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Overview of hydroxyapatite; composition, structure, synthesis methods and its biomedical uses

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Abstract

Hydroxyapatite (HAP) belongs to the family of Ca apatite. Its natural composition and structure are similar to the inorganic phase of natural bone and teeth and has a wide range of applications in the biomedical field, because of its exceptional biocompatibility, bioactivity, and biodegradability. Due to these properties, it is extensively used as implant material in bone tissue engineering (BTE), for controlled release of drugs, dental implants, toothpaste additive, matrices for bone cement, and so on. In this overview, we focus attention on the composition and structure of HAP, the techniques developed to obtain synthetic HAP, and its utilization in the biomedical field as bone and dental implant, coating material, and drug carrier in particular.

Introduction

The basic formula of the appetite structure is $Ca_{10}(PO_4)_6X_2$. The group member X in this formula represents the form of apatite and specifies to fluoride (F) group for fluorapatite, a chloride (Cl) group for chlorapatite, and hydroxyl (OH) group for hydroxyapatite (HAP) [1]. It was proposed in 1912 that HAP (-OH end-member of apatite) exists in nature [2]. It is recognized as stoichiometric HAP (ratio of Ca/P =1.67) and written as $Ca_{10}(PO4)_6(OH)_2$, containing 3.38% of OH, 18.5% P, and 39% of Ca by weight (**Fig .1**) [3].

During biomineralization, living entities are in a position to crystallize and accumulate an extensive variety of minerals [4]. Among them are calcium phosphates which are formed in mammals due to calcifications of tissues as normal (teeth, bones) and pathological (atherosclerotic lesions, urinary calculus, stones, and dental) [5]. Calcium phosphates of various types differ in solubility values and chemical formulae are depicted in **Table 1**.

Bones, 50% by weight, is composed of HAP, which gives it fantastic osteointegrative and osteoconductive properties [6, 7]. The main element of bone material is HAP which accounts for its hardness, sometimes hard tissue element is comprised mainly of carbonate-apatite, as in the case of dental enamel (**Table 2**) [8]. Approximately, 70% (wt.) inorganic/organic hybrid part of human bone is formed from calcium phosphate salts, largely is HAP, and about ~30% (wt.) is organic (collagen) [9]. The calcium phosphate salts of a bone mineral are composed of carbonate, minor quantities of sodium, magnesium, and some other trace elements. Due to similarity of HAP, both chemically and structurally, with the mineral phase of bone [10-12], it is categorized as bio-active (able to form chemical ties directly with bone tissue), extremely biocompatible (both soft and hard tissue) [13], non-virulent, bioresorbable regarding the human body [14] and by an exceptional capability to inspire bone proliferation and bone regeneration. Consequently, HAP has noteworthy applications in the field of medical as orthopedic coating, spinal surgery, dental implants, bone fillers, and maxillofacial reconstruction [15-17]. The hierarchical structure of bones is shown in **Fig .2**.

HAP can also be utilized as a drug carrier. The reason behind the use of HAP for constant release of the drug or other biomolecules is due to its exceptional properties, for example, biocompatibility and the capability to adsorb the various number of chemical species [18]. It is effective to use submicron-sized HAP nanoparticles in drug delivery systems, and the capability to load the drug ought to be high. HAP exhibits no side effects due to its non-toxicity. greater effectiveness, prolonged-release, and inevitable therapeutic response. The utilization of HAP as a drug vehicle is ought to be effective [19, 20].

In this article, an overview of hydroxyapatite, its compositional and structural aspects, synthesis methods, and uses in the biomedical area are discussed briefly. The Graphical abstract is shown in **Fig. 3**.

Chemical composition of HAP

Calcium (Ca) and phosphates (PO_4^{3-}) are organized in the building block of HAP in such arrangement that four atoms of Ca are bounded at the M1 position by nine O atoms of the phosphate moieties, and at position M2, the remaining six O atoms of the phosphate moieties surround the six other atoms of Ca. For all atoms of Ca, crystallographic positions are M1 and M2 as depicted in **Fig. 4** [21]. Irrespective of the origin, HAP also comprises minute quantities of residuals for example fluoride ions (F-), chloride ions (Cl-), phosphite ions (PO_3^{3-}), and hydroxyl ions (OH). It has been stated that Cl- and PO_3^{3-} deteriorate the structure of HAP, whereas OH- and F- are recognized to increase the strength of apatite.

Structure of HAP

HAP crystallizes in the form of hexagonal structure, even though with some exemption in a monoclinic structure [21]. The structure has a place with the hexagonal space group P63/m, with cell parameters of a=b=9.418 Å y, c=6.884 Å, with hexagonal rotational symmetry and a reflection plane. A unit cell of HAP is shown in **Fig. 5**.

Fig. 1: Hydroxyapatite powder.

Table 1: Main calcium phosphate salts [22, 23].

Name	Formula	Symbol	Ca/P	pKs at 25 °C
Hydroxyapatite	Ca10(PO4)6(OH)2	HAP	1.67	116.8
Amorphous calcium phosphate	Cax(PO4)y·nH2O	ACP	1.2-2.2	–
β-Tricalcium phosphate	Ca3(PO4)2	(β-TCP)	1.5	28.9
α-Tricalcium phosphate	Ca3(PO4)2	(α-TCP)	1.5	25.5
Octacalcium phosphate	Ca8(HPO4)2(PO4)4·5H2O	OCP	1.33	96.6
Dicalcium phosphate anhydrous (monetite)	CaHPO4	DCPA	1	6.9
Dicalcium phosphate dihydrate (brushite)	CaHPO4·2H2O	DCPD	1	6.59
Monocalcium phosphate anhydrous	Ca(H2PO4)2	MCPA	0.5	1.14
Monocalcium phosphate monohydrate	Ca(H2PO4)2·H2O	MCPM	0.5	1.14

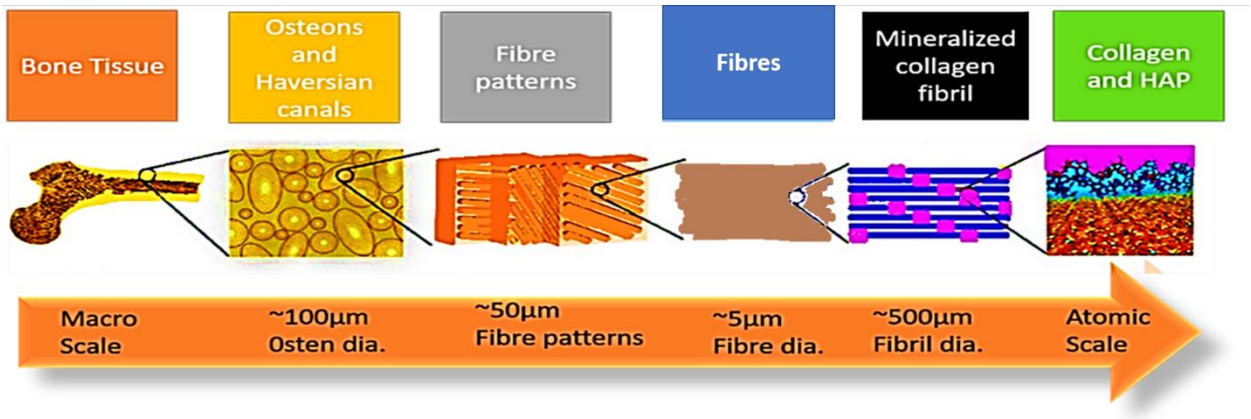

Fig. 2: Hierarchical structure of bones[25].

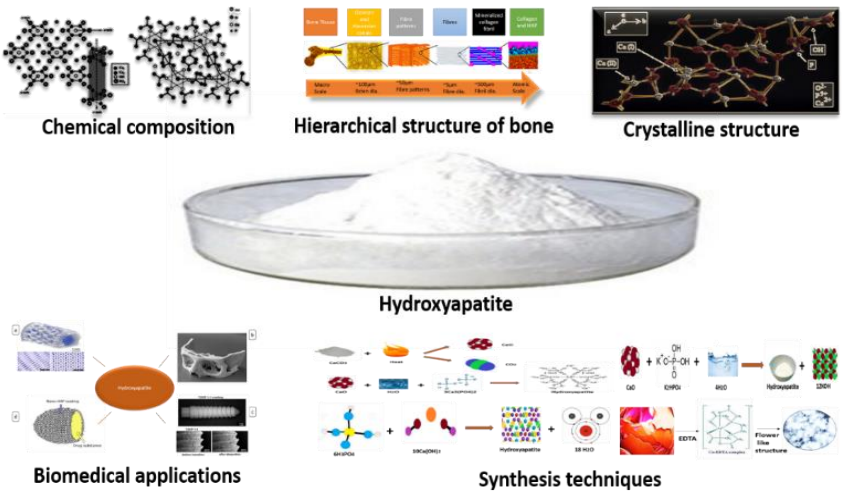

Fig. 3: Graphical abstract.

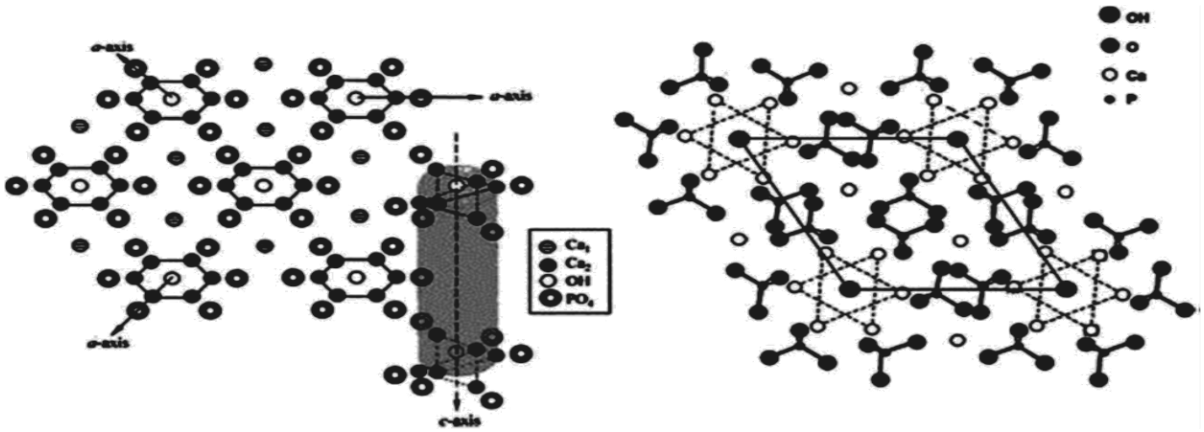

Fig. 4: Crystal structure of HAP exhibiting that the c-axis ⊥ to 3 a-axes lying at 120º of each other (left), and projection of structure of HAP on the 001 plane (right) [21].

Synthesis methods of HAP

Synthesis of HAP can be done either from natural organic-based materials (eggshell, bovine bones, etc.) or from the inorganic components. HAP obtained from natural sources also contain trace quantity of other ions, so it is non-stoichiometric (Ca/P ratio is <1.67). In both sources, these materials are viewed as biocompatible and bioactive and it is considered correspondingly well for in vitro applications, however, high cost of synthesis process to obtain HAP from the inorganic Ca and P based sources is the major issue to obtain this biomaterial from these sources [26]. Demand to obtain HAP via efficient, easy, cost-effective, and environment friendly strategy is increasing day by day. Following the advancement, the synthesis strategies and methods of HAP are progressively expanded, and significant improvement has been made in the field of clinical application. Innovative researches have been produced so far after the contribution of researchers for decades to form uniform composition, specific surface area, adaptable shape, a wide distribution of different particle sizes, fine grain, better performance, and numerous different conditions of perfect HAP crystal [27].

Aquatic sources (fish scale, fishbone), mammalian bones (Chicken, bovine, camel, etc.), shell sources (eggshell, seashell, etc.), algae, and plants are natural sources to prepare HAP [29]. The other techniques normally used to obtain HAP comprise of hydrothermal method [30], sol-gel method [31], precipitation method [32], spontaneous combustion method [33], micro-emulsion method [34], and solid-state method [35-37], respectively. Some of the above-mentioned methods are discussed here. The effect of various synthesis techniques on the characteristics of HAP is exhibited in **Table 3**. The advantages and disadvantages of applied methods are shown in **Table 4.**

Rivera et al. utilized eggshells to synthesize HAP. First of all, eggshells were given two-stage heat treatment at two different temperatures for a period of 2 hrs each to free it from organic residue and to convert into calcium oxide (CaO). The extracted CaO was then transformed into HAP by reacting it with precursors of phosphorous via the following reaction as shown in **Fig. 6**. The said procedure is novel to obtain valuable HAP biomaterial. Through optimizing annealing temperature, time, and phosphate solution composition, the concentration of obtained HAP can be enhanced further [38].

Chaudhari et al. synthesized HAP by soaking numerous amount of CaO obtained from eggshell with the solution of K_2HPO_4 at 37ºC for different soaking times (ST) via the following reaction depicted in **Fig. 7** [39]. The large quantity of HAP can be obtained through this low cost, effective, simple, and environment friendly technique.

Walsh et al. synthesized biphasic HAP from plant source (red algae) by obtaining calcium carbonate ($CACO_3$) after pyrolysis of red algae at 650-700oC (12 hrs) and then reacting it with ammonium dihydrogen phosphate at 100ºC for a further period of 12 hrs [40]. Granular-shaped HAP was formed with rough exterior having an open microporous matrix as confirmed by SEM analysis.

Khoo et al. used bones of the bovine femur to synthesize HAP. They were first cleaned, transformed into different particle size ($63 < x \leq$

Table 2: Typical compositional values of the inorganic phase of adult human calcified tissues [24].

Composition	Hydroxyapatite	Dentin	Enamel	Bone
Fluoride [wt.%]	–	0.06	0.01	0.03
Phosphorus [wt.%]	18.5	16.9	17.7	15.2
Carbonate [wt.%]	–	5.6	3.5	7.4
Sodium [wt.%]	–	0.6	0.5	0.9
Magnesium [wt.%]	–	1.26	0.44	0.72
Potassium [wt.%]	–	0.05	0.08	0.03
Ca/P (molar ratio)	1.67	1.61	1.63	1.71
Chloride [wt.%]	–	0.01	0.3	0.13
Calcium [wt.%]	39.6	35.1	36.5	34.8

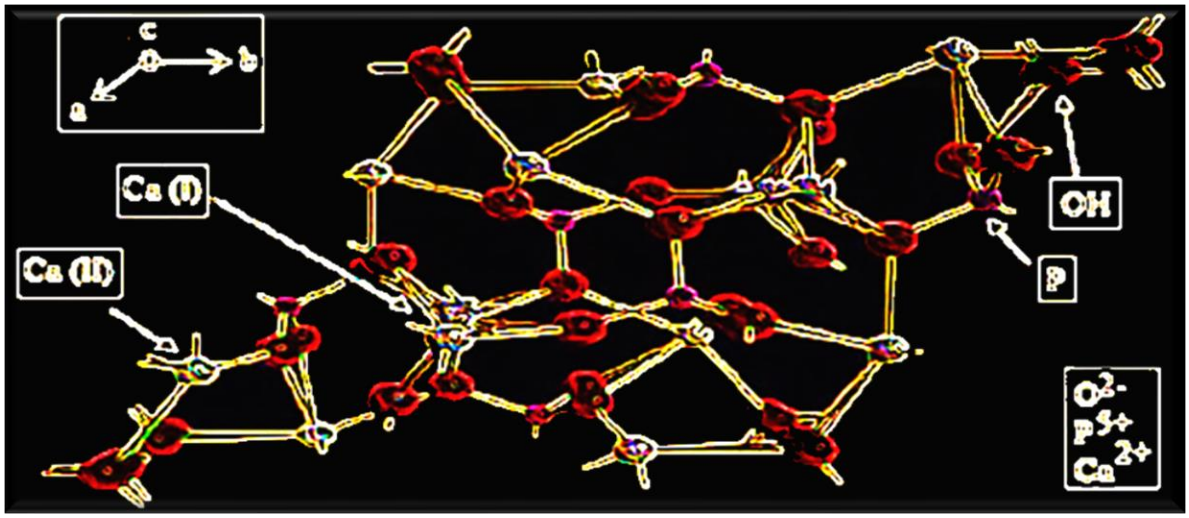

Fig. 5: Crystalline structure of HAP [28].

Table 3: Synthetic techniques used for the synthesis of HAP and characteristics of the resulting material.

Method	Cost	Degree of crystallinity	phase purity	Size (mm)	Morphology	Processing Time </>24 h)	Size distribution	Temp (ºC)	Ref.
ESp	Low	—	—	75 × 40 nm		>	—	—	[47]
FC	Variable	High	—	18.0 × 2.1	Hexagonal cylinders	<	—	500	[48]
SPC	Low	Variable	High	>0.45	Diverse	<	Wide	170–500	[33]
CP	Low	Low	Variable	>0.1	Diverse	>	Variable	RT	[49-52]
SS	Low	High	Low	>2.0	Diverse	>	Wide	1050–1250	[35-37]
Eme	High	Low	Variable	>1.0 (emulsion), >0.005 (micro)	Needle-like	>	Narrow	RT	[34]
MI	Variable	High	High	100 × 25 nm	Diverse		Narrow	—	[53-55]
SG	Variable	Variable	Variable	>0.001	Diverse	>	Narrow	37–85	[56]
HT	High	High	High	>0.05	Needle-like	<	Wide	150–400	[21]
ES	Variable	—	—	10 × 10–30	Fibers	>	Variable	—	[57]

Note: CP; chemical precipitation, HT; hydrothermal, ED; electrospinning, ESp; electrospraying, SS; solid-state, MI; microwave irradiation, SPC; self-propagating combustion, EMe; emulsion and microemulsion, surfactant-assisted precipitation, chemical vapor, FC; flux cooling.

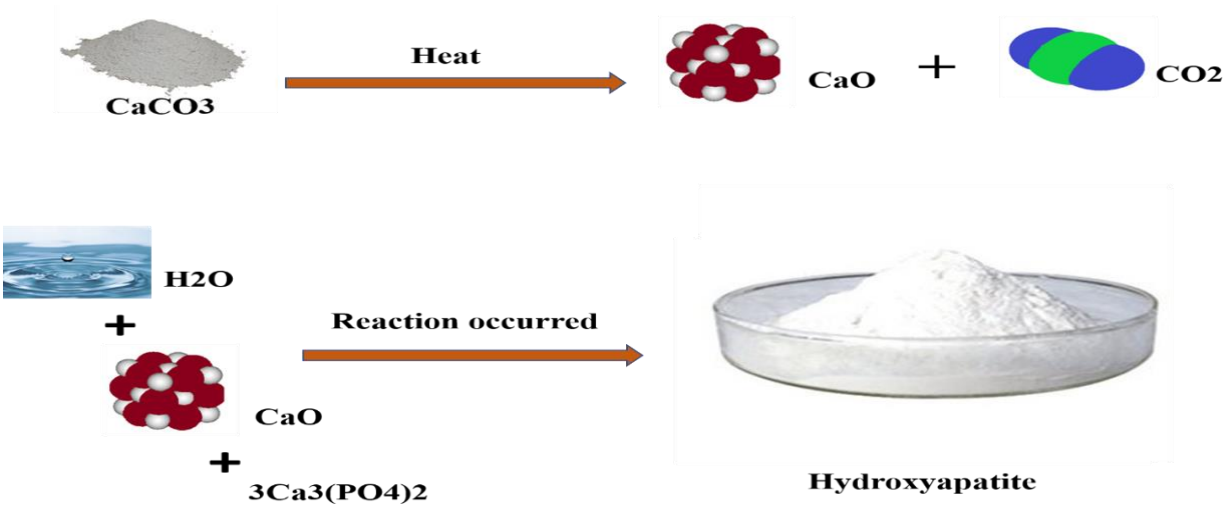

Fig. 6: Synthesis of hydroxyapatite by the reaction of calcium oxide with calcium phosphate in the presence of water.

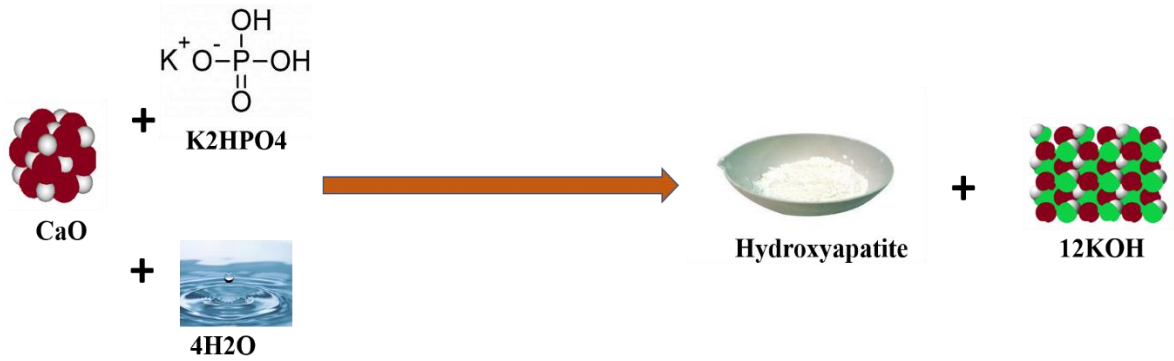

Fig. 7: Reaction of calcium oxide with dipotassium phosphate.

125 µm, 45 < x ≤ 63 µm, and x ≤ 45 µm) and then calcined at different ranges of temperatures 1100 °C, 700 °C, and 900 °C for 3 hrs and experienced that temperature for calcination affect the size of crystal, crystallinity, and composition of HAP extracted from natural source [41]. The Outcome of temperature, the method applied, and different natural sources on stability and phase decomposition of HAP has been shown in **Table 5**.

Several steps are involved in the sol-gel technique to obtain novel materials from the solution of precursors. Bernard et al. reported a nonpolluting technique to synthesize HAP by neutralizing the lime (Ca(OH)2) suspension at low temperature with the orthophosphoric acid solution as shown in **Fig. 8.** The physicochemical properties of $Ca(OH)_2$ greatly influenced the quality of HAP produced. Magnesium amongst other residues in lime exhibited the impurities contained in the lime, magnesium ion shows a robust influence on the development of HAP. Stoichiometry of obtained HAP relies upon the quality of raw materials. [42].

Tao et al. reported the co-precipitation method for the synthesis of HAP. In this method, Na2HPO4 and $PO4^{3-}$ ligand (calcium bis(2-Ethylhexyl) sulfosuccinate (Ca(AOT)2)) were utilized as Ca and phosphate ion supplier in the company of hexamethylenetetramine (HMT) as a pH regulator to regulate the supply of hydroxyl ion (-OH) in the solution during the reaction. The pH values for this process are maintained between 3-12 [43]. As the formation of HAP depends on pH, the release of -OH ion via hydrolysis of HMT resulted in the crystallization of HAP.

Guo et al. reported two routes named reverse microemulsion (rME) and conventional processing route (CP) to synthesize HAP. In the case of rME, surfactants used were Tween 80 and TX-100, n-hexanol, and n-butanol were utilized as mixed cosurfactants, whilst cyclohexane as the oil phase.

Under different weight ratios of said surfactants with different hydrophile-lipophile balance (HLB) values, rME were prepared. 0.3 M (NH4)2HPO4 solution was blended to the above-mentioned rME mixture and then little quantity of ammonia was put for pH regulating purpose (10-11) for the formation of HAP precursors. After 30 min, a transparent solution was collected and then aged exclusively of stirring at normal temperature for one day. At last, a minute quantity of alcohol was mixed to obtain white slurry and centrifuged to obtain white color colloidal particles of HAP. Through CP route, Aqueous solution of 0.3 M (NH4)2HPO4, titrated against an aqueous solution of 0.5 M Ca(NO3)2 under vigorous stirring with ammonia as pH regulating agent for the synthesis of calcium phosphate precipitates, which were then aged for a period of 24 h at room temperature. Particles of HAP obtained with an improved degree of agglomeration and smaller in size concerning conventional precipitation method [44].

Kumar et al. synthesized nanostructured HAP via microwave irradiation method of eggshells. The chelating agent ethylenediaminetetraacetic acid (EDTA) was used in this scheme. The complex recognized as Ca–EDTA was formed first, which furthermore reacted with phosphate to obtain HAP via microwave irradiation. The B-type carbonated HAP containing Mg was collected through this scheme [45] and shown in **Fig. 9**.

Kosachan et al. reported wet mechanochemical method using equimolar amounts of CaCO3, and dicalcium phosphate dihydrate (CaHPO4·2H2O), which were then mixed and milled in planary mill using ethanol and water as a liquid reagent to synthesize nanoparticles of HAP [46]. HAP of lower crystallinity could be synthesized through the use of water as liquid media.

Biomedical uses of HAP

HAP has achieved more interest for use in orthopedics and dentistry applications as an embedded material [67-69]. In BTE, surface properties improved with HAP can be utilized to build cell responses and propagation to prompt mineralization. HAP has also been utilized for a wide variety of other biomedical fields, for example, controlled release of the drug, toothpaste additive, matrices for bone cement, and so on [70]. Oonishi et al. [71] clarified the utilization of HAP composites, for bone filling deformities or spacing in clinical orthopedics, on account of its critical biological properties; for example, non-appearance of postoperative morphological variation or decrease in volume and lack of immuno-response. Other uses of HAP include the coating of HAP on metal parts for bone implants [72], and femoral plugs in total hip replacement [73].

Prabhakaran et al. [74] utilized the electrospinning technique to prepare the nanofibers of poly-L-lactide (PLLA)/Collagen (Col)/HAP and PLLA/HAP and observed that PLLA/HAP nanofibers composites are inferior to PLLA/Col/HAP nanofibers. For the formation of bone tissues, a porous interconnected structure of polycaprolactone (PCL)/HAP/Col nanofibers give excellent mechanical and facilitated production of extracellular matrix (ECM) [70]. He also reported that the blends of poly3-hydroxybutyrate-co-3-hydroxy valerate (PHBV)/HAP, PCL/HAP/gelatin (Gel), PLLA/HAP/Col, PCL/HAP/Col, and PCL/HAP were contemplated by different researchers as a substitute for BTE [74, 75]. HAP-polymeric composites-based scaffolds enhanced the innovative developments in BTE with osteoblast attachment, deposition of calcium mineral on its surface, and expanded osteointegration. Some biomedical applications of HAP are exhibited in **Fig. 10**.

Petricca et al. [76] reported PLGA/HAP based composites (PLGA; poly (D, L-lactide-co-glycolide) with improved osteogenic responses and mechanical properties and can be utilized as scaffolds for bone substitution. Hu et al. [77] reported that a slight yellow and transparent nanocomposite rods of chitosan (CS)/HAP showed high functioned, possible application as an inner obsession of bone crack. This strategy settles the issue of the accumulation of nano-sized particles in polymer lattice.

Marra et al. [82] inspected the blends of bio-decomposable polymers as scaffolds; such as poly (D, L-lactide-co-glycolide) and poly (caprolactone), for BTE applications. Porous discs were fabricated by introducing the granules of HAP into the blends. For these composites, in vitro degradation rates and mechanical properties were determined. Seeding and incubation of discs with bone marrow of rabbit or cultured stromal cells of bone marrow were carried out under physiological conditions. This investigation recommended the practical utilization of novel ceramic/polymer-based composites as a scaffold for applications in BTE.

Wang et al. [83] fabricated scaffolds and films by blending HAP into poly (3-hydroxybutyrate-co-3-hydroxy-hexanoate) (PHBHHx) and poly (3-hydroxybutyrate) (PHB). The blending of HAP into

Table 4. Advantages and disadvantages of different methods applied for the synthesis of hydroxyapatite.

Methods	Advantages	Disadvantages
Solid-State	• Cost of process is low • Choice method for commercial manufacture • Simple procedure • Excellent for HAP powder preparation	• Not so attractive for both technically and scientifically • Heterogeneity in phase composition owing to the small diffusion of ions during the reaction • Formation of agglomerates • Contaminations
Mechanochemical		• Morphology of particle in not controlled • Processing time is very long
Mechanochemical	• An effective route to obtain nanosized HAP • Popular technique in research field • There is precise control over the morphology and size of particles	• There is a problem in controlling phase purity and crystallinity of nanoparticles • Low formation temperature causes: decline in crystallinity, formation of CaP instead of HAP, and numerous ions residing in aq. solution can be incorporated into crystal structure Time consuming for large productions
Conventional chemical precipitation	• Operating cost is low • Raw materials are inexpensive • Simplicity • Reaction temperature is low • Ready availability	
Hydrolysis	• More Stable formation of HAP	• Low rate of hydrolysis of octacalcium phosphate (OCP) Capability of OCP to integrate impurities
Sol-gel	• Bioresorbability is higher than conventional powder and close to biological apatite • Enhancing the homogeneity of powder produced • Low temperature formation A stoichiometric structure with a large surface area and a small cluster size	• The occurrence of secondary phase such as CaO • Expensive raw materials such as alkoxide-based precursors Secondary CaO phase is harmful to the biocompatibility of HAP
Hydrothermal	• The highly crystalline and stoichiometric HAP is formed	• Poor capability to control the morphology and size of HAP nanoparticles Equipment utilized are very expensive
Emulsion method	• Reduces agglomeration of nanoparticles Procedure is simple to follow • Particle size is reduced • Low manufacturing temperature • Morphology is controlled • Occurs without any high-temperature requirement	
Sonochemical	• Single phase HAP could be synthesized after 15-60 min sonication HAP Growth and reactions are accelerated • Pure, small in size, and more uniform crystals with very little agglomeration	
Combustion	• Raw materials are inexpensive • Chemical homogeneity is very good • Powder is produced quickly having high purity following a single step operation Simple procedure as compared to others	
Pyrolysis	• The high operating temperature results in complete evaporation of precursor droplets followed by nucleation and growth of nanoparticles in the gas phase	• Formation of secondary agglomerates • On the basis of high temperature, decomposition of HAP into α-TCP is small Control of processing variables is poor

Table 5. The Outcome of temperature, the method applied, and different natural sources on stability, and phase decomposition of HAP.

Sources	Temperature (°C)	Techniques	Phases	Ref.
Fishbone	900	Hydrothermal	Brushite and HAP	[58]
Fishbone	900	Thermal/Milling	HAP	[59]
Bovine bone	750	Thermal	HAP	[59]
Cod fishbone	900-1200	Thermal	β-TCP and HAP	[60]
Bovine bone	650-950	Calcination	HAP	[61]
Bovine bone	800	Arc Plasma	HAP	[62]
Leaves and stalks	600-800	Thermal	HAP	[63]
Oyster shells	1000	Thermal/Ball milling	HAP, and β-TCP	[64]
Eggshells	1250	Microwave	β-TCP	[45]
Eggshells	400	Precipitation	HAP	[65]
Mussel shells	800	Precipitation	HAP	[66]

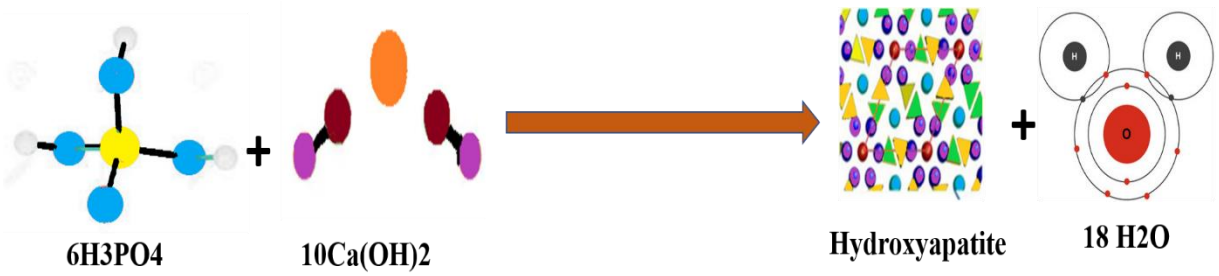

Fig. 8: Preparation of hydroxyapatite by the reaction of lime with orthophosphoric acid.

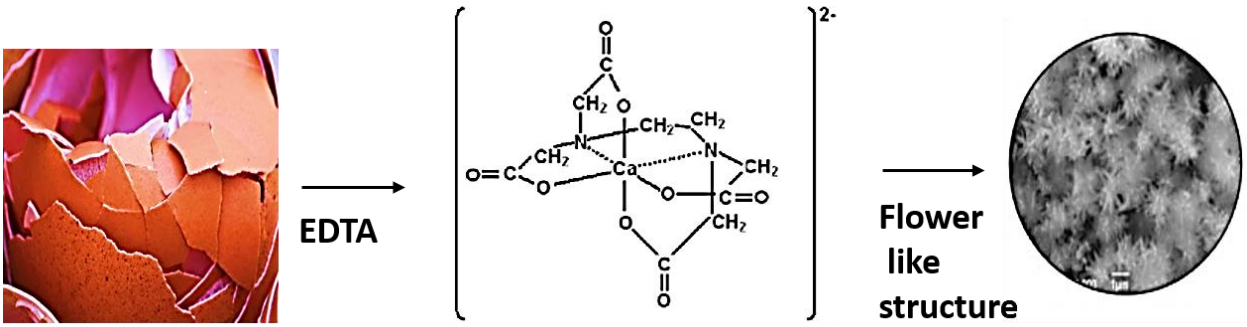

Figure 9: HAP preparation via microwave irradiation method.

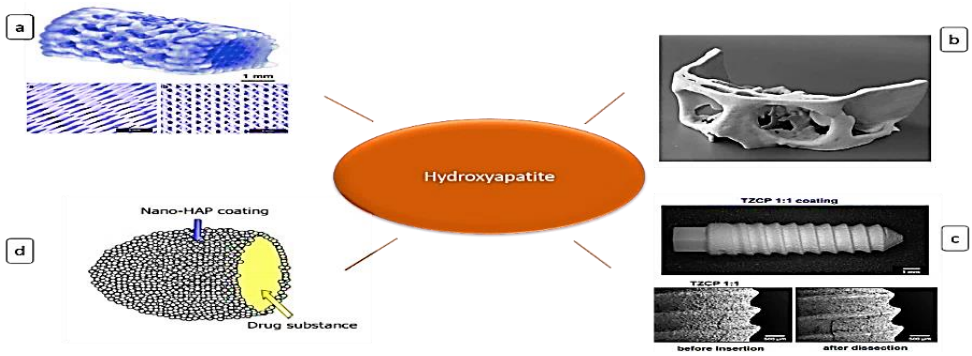

Fig. 10: Biomedical applications of HAP. (a) 3D printed cement [78] (b) bone implant [79] (c) Dental implants [80] (d) Drug delivery substance [81].

PHB showed an increase in its mechanical properties; such as maximum stress and compressive modulus of elasticity along with improvement in osteoblast responses including the activity of alkaline phosphatase and cell growth. Instead, the fabrication of PHBHHx scaffolds via salt leaching by blending particles of HAP was not able to either fortify its mechanical properties or improve its osteoblast reactions. Even though HAP is osteoconductive and bioactive, better performance cannot be achieved by its blending with PHBHHx for bone recreation [83].

Madhumathi et al. [84] placed HAP on the exterior of chitosan hydrogel membranes, and estimated the blood compatibility through employing MG-63 cells of osteosarcoma and proposed that HAP-chitosan hydrogel composite membranes are suitable for BTE applications. Hoffmann et al. [85] manufactured chitosan/starch/HAP composites based on hemostatic substance and projected it for applications in orthopedic surgery as a bone wax material or as bone filling substance.

Yang et al. [86] mentioned a relative study about HAPs blood coagulation activity with other possible bone fixing materials, for example, chitosan, calcium triphosphate, calcium consolidated attapulgite, and calcium silicate to demonstrate HAP as a prescribed hemostatic module to substitute bone wax. HAP is also prescribed as a capable module in creating hemostatic substance as an alternative to bone wax in the orthopedic application.

Rahavi et al. [87] reported that the growth of cells was encouraged together with nano-powders of HAP attained from the bones of humans and horses through using MTT assay. Such kind of HAP can be practical and economical for use as a graft material.

Baradaran et al. [88] prepared in situ fortified HAP nano-tube (nHAP) composites through using graphene oxide (rGO) employing simple HT method in a mixed solvent arrangement of N, N-dimethylformamide (DMF), water, and ethylene glycol (EG), without utilizing any reducing agents. Feasibility test and investigation of cell culture demonstrated that by adding rGO, proliferation and osteoblast adhesion enhances, and biocompatibility of composite nHAP/rGO increases.

Nanoparticles of HAP has been appropriate for both therapeutic and bioimaging applications. Morgan et al. [89] reported the utilizing of different fluorescent dyes, for example, fluorescein sodium salt, rhodamine WT, 10-(3-sulfopropyl) acridinium betaine (SAB), Cy3 amidite, and cascade blue, to synthesize originally doped nanoparticles of calcium phosphate in the diameter range of 20-30 nm and found that, for the free and embodied dye, fluorescence quantum proficiency can be expanded by 4-overlap from 0.045 to 0.202.

Palazzo et al. [77] examined the desorption and adsorption features of anti-cancer medications such as new platinum (II) complex di(ethylenediamineplatinum) medronate (DPM) and cis diamminedichloroplatinum (II) (CDDP, cisplatin), along with clinically pertinent bisphosphonate alendronate, through using two synthetically produced biomimetic HAP nanocrystalline ingredients, with either plate-shaped or needle-molded shapes and diverse chemical /or physical characteristics. Current practice showed that the features of nanocrystals of HAP can be balanced to create conjugates of biomolecule/HAP that are custom-made for explicit remedial applications [90].

Hu et al. [77] reported that a slight yellow and transparent nanocomposite rods of chitosan (CS)/HAP showed high functioned, possible application as an inner obsession of bone crack. This strategy settles the issue of the accumulation of nano-sized particles in polymer lattice.

Nguyen et al. [91] evaluated the efficiency of HAP coating to improve the osteoconductivity in BTE and used biocompatible alloys (Ti-6Al-4 V) having voids on its surfaces. The HAP surface was shaped by utilizing the sol-gel coating method to enhance post-implantation osteoconductivity and bone ingrowth. The coating of HAP was carried out on the porous exterior of cylindrical implants. Through utilizing this alloy, the in vivo experiment of rabbit bone was carried out and found that osteoconductivity was improved by escalating privileged adsorption of protein.

Numerous researches have been established for 3D printing of ceramic-polymer based composites, out of them, HAP-polymer based composites are of extraordinary intrigue [92, 93]. Both in vitro and in vivo experiments revealed that the 3D-printed scaffolds of BTE, in the light of poly(propylene fumarate) (PPF)/HAP [94], polycaprolactone (PCL)/HAP [93, 95], or polylactide (PLA)/HAP [92, 96] permit bone healing.

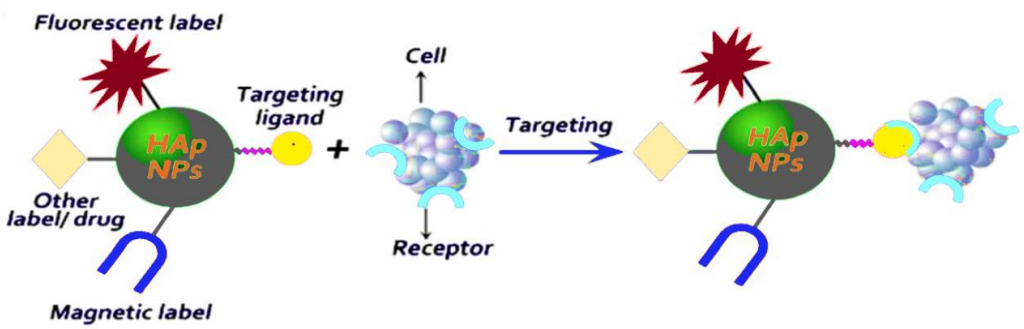

Fig. 11: Schematic illustration of targeting of HAP based nanoprobes for drug delivery and bioimaging [97].

Targeted drug delivery system is a prevalent area in the research field. In the case of osteoconductivity feature, the occurrence of polar charge, and hydroxyl (-OH) group over the surface of HAP makes it valuable to attract and preserve peptides and DNA, making it suitable for use as a drug carrier [98]. HAP, amongst other Ca-based bio-ceramics, is perceived as an appropriate analog to apatite that occurs in natural bone structure. It can deliver drugs containing stem cells based biomaterials and can also focus on the damaged territory of bone [99]. The drug molecules can be associated physiochemically by the said bio-ceramics and delivered in suitable timespan under controlled way [100]. Biodegradable nano-carriers of various sorts have been accounted for in literature, and among them are polymeric nanoparticles, silica, or HAP nanoparticles. The drug carrier which is well accepted is HAP [101]

In some studies, Zhao et al. [102] synthesized well-made nano-particles of amine-functionalized hydroxyapatite (NHA) to deliver the nanoparticle of candesartan (CD) and p53 (NHA/CD/p53) to treat breast cancer. Nowadays, HAP is accepted as a suitable molecule for gene therapy. Klesing et al. prepared activated HAP nano-rods with PEI (polyethylene mine) along-with numerous quantities of EGFP encoding DNA added for dispersion purpose and monitoring of dispersion stability was carried out via dynamic light scattering. Considering two cells named MG-63, and HeLa, reduction in surface zeta-potential of the delivery system consist of HAP-PEI occurred. Effective uptake of cells and high zeta-potential by negatively charged cell membrane was shown by nanorods supplemented with little quantity of DNA. Li et al. [103] constructed mesoporous strontium HAP (SrHAP) and gadolinium (Gd) doped luminescent HAP nanorods and revealed that aptamers modified with HAP can be utilized as healing mediator against cancerous cells as shown in **Fig . 11**. Sun et al. [104] prepared nano-rods of HAP loaded with doxorubicin (Dox), modified with folic acid (FA) as a prevailing anticancer treatment. To load drug in HAP materials, the drug carrier (DOX@HAP-FA) were engineered to imply as a novel template. In neutral solution, DOX@HAP-FA showed excellent stability, and release with no side effects through little pH circumstances. Son et al. [105] utilized HAP coated with discs of titanium (Ti) for the transport of drug molecules which are biologically effective (dexamethasone (DEX)) through decomposable nano-particles of poly(lactide-co-glycolide) (PLGA). Ti surface was coated with HAP and immobilized nanoparticles of PLGA loaded with DEX on the coated surface. For 30 days, the S3 sample having lowermost surface roughness exhibited not only a controlled release of DEX but also produced further extracellular matrix (ECM) on it **Fig. 12(a).** Ibrahim et al. [106] prepared mesoporous HAP nano-powder with improved properties at room temperature from wasted eggshells via uncomplicated two-step process and reported that the produced HAP nano-powder exhibited high loading of model dug ibuprofen and fair solubility and sustained release of drug through solute-saturated supercritical CO_2 was detected **Fig . 12(b).**

Conclusion

It can be summarized from the above-mentioned study that hydroxyapatite, because of its exceptional properties; such as biocompatibility, bioactivity, and biodegradability, is seemed to be a remarkable material for biomedical uses. It is used as an embedded material both in orthopedics and dentistry applications because of its compositional and structural resemblance to the inorganic phase of natural bone and teeth. It is also used as a coating material, for controlled release of drugs, BTE, and so

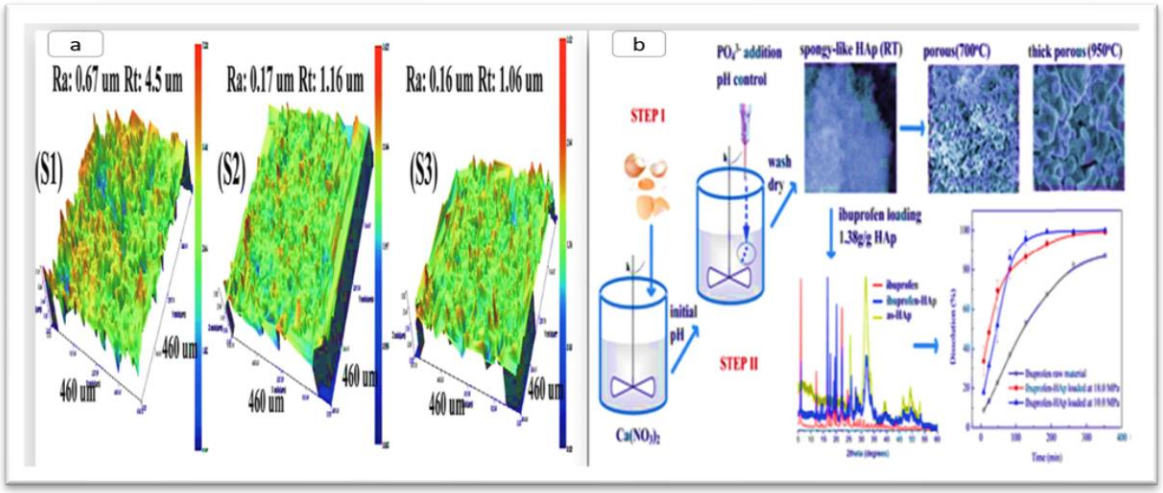

Fig. 12: (a) Optical profiling of Ti disc surfaces has been done to obtain interactive 3D display images. (S3) DEX-loaded PLGA particles immobilized on a HAP-Ti disc, (S2) RBM on a HAP-Ti disc, (S1) Resorbable blast media (RBM) on a Ti disc, Rt: roughness height, and Ra: roughness average [105] (b) Description of the morphology, methodology, and drug release profiles of the spongy-like mesoporous HAP formed using raw eggshells [106].

on. Several techniques are now developed to obtain synthetic HAP, but the development of HAP from Ca and P sources is expensive. So, researches are in progress to obtain HAP via efficient, easy, cost-effective, and environment friendly strategies. This review gives general information compositional and structural aspects of HAP, synthesis methods, and its applications in biomedical areas.

Conflict of interest

The authors declare no conflict interest.

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