based biomaterials, hence, find wide biomedical applications especially in orthopedics, dentistry, and tissue engineering due to their biocompatibility, bioactivity, osteoconductivity, and similar chemical composition of HAp to that of minerals present in animal bones. Different physicochemical synthetic methods and available natural biogenic sources have been reported for the preparation of nano-HAp. However, particle size, aspect ratio, morphology, crystallinity, and the distribution of HAp in biomaterials have significant effects on their biomedical applications. This paper has summarized some methods of extraction of nano-HAp from different biogenic sources including bio-wastes. Furthermore, it focuses on some facile wet chemical synthetic routes of preparing nano-HAp with controlled particle size and morphology, higher crystallinity, and native bone architectures. This review article aims to correlate some simplistic and cost-effective biosynthetic approaches of nano-HAp, its properties, characterization techniques, and its size and morphology-dependent biomedical applications.

Keywords: Hydroxyapatite, wet chemical methods, sustainable biogenic sources, biomedical applications

Introduction
Hydroxyapatite (HAp) [$Ca_{10}(PO_4)_6(OH)_2$], one of the specially developed bio-ceramics, composed of major components of the animal bones and teeth is widely used for biomedical applications and dental implants [1-5]. HAp contains calcium, hydroxyl groups, and phosphate groups as its major components in crystalline form and has hexagonal crystal structure as shown in Figure 1 [6]. The calcium to phosphorous molar ratio 1.67 is taken as the best one for its biomedical applications specially in bone regeneration and substitution. HAp is present in animal bones being connected with organic collagen fiber (matrix). Its biocompatibility, non-toxicity, osteoconductivity, and similar chemical composition and structure to the natural bones, host response in a biological environment etc, attracts the attention of scientists to prepare it as an essential biomaterial in tissue engineering, bone fillers, soft tissue component, in drug delivery systems, etc. [4,7-12]. On the other hand, its poor mechanical and rheological properties have attracted other biomaterials for their combination to generate strong and high-value hybrid biomaterials [3,13-17]. Though it is limited in direct load bearing applications, it is widely used for biomedical applications as a bone graft substitute and implant coating agent [18]. HAp based biocompatible hybrid materials have received considerable attention in this regard because of hemostatic properties, bone healing functions and their ability to mimic natural bones [16,17]. However, the size, morphology, and crystallinity of HAp particles greatly alter the functional performance of these biomaterials in biomedical applications mostly in bone regeneration, reconstruction and replacement [19].

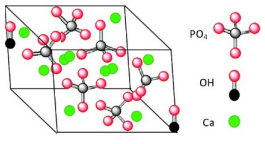


Figure 1: *Crystalline structure of hydroxyapatite and its basic components [6]*

Incorporation of dual bioactive ions into nano-HAp particles produces biomaterials with improved bioactivities and osteo-conduction applicable for line cell imaging [20]. Nano-sized HAp better improves cytophilicity and possesses greater bioactivities, biosorption and proliferation to bone marrow optimizing biological functionality if compared to conventional micro/macro-sized HAp [19,21,22]. Similarly, crystalline HAp provides a comparatively suitable substrate to mesenchymal cells of bone marrow in terms of their adhesion, proliferation, and differentiation to osteoblasts than amorphous HAp even with their comparable size [23]. Rod and needle-shaped HAp particles disperse better in a matrix than spherical, cuboidal, and mixed shaped HAp [24]. Hence, crystalline structure with precisely controlled nano-size, phase, morphology, composition, Ca/P ratio, etc. are the fundamental criteria for HAp to find biomedical applications [23]. On the other hand, the limitation of its poor mechanical and compressive strength can be overcome by its combination with natural and biocompatible polymers to prepare elastic and tough biomaterials for biomedical applications. [9,22]. Synthetic conditions and parameters (mostly in wet chemical methods) such as concentration, temperature, pH value, addition rate of reactants, solvent system, drying conditions, etc. adopted for the preparation of HAp greatly affect the particle size, morphology, crystallinity, and calcium to phosphorous ratio of the materials [25,26]. Similarly, the conditions employed for the extraction of HAp from biogenic sources alters the size, phase and geometry of HAp particles [27,28], HAp, as an essential nanomaterial for the preaparation of most of the high-value biomaterials of biomedical importance can be prepared *via* facile routes from various naturally available biogenic sources (including bio-wastes) and some wet chemical synthetic methods in ordinary laboratories [29]. Such biogenic sources include egg shells, animal bones, sea shells, fish scales, etc, while wet chemical methods include precipitation, sol-gel, hydrothermal, hydrolysis methods etc. Moreover, these naturally available biogenic sources can be the potential and sustainable HAp-sources leading to the biomedical applications with ecological management (explained later) [29-32].

This review article summarizes the methods of preparating nano-HAp adopting facile wet chemical techniques and its extraction from naturally available biogenic sources (bio-wastes) in a cost effective way, characterization of their composition, structure and morphology, and size and crystallinity dependent biomedical applications of related bio-nanomaterials.

Facile preparation of HAp

Different mechanochemical, wet chemical, and thermal techniques of HAp synthesis are reported in literatures. Some facile wet chemical methods and biogenic sources of preparing nano-HAp in an ordinary chemistry laboratory are discussed here.

I. Wet chemical routes

It comprises different synthetic routes such as precipitation, sol-gel, hydrolysis**,** hydrothermal, sonochemical, emulsion method etc, [18,33-39]. All of these methods can be employed to produce crystalline HAp, however, some of them require thermal treatment of the materials at elevated temperature for higher crystallinity. Meanwhile, phase and morphology transformation may occur at higher trremperature [26,40]. Different wet chemical parameters such as the concentration of starting solutions, the addition rate of reactants, temperature, pH value, *etc.* should be controlled to produce monophase crystalline HAp [41]. Precipitation and sol-gel methods are summarized here as facile wet chemical methods of preparing crystalline HAp.

a) Precipitation method

It is the mostly used wet chemical technique for the synthesis of HAp by the precipitation reaction using calcium oxide (CaO), ortho-phosphoric acid (H_3PO_4), calcium hydrogen phosphate [$Ca(H_2PO_4)_2$], ammonium hydrogen phosphate [$(NH_4)_2$ HPO_4] as calcium and phosphorous precursors [41,42]. The chemical reactions occurring in this method are presented as follows [29,37].

$$CaO + 3H_2O \longrightarrow 3Ca(OH)_2$$

$$3Ca(OH)_2 + 3H_3PO_4 \longrightarrow 3CaHPO_4 + 6H_2O$$

$$5Ca(OH)_2 + 3H_3PO_4 \longrightarrow 1/2Ca_{10}(PO_4)_6(OH)_2 + 9H_2O$$

$$10Ca(OH)_2 + 6(NH_4)_2HPO_4 \longrightarrow Ca_{10}(PO_4)_6(OH)_2 + 6H_2O + 12NH_4OH$$

$$Ca(OH)_2 + 3Ca(H_2PO_4)_2.H_2O \longrightarrow Ca_{10}(PO_4)_6(OH)_2 + 15H_2O$$

Hence, nano-HAp can easily be prepared *via.* precipitation method, however various factors greatly affect the resulting HAp particles. pH value and temperature affect the HAp phase (Ca-deficient, oxy-HAp and carbonated HAp) while drying methods, solvent systems, and dispersant species affect size, morphology, crystallinity, homogeneity, and dispersibility of the particles [25,26,40]. Suitable solvents and concentration of solutions and controlled pH value should be employed to achieve a suitable Ca/P ratio (1.67) because most of the thermal and biomedical properties of the materials depend on this ratio. HAp with this standard Ca/P ratio is thermally stable up to 1400°C but Ca-deficient HAp converts

into ß-tri-caclcium phosphate (TCP) at 900°C [26]. Drying and sintering temperature can be increased for the hardness of materials, however, needle-like morphology (the best suitable for biomedical applications) can be transformed into spherical morphology [40]. Therefore, the '*Heat and Trial'* method as well as '*Single Factor Test Method'* can be adapted to determine the particular conditions of these parameters and minimize above mentioned effects. Another most significant way is to use capping agents in the reaction mixtures which avoid individual particles from nucleation (agglomeration) and modification of size, shape, and morphology [40-43]. Zhang *et al*. has reported the sodium salt of carboxymethyl cellulose (CMC) approach to control the HAp particle size in co-precipitation method. HAp particles with suitable size and orientation to human bones can be prepared adopting this approach. CMC molecules attract Ca^{++} ions from HAp by chelation effect forming Ca-CMC complex which controls the agglomeration of HAp [44].

b) Sol-gel method

The sol-gel method is taken as an efficient and attractive method from economic point of view for the preparation of HAp with higher bioresorbsability and resembling to bone apatite [45]. In this method, solutions of calcium and phosphorous precursors (source of calcium and phosphorous) are used for the preparation of HAp. Aging of these calcium and phosphorous precursor solutions at low temperature to obtain a sol followed by at higher temperature producing a gel is carried out due to which it is named as sol-gel method. Calcination of gel thus obtained at elevated temperature produces HAp [45,46] The mostly used Ca-precursors are calcium nitrate $[Ca(NO_3)_2]$ and calcium diethoxide $[Ca(OEt)_2$ whereas P-precursors are ammonium hydrogen phosphate $[(NH_4)_2HPO_4]$, triethyl phosphate $[(C_2H_5)_3PO_4]$ and triethyl phosphite $[(C_2H_5)_3PO_3]$. Corresponding solutions of these materials are mixed together in drop-wise manner with vigorous stirring under controlled pH and temperature. Continuous stirring of reaction mixture produces an aged gel which is washed until neutral pH and dried. The chemical reaction involved in this method are as follows [29,30,45,47].

$$10Ca(NO_3)_2 + 6(NH_4)_2HPO_4 + 8NH_4OH \xrightarrow[pH=10\text{-}11]{75\ ^\circ C} Ca_{10}(PO_4)_6(OH)_2 + 20NH_4NO_3 + 6H_2O$$

$$Ca(NO_3)_2 + (C_2H_5)_3PO_4 \longrightarrow Ca_{10}(PO_4)_6(OH)_2 + \text{Biproducts}$$

The size and crystallinity of HAp produced also depend upon the medium (ethanol and water) along with other parameters like temperature, pH, etc, [41,48]. Figure 2 shows the synthetic scheme of HAp from the sol-gel method [45].

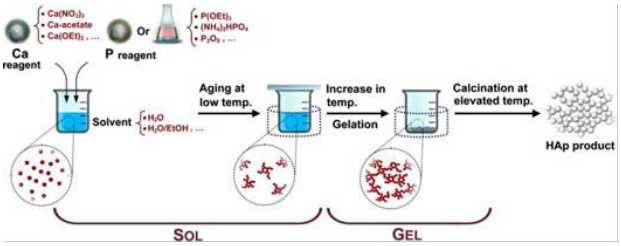


Figure 2*: Schematic synthesis of HAp from sol-gel method [45]*

II) Biogenic routes

Crystalline nano-HAp for biomedical and clinical applications can be extracted from different biogenic sources and bio-wastes adopting different mechanochemical methods [49]. These sources include animal sources (bones, egg shells, etc.), plant sources (fruit peels, leaves, stems, roots, etc), and aquatic sources (corals, sea shells, fish scales/bones, etc.) [50]. Animal and aquatic sources contain HAp in maximum whose calcination gives nano-HAp. Similarly, eggshells are rich in $CaCO_3$ content from which CaO can be derived which can be further converted into HAp as follows;

$$CaCO_3 \xrightarrow{1000\ ^\circ C} CaO + CO_2$$

$$CaO + 6H_3PO_4 \longrightarrow Ca_{10}(PO_4)_6(OH)_2 + 8H_2O$$

Different bio-wastes are used for the extraction of HAp *via* calcination method. Table 1 presents various animal bones, and the related parameters for the extraction of HAp through calcination and sintering.

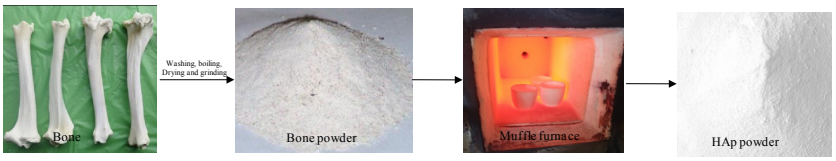
Table 1: *Various animal bones as sources of HAp via calcination and sintering*

Bio-wastes	Temperature (° C)	Time (hour)	References
Fish bones	1300	-	[51]
Pig bones and pig teeth	650, 1050	2	[52]
Human teeth	650, 1050	2	[52]
Bovine bones	750	6	[53]
Buffalo bones	1000	6	[54]
Camelus bones	1000	-	[55]
Pigeon bones	1050	2.5	[56]

Extraction of HAp from various biogenic raw materials require different calcination temperatures time and slightly different procedures. Crystalline HAp can be obtained from these biogenic routes [51-56]. Scheme 1 presents the extraction of HAp powder from buffalo bones.

Comparison of synthetic and bio-derived HAp

Physicochemical and morphological properties of HAp depend on its origin and the employed methods and conditions of preparation [27]. Natural HAp



Scheme 1: *Experimental flow chart showing the extraction of HAp from buffalo bone*

extracted from animal bones *via* calcination process possesses higher crystallinity whereas synthetic hydroxyapatite exhibited low crystallinity [27,28]. Similarly, HAp derived from biogenic sources much more resembles the biological apatite in morphological, structural, and compositional aspects rather than that synthesized by wet chemical methods. Additional minerals essential for human physiology such as Mg^{++}, K^{+}, Si^{++}, Na^{+}, Zn^{++}, Ba^{++}, F^{-} *etc.* will be present in trace amount in bio-derived HAp that are not possible in chemically synthesized HAp. Furthermore, biogenic sources of HAp are calcium and phosphorous precursors themselves due to which HAp derived from them will be rich in the minerals of natural bones [22,24,30,50]. Therefore, it further enhances the bone restoration and bone healing process forming tight and stable bond to the bones in comparison to synthetic HAp. Biogenic sources can be sustainable sources of HAp for biomedical applications not only with better accessibility, extra osteoblast proliferation, and biocompatibility but also from the economical, ecological and environmental points of view [30,50].

Characterization techniques

X-Ray, spectroscopy, and microscopy-based techniques are generally used to investigate phase and crystallinity; chemical composition and functional groups; and morphology of HAp respectively. Spectroscopic techniques such as Fourier transform infrared (FTIR) and Raman spectroscopy are used to elucidate functional groups present in the materials and their chemical composition respectively. Similarly, X-ray photoelectron spectroscopy (XPS) provides elemental composition at parts per thousand range and information about empirical formula, and chemical and electronic state of the elements within the materials. Microscopic techniques such as scanning electron microscopy (SEM), transmission electron microscopy (TEM), and atomic force microscopy (AFM) provide information about the shape, morphology, and dispersion of HAp. X-ray diffraction (XRD) patterns show characteristic diffraction peaks of HAp at various angles to confirm the crystallinity and phase existence of the materials [9,30,54,57-60].

X-ray diffraction (XRD) patterns

X-ray diffraction (XRD) patterns of chemically synthesized hydroxyapatite (C-HAp) and fish bone processed hydroxyapatite (FB-HAp) powders compared with JCPDS data are presented in Figure 3. Intense peaks with lower width of FB-HAp signify its higher crystallinity in comparison to that of C-HAp. On the other hand, few peaks of C-HAp below 25° of 2θ values are not intense and distinguishable. Absence of any additional peaks and peak shifting in C-HAp corresponds to the absence of any impurities and other HAp phases. Furthermore, the most intense peak at (211) plane and 31.6° of 2θ is preferentially expected during the preparation of these materials which is the characteristic peak of HAp. The width of this peak is taken into account to calculate the particle size of HAp synthesized using the Scherrer equation and employing full width at half-maximum

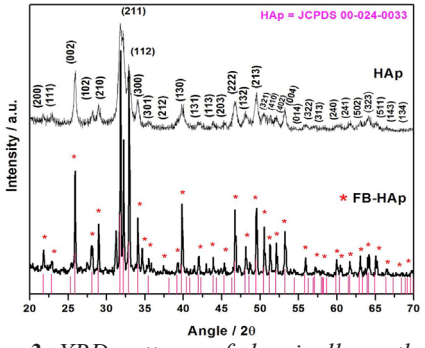


Figure 3: *XRD patterns of chemically synthesized hydroxyapatite (C-HAp) and fish bone processed hydroxyapatite (FB-HAp) [30]*

(FWHM) values. Peaks at miller indices (002), (210), (112), (130), (222), (213), (004) corresponding to 25.8°, 28.8°, 32.1°, 39.7°, 46.6°, 49.4°, and 53.2° of 2θ values respectively are the characteristic peaks of HAp mentioned by its JCPDS number [29,30,58]. From Figure 3 taking the most intense peak at 31.6° of 2θ value, the size of HAp from the chemical process and biogenic routes (fish-bone) is found to be 88.3 nm and 72 nm, respectively [30].

Structural characterization

Comparative FTIR spectra of natural (derived from femoral bones of pig) and chemically synthesized HAp are presented in Figure 4. Phosphate (PO_4^{3-}) and hydroxides (OH^{-}) are the characteristic functional groups present in HAp. OH^{-} groups appeared at the

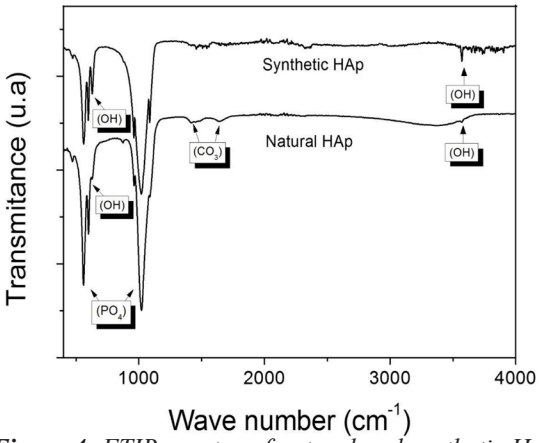


Figure 4: *FTIR spectra of natural and synthetic HAp powders [58]*

wave numbers 629 cm^{-1} and 3570 cm^{-1} are attributed to their bending and stretching respectively. PO_4^{3-} groups appeared at 561 and 598 cm^{-1} correspond to its asymmetric bending while that at 1021 and 1087 cm^{-1} correspond to their asymmetric stretching. The presence of PO_4^{3-} at 961 cm^{-1} is attributed to symmetric stretching. Carbonate $(CO_3)^{--}$ can also be present in HAp depending on the synthetic routes [9,58] which is generally found intense in bio-derived HAp whereas weaker in synthetic HAp [58,60].

Chemical composition

Investigation of the elemental composition of materials is carried out by XPS spectra analyses. XPS spectra are measured by the irradiation of materials with a beam of excited photons to measure kinetic energy and the number of electrons that escape [61,62].

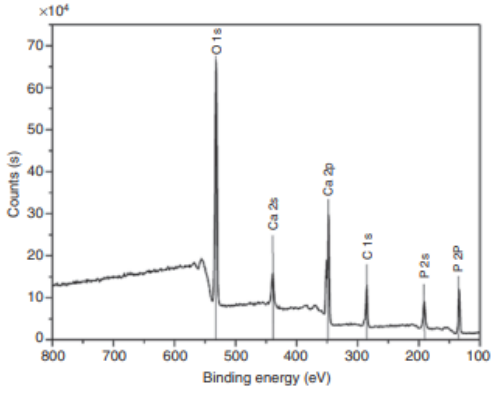


Figure 5: *XPS spectra of pure HAp [59]*

XPS spectra of pure HAp is presented in Figure 5. The peaks appearing at 134 eV is attributed to P 2p spectra of HAp and those at 532 and 347 eV correspond to O 1s and Ca 2p respectively. From these values, Ca/P (standard value: 1.67) ratio in the materials is calculated. These spectra can be resolved into further peaks (under high resolution) with corresponding binding energy values (not shown here). Different functional groups of HAp i.e. OH^-, PO_4^{3-}, CO_3^{2-} can also be assigned from these values [59].

Morphological characterization

Surface morphology of HAp derived from biogenic sources (sea squids) and that of synthetic HAp are depicted in Figure 6. The discrete, elongated and somehow spherical particles of HAp can be observed but their agglomeration can hardly be depicted from Figure 6a. On the other hand, porous structure of HAp can be predicted which is essential to provide a favorable environment for cell growth in biomedical applications. Similarly, the synthetic HAp (Figure 6b) also shows discrete HAp particles alongwith slightly agglomerated morphology. From these observations, it is concluded that morphology of bio-derived HAp is suitable for the cell-materials interaction in biomaterials than chemically synthesized HAp [50,59,63]. However, it is reported that higher porosity can be obtained mostly from wet chemical methods where as higher crystallinity can be obtained from biogenic sources [27].

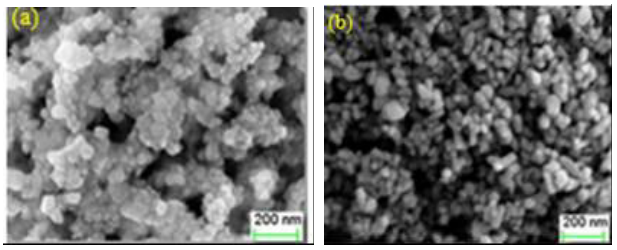


Figure 6: *SEM micrographs (a) Squid pen derived HAp and (b) Synthetic HAp [50]*

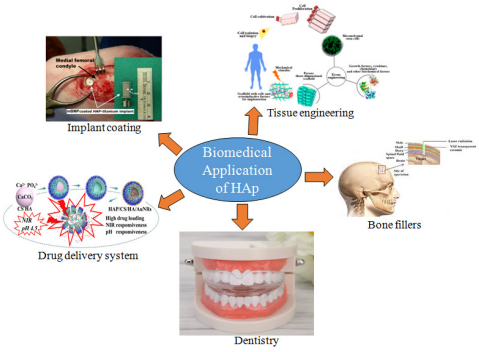
The mechanical property of HAp becomes its wide application in biomaterials, regenerated hard tissues, and in medicine [15,64,65]. The mechanical properties of the HAp and OH carbonated HAp single crystal are different than that of dense HAp ceramic air. It is reported that the bending strength of single-crystal HAp and OH carbonated HAp is 2.5 times higher than that of dense HAp ceramic air [66]. The mechanical properties of HAp are improved by the preparation of composites (for example; HAp-chitosan composite, HAp nano-rods, HAp-Al_2O_3 composites, etc.) [3,14,17,67]. The microstructural and mechanical properties of HAp-Al_2O_3 composites were increased when external commercial inert gas (CIG) was applied in increasing increase order [3].

The physicochemical and morphological properties of HAp depend upon its origin and methods of preparation [27]. Natural HAp obtained from animal bones *via* calcination at 800°C possessed high crystallinity whereas synthetic hydroxyapatite

exhibited low crystallinity, with high porosity and more surface area [27,28,68-70].

Biomedical applications of HAp

Due to biocompatibility, osteoconductivity, porosity, and similar chemical composition to the natural bones, HAp largely finds biomedical applications especially in dental applications, bone substitution and filling, tissue engineering, drug delivery systems *etc.* [21,71,72]. Some important biomedical applications of HAp reviewed in this section are illustrated in Scheme 2.



Scheme 2: *Illustration of biomedical applications of HAp*

Tissue engineering scaffolds and bone fillers

The best therapeutic effect with an artificial bone localization in human body can be attributed only by self-cementing biomaterials. A good scaffold for tissue engineering should be biocompatible, biodegradable, porous and its degradation rate should match the healing rate of new tissue to be used for the construction of new biological tissues [73]. Therefore, HAp can be a promising material for these purposes. Transformation of different morphologies and phases of calcium phosphates into HAp during materials setting further support it in these applications [73]. HAp based biomaterial scaffolds are used in tissue engineering for bio-factors delivery including cells, genes, protein, blood cells, etc [67].

Juhasz *et al*., incorporated 10 wt.-% of carbonate substituted nano-HAp particles into poly-2-hydroxy methylmethacrylate/polycaprolactone (PHE-MA/PCL) hydrogel which exhibited significantly greater cellular activity on human osteoblast than that of pure hydrogel and micro/macro HAp filled hydrogels in terms of bioactivity and exposed surface area [74]. Similarly, Li *et al.* has reported that nano-size of HAp has more pronounced effect in cell proliferation than its morphology [75].

Similarly, polycaprolactone (PCL)/HAp, polylactide (PLA)/HAp, and poly (propylene fumarate) (PPF/HAp) scaffold systems are found to enable both *in-vitro* and *in-vivo* tests in bone healing [72]. Liu *et al*., performed *in vitro* and *in vivo* tests of 3D printed - osteogenic PLA/HAp screw-like scaffolds loaded with mesenchymal stem cells (MSCs) with in the bone tunnel and concluded the promotion of bone growth as well as bone graft [76]. These results open the way for the applications of 3D printed HAp biomaterials in bones and tissue engineering. Ishak and coworkers have reported that 3D printed HAp/β-tri-calcium phosphate (TCP) scaffolds coated with the dipyridamole agents and bone morphogenetic protein-2 (BMP-2), stimulates A2A receptors and promotes critical bone defects regeneration [77]. Similarly, nano-HAp/silk fibroin composite scaffolds loaded with bone morphogenetic protein-2 (BMP-2) exhibited improved osteogenesis capacity and accelerated early-stage bone formation [14,78-80].

Drug loaded HAp based bioactive nanocomposites are utilized for the treatment of teeth and bone problems and provocative response after surgery or remedial action of diseases [81]. They are particularly utilized for filling voids of bones and drug delivery carriers to keep the burning and infection response in the harmed tissues [82]. HAp metal composites such as HAp/Titanium HAp/Magnesium are commonly used as bone replacement materials than HAp-polymer composites because of the reliable mechanical strength of the metals [14,71,83].

Furthermore, natural bones possess various electric properties i.e piezoelectricity, pyroelectricity, dielectric constant, and ferroelectricity [68]. It is reported that bone derived HAp also exhibits these properties which help to enhance the healing process of large defects in fractured bones [61,62]. Higher dielectric and piezoelectric properties of HAp-metal composites are reported than that of pure HAp [62,69,70]. Hence, nano-HAp (derived from bones)/metal (Ti or Mg) composites are the promising materials for bone substitution in terms of their electric and mechanical properties.

Nano-HAp with the average particle size in the range of 20 nm is taken as the best for reconstruction and replacement of bones. Similarly, HAp particles in the range of 40-80 nm are reported as suitable nanomaterials for these purposes [19].

Drug delivery systems

HAp can be used as a carrier unit in drug delivery systems for different drugs and proteins. The polarization property of HAp (preferential binding of matrix proteins) as a bio-ceramic is important to form a drug delivery system [84-86]. Many drug delivery systems have been developed using coralline HAp and biodegradable poly(lactic acid) (PLA) [76]. The high stability, adsorption capacity, selectivity,

degradation resistance, and biocompatibility of HAp make it applicable as an adsorbent and purifying agent for the separation of proteins, nucleic acid, and antibodies [87,88]. The rough surface of HAp due to the presence of Ca and P constituents facilitates protein binding [89].

Though all of the obligations of biomedical processes are not fulfilled by HAp, it can be applied in different modified forms such as HAp reinforced polymer nanocomposites, HAp integrated ceramics, HAp based hydrogels, and bio-nano-materials, *etc.* for various applications of drug delivery systems, therapeutics, and cancer treatment [57,89].

Dentistry

Nano-HAp has bioactive properties and capability of inducing the mineralization process due to which it has been widely used as oral care ingredients. It is incorporated into several products prepared for enamel remineralization and counteract dental hypersensitivity [90]. Nano-HAp is used in various dental domains such as implantology, surgery, direct pulp capping, pulpotomy, dental tissue regeneration, dental drug delivery, periodontology, esthetics, prevention *etc*. [46,91]. It has a great ability to inhibit both gram-positive and gram-negative bacteria due to which it is used as a coating material for dental implants [91]. HAp-based composite microspheres amoxicillin and erythromycin are released for the treatment of periodontitis [46].

Implants coatings

Osteogenic property of HAp is the reason for its wide use in implants coating. Metal implants coated with HAp have the ability to form bonds with the host bone tissues [92]. Crystalline nano-HAp shows better biocompatibility, bioactivity, and mechanical performance rather than microcrystalline or bulk HAp, thus, it can be used in designing superior biocompatible implants coating [29]. Many researchers have introduced surface modification strategy using HAp nanoparticles as a bioactive coating on the metallic implants for enhancing bone-bonding ability [93]. HAp is used in the coating of hip, knee, ankle, hand, and spine implants [94]. It is reported that survival rates of HAp-coated implants remain unaffected by the coating along with biological advantages which activate researchers for further investigation of HAp applications in such implants [94,95].

Conclusion

Based on the above review and summary, it is concluded that HAp, a major component of animal bones and teeth can be synthesized *via,* various facile and cost effective methods. Wet chemical (precipitation and sol-gel) methods to prepare synthetic HAp and the mechanochemical methods to derive HAp from biogenic sources are recommended in this connection. However, HAp derived from biogenic sources under optimized conditions can have better crystallinity, mechanical, and electric properties as well as better applicable for biomedical applications because of their extra bioactivity, antibacterial activity, presence of essential minerals, and suitable Ca/P ratio. Therefore, biogenic sources can be sustainable nano-HAp sources for biomedical applications deserving ecological and environmental significance. Investment of mechanical and thermal energy will be sufficient for the preparation of these high value materials reducing the use of chemical reagents and solvents.

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