

# A Brief Review on Biomedical Applications of Hydroxyapatite Use as Fillers in Polymer

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**Abstract:** Preparation of hydroxyapatite (HA) through natural sources, such as fish scales or synthetic HA produced from the chemical reaction has been widely used as biomedical materials because HA is bioactive, non-toxic and osteoconductive with a crystallographic structure almost similar to that of the bone mineral. In addition, HA with particle size < 10 microns is classified as common inorganic filler used to improve the mechanical properties and biocompatibility of polymer composites. The purpose of this review is to collect information related to HA, and to provide readers with information about synthesis methods, advantages of hydroxyapatite as biomaterial, biomedical applications of polymer/HA composites.

**Keywords:** Biomedical, hydroxyapatite, polymer, fillers.

## 1. Introduction

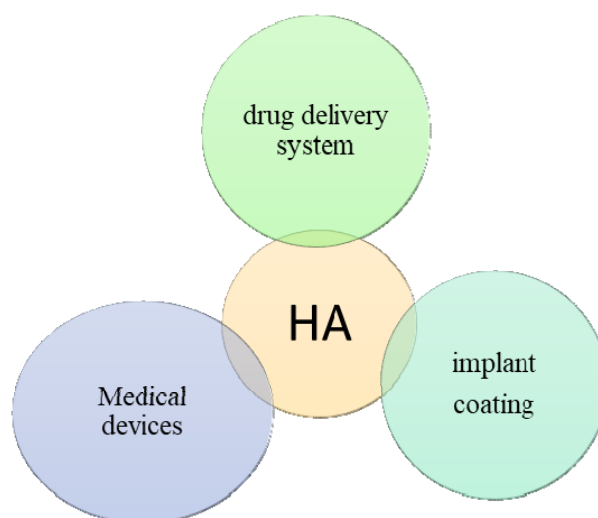
### 1.1 Hydroxyapatite (HA)

HA is a type of calcium phosphate with a chemical formula of  $\text{Ca}_{10}(\text{PO}_4)_6(\text{OH})_2$  [1-4]. Pure HA is a stoichiometric apatite phase with a Ca/P molar ratio of 1.67, the most stable calcium phosphate salt at normal temperatures and pH between 4 and 12 [5]. The crystal structure of HA most frequently encountered is hexagonal, having the  $P6_3/m$  space group symmetry with lattice parameters of  $a = b = 9.432$ ,  $c = 6.881$  Å, and  $\gamma = 120^\circ$ . Many studies have drawn great interest of hydroxyapatite because HA is widely used as biomedical material [6, 7]. HA is a ceramic material with osteoconductive and biocompatibility properties similar to those of bones' mineral phase [4, 8-12]. HA can also enhance the growth of bones and assimilate

with the surrounding bone tissues. It serves as a support and filler to the bones [13-16]. Given its incompetence properties, HA is a very promising biomaterial source [17-20]. In addition, hydroxyapatite (HAp) is also exploited as a model compound to mimic the biomineralization process [21, 22]. However, HA with particle size < 10 microns is classified as common inorganic filler used to improve the mechanical properties and biocompatibility of polymer composites [23-29], because of its excellent biocompatibility properties, non-toxic, non-immunogenic and osteoconductive [23, 30-34]. It is similar to the silica powder used in polymer composites [35-38]. The human bone is a calcified tissue composed of 60% inorganic component (hydroxyapatite), 10% water and 30% organic component (proteins) [39]. Technically, bone tissue has a nano-scaled classified structure composed of HA crystals within a matrix of collagen fibers and other proteins [40]. Fig. 1 displays biomedical applications of HA.

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**Fig. 1** Schematic illustration of biomedical applications of hydroxyapatite.

### 1.2 Synthesis of HA

HA can be synthesised as new biomaterials from different sources. Commercially available HA is chemically synthesised through chemical reactions, such as chemical precipitation [41-45]. Several techniques for HA synthesis have been established, such as sol-gel [42], wet chemical precipitation [46], sonochemical [47] and microwave [48]. Wang et al. [32] synthesised nanocrystalline HAp through precipitation reaction between calcium nitrate and diammonium phosphate, and the pH was confirmed using ammonia,  $\text{NH}_4\text{OH}$ . At temperatures as low as  $300^\circ\text{C}$ , combustion occurs and the synthesised powder produces grains with sizes ranging from 50nm to 100 nm [32]. In reference to Saeri et al. [49], the completion of precipitated HA at  $850$  and  $12,000^\circ\text{C}$  for 2 h may cause the reduction of water availability and increment of crystallinity. This phenomenon occurs when the suspension is left after dropping the acid solution [49].

Similarly, Sadat et al. [21] produced HA nanorods by using a simple hydrothermal method. An appropriate amount of ammonia and calcium nitrate solution was dissolved, and the molar ratio of Ca/P was adjusted to 1.67. At  $200^\circ\text{C}$ , the HA precursor was hydrothermally treated for 6 h. A similar method was

also reported by Zhu et al. [33]. The outcome revealed that the synthesised HA nanorods contain high crystallinity with high aspect ratio. Kalita et al. [48] synthesised HAp at the lower end of the nanoregime by using microwave. Through this method, calcium nitrate tetrahydrate and sodium phosphate anhydrous were used as the starting materials to synthesise the powder. This method produces an average crystallite size of around 12 nm and highly crystalline nanopowder with sizes ranging from 5nm to 30 nm. Meanwhile, Yoshimura et al. [50] produced HA whiskers under hydrothermal conditions in the presence of disodium ethylenediaminetetra-acetic salt ( $\text{Na}_2$  EDTA). The morphology of HA was significantly affected by the pH,  $\text{Na}_2$  EDTA/Ca ratio and reaction temperature; HA microspheres with high crystallinity resulted from conditions with high pH, high temperature and moderate retention time.

### 1.3 Natural Hydroxyapatite

Commercially available HA is chemically synthesised through chemical reactions, such as chemical precipitation [45, 51, 52]. However, in consideration of the high cost associated with chemicals used in the synthetic process, other natural sources were explored for the inexpensive production of HA. Biological sources, such as fish scales, fish

bones, bovine bones, egg shells, snail shells, teeth and bones of pig, are among the major sources of natural HA [1, 2, 25, 53-59]. Fish scales contain abundant valuable organic and inorganic components, mainly collagen and HA [60]. HA from biological sources was prepared because it is biologically safe and economical. Several methods, including alkaline digestion, enzymatic and direct burning method, have been developed to extract HA from fish scales. Direct burning is an easy and cheap way of obtaining natural HA. Fish scales are burned at high temperature to remove organic component, and HA is retained as ash [53, 56, 57, 61]. Rosen et al. [62] studied the characteristics of HA from processed bone and found that the bone HA exhibits significant differences in crystal morphology compared with synthetic HA.

## 2. Advantages of Hydroxyapatite as a Biomaterial

The new rage in biomaterials research focused on nanocrystalline calcium phosphate-based bio ceramics. In nanobiotechnology, many researchers studied various methods to overcome the limitations of calcium phosphate and to fabricate nanostructured scaffolds to mimic the dimensional and structural details of natural bone. Calcium phosphate-based materials are ideal for bone grafts in hard tissue engineering because of their superior bioactivity and biocompatibility. Nevertheless, bioceramics have poor mechanical performance, which limits their applications in load bearing. The recent trend in bio ceramic research is mainly concentrated on bioactive and bioresorbable ceramics, i.e., HA, tricalcium phosphates and biphasic calcium phosphates, and bioactive glasses because of their superior biological properties over other materials [51, 57, 60, 63-66].

Nano-HA bioceramics have different applications, including bone tissue engineering, bone void fillers for orthopaedic, traumatology, spine, maxillofacial and dental surgery, orthopaedic and dental implant coating, restoration of periodontal defects, edentulous ridge

augmentation, endodontic treatment (e.g., pulp capping, repair of mechanical furcation perforations and apical barrier formation), fillers for reinforcing restorative glass ionomer cement, desensitizing agent in post teeth bleaching, remineralising agent in toothpastes, early carious lesions treatment and drug and gene delivery [56, 61, 67-69]. The bone mineral consists of small HA crystals in the nano-regime. Nanocrystalline HA improves densification and sinter ability due to higher surface area, which improves the fracture toughness and other mechanical properties. HA has better bioactivity than other orthopaedic and dental implant materials [70]. It has many valuable properties that may remedy or reduce some undesired outcomes associated with metallic implants. HA is neither toxic to the body tissue nor targeted by the immune system as foreign body because it is a part of bone and teeth. Titanium and stainless steel implants are often covered with HA coatings to trick the body and reduce the implant rejection rate. HA can also be used in bone voids or defects. HA in the form of powders, blocks or beads is placed in the affected areas of bone. Given its bioactivity, HA encourages the bone to grow and restore the defects. This process can be an alternative to allogeneic and xenogeneic bone grafts. In addition, the use of HA shortens healing time [69, 71]. Synthetic nano-hydroxyapatite mimics the size of natural dentinal HA or enamel apatite. Experimental results have demonstrated the advantages of nano-HA in enamel repair [1, 69]. Thus, HA has been incorporated in toothpastes and mouth-rinsing solutions to promote the restoration of demineralised enamel or dentin surfaces by depositing HA nanoparticles in the defects [11, 72].

## 3. Biomedical Applications of Polymer/HA Composites

Nowadays, advances in medical science prolong the life span of a human and improve their standard of living. In the 1960s, the life expectancy at birth was about 69 years, but this was prolonged to 80 years in

2010. This expectancy corresponds to the increase rate of life probability to 2.2 years per decade; this increase in life expectancy can be ascribed to the advances in medical science that addressed more illnesses and its associated diseases with old age, including wear on bodily tissues, especially long bones. Human bones, which are composed of calcium and type I collagen, produce both white and red blood cells and provide structural sustenance for the body. The bone structure comprises inorganic mineral calcium phosphate in calcium HA (a type of bone mineral for bone rigidity) and collagen, which is an elastic protein that helps improve fracture resistance [73].

However, tissue deterioration gradually occurs with age and contributes to the requirement of spare parts for the body. Trauma, desorption and pathology contribute to the fracture of bone tissue [74]. As age increases, the total calcium pool of the bone and bone density decreases [75]. The decrease in bone density may be due to less growth of bone, which then becomes less productive in engaging new bones, and progressively slows repairing mechanism of micro-fractures. These symptoms are more severe in women than in men because of the hormonal changes during the menopausal phase [12, 76]. The elderly are prone to hip fracture or collapsed vertebrae and spinal problems because of the weak bone strength due to low bone density. Nickel, cobalt, molybdenum, chromium, zirconium and titanium alloys are orthopaedic implants, whereas stainless steel is used to fix the orthopaedic devices, such as screw plates [77]. According to Teo and Schmallock (2016) [78], metal allergy occurs due to complication after joint replacement. Since the discovery of this phenomenon, the number of awareness and reported incidence has increased. Although the connection between metal implant failure and allergy is well documented and reported, the relationship between the two is still poorly understood and remains relatively unpredictable and highly debated.

HA is superior to other natural and synthetic

materials with similar chemical compositions. The strong mechanical support is due to the unique structure of bone tissue in the body. In the human body, collagen is a type of protein with a triple helix structure [40]. Understanding the natural structure, composition and formation of bone tissue as well as new fabrication techniques is important in the development of new materials and improvement of current technologies. For instance, the degradation of bone tissue, especially in certain joints, such as the knee or the hip, results in the need to replace them with orthopaedic implants [12, 31, 56, 79]. Biocompatible and bio-stable polymers comprise few polymers that are potential matrices of bone analogues. These polymers are poly(methyl methacrylate), polyethylene (PE), polypropylene (PP), polyurethane, polytetrafluoroethylene, poly(vinyl chloride), polyamides, polycarbonate, poly(ethylene terephthalate), polyetheretherketone, polysiloxanes, epoxy resin [25, 80-84]. Biodegradable polymers have received considerable attention in the field of tissue engineering. These main class polymers comprise bioresorbable compounds known as alpha-polyesters or poly(alpha-hydroxy) acids [85], and poly(acrylonitrile-co-butadiene-co-styrene) (ABS) [86]. Many studies reported that polymers modified with HA filler improve the mechanical properties, such as tensile strength, flexural strength, impact energy and hardness, as well as biocompatibility of composites [23, 27, 87-90]. This finding can be ascribed to the excellent biocompatibility of HA [91].

Meanwhile, Scalera et al. [26] prepared epoxy/HA suspensions for stereo lithography to be applied to bone tissue engineering. The prepared epoxy/HA exhibits good mechanical properties. Similarly, Oladele et al. [25] prepared epoxy/HA composites and found that the composites display optimum mechanical properties, including flexural strength, tensile strength, impact strength and hardness. These mechanical properties of epoxy/HA composites render them structurally suitable for biomedical applications. Monmatrapoj et al. [27] prepared poly(lactic acid)/HA composites and found

that the composites display good mechanical properties and are suitable for biomedical applications. In addition, Alhussein et al. in 2019 studied the improved mechanical properties and biocompatibility of epoxy resin through addition of fish scales hydroxyapatite powder (FsHAp). They found the highest flexural strength of epoxy/nHAp composite was recorded when the nHAp filler was 10 wt% which is 77 % increment as compared to epoxy alone. The impact strength was increased up to twofold as compared to neat epoxy.

#### 4. Conclusions

Due to the high cost associated with chemicals used in the synthetic HA process, other natural sources were explored for the inexpensive production of HA such as fish scales and fish bones. HA is a biocompatible and bioactive material while HA with particle size below 10  $\mu\text{m}$  is classified as fillers in polymer. The mechanical properties and biocompatibility of polymers were improved through addition hydroxyapatite as fillers.

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