Three common preparation methods of hydroxyapatite

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Abstract. Hydroxyapatite has good stability, biological activity and biocompatibility, the calcium ions can be a variety of metal ions by ion exchange reaction, form M apatite of the corresponding metal ions (M on behalf of metal ions that replace calcium). Hydroxyapatite also has a good ability of bone conduction, bio decomposition and bone formation induction, make it an excellent and nearly ideal repair and replacement material for human teeth and bones when damaged. However, due to its low strength, poor toughness, difficult to form, poor corrosion resistance, hydroxyapatite has not been widely used. Therefore, the preparation of hydroxyapatite with superior comprehensive properties and more ideal composite materials has become the focus of research in recent years. This article is written based on the research status of hydroxyapatite, summarizing the origin, development, preparation, application and development prospect of hydroxyapatite. Emphatically analyzing the advantages and disadvantages of three common methods, including hydrothermal method, solvothermal method and homogeneous precipitation method, the structure, size, properties and application of hydroxyapatite obtained using these methods are also discussed. Views on the future development prospect and research direction of hydroxyapatite are also put forward.

1. Introduction

Apatite (AP), as an important mineral component of human and animal bones, is a natural inorganic material recognized and used by humans for a long time. In the 1970s, after the successful synthesis of hydroxyapatite (HAP) [1], apatite began to be studied and used as an artificial synthetic material. Hydroxyapatite (HAP), theoretical chemical formula of Ca10(PO4)6(OH)2, hexagonal crystal system, density 3.14~3.16 cm2, not only has good stability, biological activity and biocompatibility, no rejection reaction and irritation in vivo, but also has good bone conduction, bio decomposition and bone formation ability. Moreover, human bones contain 60% ~ 70% acicular hydroxyapatite and collagen fibers with a length of 20 ~ 40 nm, and a thickness of 1.5 ~ 3.0nm. Therefore, HAP is an ideal material for bone repair and bone replacement when human bones are damaged.

Although the hydroxyapatite (HAP), as a bone repair and bone replacement material, has nearly ideal performance advantages, at the same time, when used, the pure HAP material also has disadvantages of low strength, low toughness, low brittleness, not easy to form, and low fatigue resistance in physiological environment, so it is difficult to meet the biological and medical application requirements. How to solve its performance defects and obtain HAP materials that meet the biochemical and physical conditions implanted in the human body and have various excellent properties has become a problem that has been studied and discussed by researchers of many disciplines including materials science and medicine. Over the years, researchers have been continuously changing the corresponding preparation methods and processes to prepare nanometer hydroxyapatite and its composite materials with different properties. Although the most ideal bone
repair and replacement materials have not been obtained, the preparation technologies and processes have been constantly improved and diversified, and the materials prepared have been increasingly optimized. In this paper, the author summarizes the origin and development, preparation methods, research progress and development prospect of hydroxyapatite in recent years from its research status, and analyzed the hydrothermal method, solvothermal method and the homogeneous precipitation method in the precipitation method and the advantages and disadvantages of the three common methods, as well as the structure, size, properties of hydroxyapatite and its application of the corresponding method.

2. The origin, development and preparation of hydroxyapatite

Human have comprehend and studied hydroxyapatite for hundreds of years [2]: When Werner first discovered it in 1790 and named it apatite in the Greek script, there was no characteristic that it was worth using; but after X-ray diffraction came along, in 1926 Bassett tried to scan teeth and human bones and found that the mineral composition was very similar to hydroxyapatite, which intrigued researchers; subsequently, in the 1980s, Japanese scholar Aoki and his team synthesized hydroxyapatite and burned it into ceramics, and found that even if the sintered hydroxyapatite did not crystallize, it still had good biocompatibility [3, 4]. It is the beginning of the extensive basic research and clinical research of hydroxyapatite materials. After years of development, the preparation methods and techniques of hydroxyapatite are increasingly diversified and perfect, and considerable progress has been made in the research of clinical application.

In order to prepare shape adjustable, uniform composition, narrow particle size distribution, large specific surface area, fine grain, no reunion, superior performance and many other conditions of ideal nano HAP crystals, researchers have been innovation, after decades of research and development, HAP preparation methods are also constantly update and development, a lot of ways also gradually mature. Commonly used methods to prepare HAP mainly include hydrothermal method, precipitation method, solvothermal method, spontaneous combustion method, micro-emulsion method, ultrasonic synthesis method, bionic method and solid state reaction method, namely wet method and dry method. Among them, the most widely used, the lowest cost and the best HAP comprehensive properties obtained are also three main methods used by scientific research workers in recent years: hydrothermal method, solvothermal method and precipitation method. Starting from the three methods, this paper will discuss and study the effects of different methods and reagents on the preparation of HAP with different shapes and sizes and the effects of its mechanical, physical and chemical properties.

3. Hydrothermal method

Hydrothermal method is refers to use high temperature and high pressure aqueous solution (or steam) as reaction medium, in high temperature and high pressure airtight pressure vessel (autoclave) by controlling the temperature of the solution within the autoclave to produce convection in supersaturated state formation, so that the insoluble in atmospheric conditions dissolved, or reaction to generate the lysate of the substance in order to recrystallize it.

The reaction equipment and reaction conditions for preparing hydroxyapatite by this method are simple, the synthesis temperature is relatively low, and the reaction conditions are moderate. Besides, the calcination and grinding parts are omitted, and the obtained products have high crystallinity, which generally does not need subsequent high-temperature treatment, have complete crystal development, small particle size, particle agglomeration, high purity and controllable shape and size. In recent years, hydrothermal preparation of hydroxyapatite has become increasingly mature. Studies have found that the shape and size of hydroxyapatite can be regulated by changing the hydrothermal temperature, hydrothermal time and reaction concentration. According to this method, researchers have prepared high-purity hydroxyapatite of different shapes, such as nano spherical, rod-like, needle-like, flake, hexagonal prism, small plate and spine-like [5-8].

Because the shape and size of HAP vary with various factors during synthesis, this method will be introduced in this paper according to raw materials, chelating agents and regulators, substrates,
hydrothermal conditions.

3.1 Raw materials, chelating agents and regulators

Because HAP is widely available, has easy-gained chemical structure, and can be obtained by using calcium-containing substances and phosphates, so it has a wide range of raw materials. Generally, researchers use ingredients containing calcium ions as reactants and amines are used as chelating agents or regulators. All these ingredients are collectively referred to as raw materials in this paper.

Each material added in the HAP synthesis process is adjusted according to the desired result, and also varies with the substrate and reaction conditions. In recent years, with the development of HAP nanometer membrane technology and the discovery of many different metal HAP conjugates, scientists have used different raw materials to produce HAP with different structure sizes, physical and chemical properties and properties.

Suchanek and Bartkowiak [9] prepared acicular hexagonal hydroxyapatite crystals using Ca(EDTA)\(^2^-\) and NH\(_4\) (2HPO\(_4\)) solutions; Bensala et al. [10] prepared hydroxyapatite nanorods from phosphogypsum waste (PG) and potassium dihydrogen phosphate (KH\(_2\)PO\(_4\)); Daryan and his research group [11] used EDTMP as chelating agent or regulator to obtain the microspheres with radial growth nanorods (HAMNR) or nanorods (HAMNS); while Chinese scientists Zhou and Yang [12], used a combination of calcium hydroxide, orthophosphate and vitamin C to obtain mesoporous rod shaped HA nanoparticles; and Tran, Nguyen and Luu [13] synthesis of HAP nano-rod-like particles from cetyl trimethylammonium bromide (CTAB); Bucur et al. [14] prepared long hexagonal hydroxyapatite using tartaric acid (TA) as raw material; at the same time, Wen's research group [15] prepared porous hollow hydroxyapatite microspheres (PHHMs) in Na\(_2\)HPO\(_4\) solution with calcium titanate as raw material; Fu et al. [16] used CaHPO\(_4\) and Ca(H\(_2\)PO\(_4\))\(_2\) solutions to synthesize titanium dio2-hydroxyapatite nanofilms on the surface of Nitinol alloy in one step. Néstor et al. [17] took CaNO\(_3\), KOH, K\(_2\)HPO\(_4\) and glutamic acid as precursors and used microwave assisted synthesis of hydroxyapatite hexagonal acicular nanofibers; Xin et al. [18,19] not only synthesized hyaluronic acid nanorods and nanowires with riboflavin-5'-phosphate-sodium salt (RP) as phosphorus source, but also hydroxyapatite nanorods with pyridine-5'-phosphate as phosphorus source; Ya et al. [20], also from China, prepared mesoporous carbonate hydroxyapatite microspheres (MCHMs) from calcium carbonate microspheres (CCMs); while Zhang et al. [21] prepared hydroxyapatite nanorods with uniform size in the presence of alanine and glutamic acid; and Xu et al. [22] synthesized microporous hydroxyapatite crystals from calcium nitrate and phosphorus oxide; Zhang’s [23] study was on preparation of HAP whiskers with good crystallization, uniform structure and high aspect ratio by using acetamide (AA) as raw material; A.RajeswariaV, GaneshKumarbV, KarthickbT [24] use LMWH to synthesize hydroxypatite board; Xiao et al. [25] prepared colloidal hydrophilic hydroxyapatite nanorods from sodium citrate. In addition, simple HAP can also be synthesized by using Ca(NO\(_3\))\(_2\) and 4H\(_2\)O and H\(_3\)PO\(_4\), EDTA and monoethanolamine, hexamethylene tetramine (HMTA), cetyl trimethylammonium bromide (CTAB), etc. [26-28]. So many raw materials can be used to synthesize HAP that the articles containing large amounts of calcium and amine in daily life, such as freshwater clam shell biological waste and calcite [29, 30], can be used as raw materials to synthesize HAP.

3.2 Substrates

For hydroxyl can be easily replaced by fluoride, chloride and carbonate, generate fluorine apatite or chloride apatite; calcium ions can also be replaced by a variety of metal ions by ion exchange reaction, form the corresponding metal ions M apatite (M on behalf of replacing calcium metal ions), therefore the shape and size of HAP also varies with its substrates in the preparation.

Suchanek and Bartkowiak [9] found that, after chemical treatment and heat treatment, hydroxyapatite acicular hexagonal symmetric crystals only nucleated and grew on titanium matrix. However, no hydroxyapatite phase was detected on the acid-etched titanium surface. Those results indicate that only specific titanium surface treatment can effectively induce apatite nucleation under hydrothermal conditions.
While for titanium with TiO$_2$ as substrate or shape like TiO$_2$ on surface, for example, bioactive surface modified nickel-titanium alloy [16], titanium hydroxyapatite (TiO$_2$-HAP) powder [31], 70Ti-30Ta alloy modified by EDC [32], hydroxyapatite - titanium dioxide (HAP-TiO$_2$) coating deposited on anodized Ti$_6$Al$_4$V substrate by water thermoelectric method [33], bioactive titanium dioxide nanotubes prepared by titanium anodic oxidation [34], etc. after these reaction, HAP coating film can be formed, that is, TiO$_2$ contributes to the adsorption of HAP into film. The research of Xiao et al. [34] shows that HAP coating is formed in a special two-layer structure. Under the appropriate hydrothermal temperature, solution concentration and PH value, the bottom layer presents the criss-cross propagation of low crystallinity short rod-like HAP, while the top layer presents the scattering propagation of high crystallinity long rod-like HAP. With the increase of cooling time after hydrothermal treatment, HAP coating coverage increases, HAP distribution is more uniform, and the upper long rod-like HAP grain increases obviously. The increase of solution concentration makes the boundary of HAP two-layer coating not clear and gradually disappears. But the too low water heat temperature, will cause the bottom layer cannot form the cross structure coating.

While in the synthesis of hydroxyapatite/alumina composites (hexahedral hydroxyapatite and monocline alumina phases), Sivaperumal et al. [35] found that direct synthesis of hydroxyapatite/alumina composites could prepare alumina-based hydroxyapatite biomedical implants without forming any intermediates similar to calcium aluminate. As secondary phase, alumina and titanium dioxide nanoparticles had the same effect, which improved the densification and mechanical properties of apatite, and delayed the decomposition of apatite to tricalcium phosphate (TCP) phase at high temperature. [36]

Bioapatite is a calcium-deficient apatite with many ways of substitution of divalent and trivalent ions. Almost all cationic substitution agents can maintain apatite phase, with the crystal size and crystallinity decreased significantly. The lattice parameters (a, c) of HAP hexagonal system are also affected according to the type and number of substituted cations. Zn$^{2+}$ and high concentration Mg$^{2+}$ significantly inhibited the formation of whisker apatite and promoted the formation of hexagonal prismatic and lamellar bundles, or hexagonal and polyhedral shapes. While Sr$^{2+}$ has the least inhibiting effect on HAWs formation. [37]

Among them, after adding magnesium, lattice parameter $a$ increased slightly, lattice parameter $c$ decreased more significantly, and lattice spacing $d$ increased, while the size of precipitated crystal did not change significantly, so the grain size of Mg-doped HAP (MHAP) did not change significantly. In addition, the addition of impurity ions to the HAP lattice does not change the stability of the high-temperature phase that is normally treated. The comparison of HAP and MHAP samples before and after heat treatment shows that apatite structure does not decompose or change phase at high temperature. All of them are single-phase hexahydrate apatites. [38, 39]

In silicon replaces hydroxyapatite (Si-HAP), silicon is incorporated into the HAP lattice by partially replacing the phosphate (PO$_4$)$^{3-}$ group with a silicate (SiO$_4$)$_2^-$, thus form a Si-HAP called Ca$_{10}$(PO$_4$)$_6$$(SiO$_4$)$_x$$(OH)_{2-x}$. Silicate substituted phosphate groups will cause a certain OH$^-$ loss, so as to maintain the charge balance and change the crystal lattice parameters of HAP. The crystal shape of silicon hydroxyapatite does not change, but the addition of silicon reduces the size of silicon hydroxyapatite crystal. Si-HAP has higher biological activity than pure hydroxyapatite. [40]

For the HAP doped with Co, Fe, Ni, etc. The crystallinity decreases with the increase of magnetic ion incorporation. When adding them, carbon dioxide will be brought in which will cause significant reduction of HAP size and morphological changes (spherical to hexagonal rod). The existence of magnetic ions leads to the formation of superparamagnetic porous structures composed of hexagonal nanoroids and nanospheres. The addition of magnetic ions sharply increases the magnetization and dielectric constant, it has strong ferromagnetism and the magnetization increases with the increase of magnetic ion content. It plays an important role in magnetic imaging, tumor-targeted drug delivery and magnetic hyperthermia. [41, 42]

For strontium (Sr), SrHAP nanorods longer than 100nm have better biological properties in cell proliferation and differentiation, while HAP nanoparticles with lower length have better biological
activity. The subtle differences between nano HAP and SrHAP in vivo (including size, crystallization, specific surface area and degradation rate) may affect cell growth, which may affect bone growth. [43]

3.3 Hydrothermal conditions
At the same time, different hydrothermal conditions (heating time, heating temperature, cooling time, pH value, reactant concentration, etc.) will also lead to different properties of HAP obtained. Even in order to obtain some special properties, researchers will use some limit conditions to prepare HAP. Some results show that with the increase of hydrothermal reaction time, reaction temperature and reactant concentration, crystal growth becomes more complete and length-diameter ratio tends to increase. The pH value of the system has a great influence on the growth of HAP crystal. With the increase of pH value, HAP grain size and length-width ratio decreased significantly. Increasing hydrothermal temperature and prolonging hydrothermal time can significantly increase the crystallinity of HAP nanorods and increase the size of HAP nanorods, but decrease the colloid stability of HAP nanorods. It is noteworthy that the increase of hydrothermal temperature and time has a far greater impact on the increase of pipe diameter than on the increase of pipe length: when colloidal hydrophilic hydroxyapatite nanorods were prepared by thermal decomposition with sodium citrate as raw material, the colloidal stability would be seriously deteriorated when the hydrothermal temperature was above 180℃ for 24h or above 150℃ for 48h. At this time, HAP nanorods were obviously dispersed and stabilized within 2 months. The results showed that although the charge density of HAP nanorod had no significant effect, the dynamic diameter of HAP particle was greatly increased, thus reducing the colloidal stability of the dispersion. [23, 25, 26, 30, 34]

In fact, with the different reaction conditions, the obtained HAP properties are also different. However, most HAP synthesis occurs between the temperatures of 100℃-250℃, the time of 15m-12h, and the pH value of 10-12. The optimal reaction conditions vary with the actual situation, and in general, the formation range of rod-like HAP is wide, and the formation range of hexagonal shape and long strip-like is narrow. Therefore, it is easier to obtain rod-like HAP membrane when preparing.

At present, it is thought that the mechanism of HAP crystal growth may be the effect of growth conditions on ion concentration, i.e. the effect of calcium and phosphorus ratio, so as to change the growth rate of HAP crystal along different crystal axes.

4. Solvothermal method
Solvothermal method is developed on the basis of hydrothermal method, refers to a closed system such as autoclave, using organic or non-aqueous solvent as a solvent, at a certain temperature and the pressure of the solution, a synthesis method that the original mixture reacts.

Now sol-gel method is often used instead of solvothermal method. The original principle is to hydrolyze metal alkoxide or inorganic salt, polymerize solute, dry and roast the Gel, and finally get inorganic materials. As an inorganic material preparation method, this method appeared in 1960s and was widely used. However, the preparation of HAP by sol-gel method has only emerged in recent years. This method uses the reaction of calcium citrate or calcium acetate with phosphoric acid to obtain sol, and the sol is aged into gel under certain conditions. The gel is dried at low temperature and calcined at high temperature under vacuum to obtain nanometer hydroxyapatite [44]. Some study found that the condition changes such as the initial concentration of the solution [45], reaction atmosphere and mole ratio of calcium and phosphate [46, 47], hydrolysis time [48], add way and speed, aging time, the gel treatment method [49, 50], calcination temperature [45], etc. will have more or less impact on crystal morphology, crystallization degree and performance of the obtained HAP powder. By changing raw materials, relevant parameters and processes, HAP powders with good uniformity, high purity, fine particle size, various morphology, good crystallinity and high surface activity can be prepared under different conditions.

This method is characterized by uniform mixing of raw materials and easy control of the proportion of each component, which can accommodate insoluble components or non-precipitating components. The product size is small, the lattice is relatively complete, the purity is high, the sintering temperature
required is low, can be used to prepare nano composite materials, is hotspot of HAP nano powder preparation in recent years. However, its chemical process is complex, crystallinity and sintering property is poor, preparation cost is high, the solvent required has strong toxicity which will cause great harm to human body and environment, and easy agglomeration during calcination, these greatly limits the development and application of sol-gel method. Therefore, environmental protection, namely the use of surfactant as little as possible, has become the main research direction of researchers.

In order to avoid toxicity and pollution in the synthesis process of HAP, the researchers found that non-toxic organic salts such as phosphorus, sodium and calcium could be used as raw materials to obtain HAP nanorods and nanowires that are not only environmentally friendly and safe, but also contain no surfactant and have good properties. For example, Yang et al. [51] found that hydroxyapatite nanorods can be prepared by using sodium lignosulfonate (SS) as raw material, and the stirring time and SS concentration of the reaction solution both affect the crystal structure and aspect ratio. When Yu et al. [52] used trimethyl phosphate as the source of organophosphate and used solvothermal method synthesis of nanoparticles to assemble dendritic superstructure (NADs) and macroparticle assembled ordered arrays (MAOAs), the morphology of prepared hydroxyapatite products changed significantly with the change of sol thermal temperature and sodium hydroxide content. And the prepared products have good biocompatibility. While hydroxyapatite Nested bundles (HNBs) can be synthesized directly without any surfactant by simple solvothermal method by using nanomaterials as nanoscale chunks. It can be used for effective photodegradation of cationic dyes [53]. Qi and his research partners [54] found that using adenosine 5'-sodium phosphate (AMP) as organophosphate source solvent can synthesize HAP of various morphological structures (including nano particles, ultra-small nanotubes, nanorods and nanoflower hierarchy). In this research, AMP biomolecule forms HAP nanostructure as an organophosphorus source, and solvent concentration has an impact on the morphology of products. When Ca(NO3)2•4H2O and P2O5 are used to synthesize nano and sub-micron monodisperse HAP particles, Maïssa Dardouri [55] controlling the basicity and temperature of sol heat treatment and other synthesis conditions in order to control the growth, evolution and purity of HAP nanoparticles and cut HAP. With the increase of basicity ratio, the morphology of fine particles changed from anisotropic shape (nanorod, submicron rod) at pH9, short rod particles at pH9.5 to spherical particles at pH≥10.

Oleic acid and oleates are also ideal raw materials that researchers have paid more attention to in recent years:

Jiang, Zhu, Chen and Wu [56] of Shanghai Chinese Academy Of Sciences first invented a method to synthesize submillimeter ultra-fine hydroxyapatite nanowires in a series of single hydroxyl alcohol by sol-thermal method using calcium oleate as precursor and NaH2PO4 as phosphorus source. They are tens of nanometers in diameter and range in length from a few hundred microns to nearly a millimeter. This method is simple, no surfactant and environmental protection, not only applicable to methanol, ethanol, 1-propanol, 2-propanol, 1-butanol, 1-pentanol, 1-hexanol and a series of single hydroxyl alcohols, but also can be used for large-scale production. Meanwhile, ultrafine hydroxyapatite nanowires can also be synthesized in the mixed solvent of ethanol and water by using calcium oleate as the calcium source and precursor and different kinds of sodium phosphate as the phosphorus source. The advantage of this method is that can prepare ultrafine hydroxyapatite nanowires with various phosphate sodium salts including Na2HPO4•12H2O, NaH2PO4•2H2O, Na3PO4•12H2O, Na5P3O10 and Na4P2O7•10H2O as phosphorus sources. [57] The prepared nanowires have broad application prospects in bone tissue engineering, drug delivery, organic pollutants and heavy metal ion adsorbent, non-flammable inorganic paper and other fields.

Using calcium carbonate, sodium hydroxide, (NaPO3)6, oleic acid, water and ethanol as raw materials, Zhang et al. [58] synthesized monodisperse single-crystal ultrafine hydroxyapatite microtubules by solvothermal method. This super long HAP microtubule has unique tubular structure, good biocompatibility, good drug loading and sustained release performance, and has broad application prospects in the biomedical fields such as drug/gene transmission and bone defect repair.
In terms of polymer polymerization raw materials, Saeed et al. [59] prepared a non-aqueous polymer solution containing calcium and phosphorus precursors by solvothermal method, and conducted in situ treatment in closed autoclave at different temperatures of 60 ~ 150℃ to obtain a hydroxyapatite nano-reinforced polycaprolactone. HAP nanorods are hemicrystalline, and the aspect ratio changes with the processing temperature, while the calcium and phosphorus ratio increases with the processing temperature. The elastic modulus and strength (~ 15%) of the nanocomposite prepared by in-situ method were better than that of the in-situ sample (HAP nanorods mixed with polymer sol). Besides, the in vitro bioactivity test in saturated simulated body fluid also showed that the cell survival rate and proliferation ability were improved, namely the bone regeneration ability was enhanced. This biodegradable polymer based nanocomposite scaffold with in vitro bone regeneration potential is expected to be used in orthopedics and maxillofacial surgery.

5. Homogeneous precipitation method

Precipitation method is under the certain condition of pH and temperature, make corresponding molar ratio of calcium salt and phosphate solution mixing, stirring constantly, and make the calcium and phosphate ions in alkaline conditions generated colloid HAP precipitation, then by drying the precursor precipitate and calcining it at 900 ~ 1200 ℃, prepare the HAP with well-crystallized and ultrafine particles. It is the most basic method to prepare HAP. Nowadays, most methods to prepare nano-hydroxyapatite are developed from precipitation method. This method is widely used to prepare medical hydroxyapatite powders due to its advantages of simple technology, low reaction temperature, low cost, simple operation, small product particles and high purity [60]. However, the HAP particles prepared by the precipitation method have a poor uniformity, and may be agglomerated, which is possible to generate calcium-deficient apatite with lattice defects and a Ca/P ratio less than 1.67. Therefore, the control requirements on the preparation process conditions are relatively high, so the reaction conditions must be strictly controlled to make it fully react at a reasonable temperature, pH and reaction time, add appropriate dispersants, control the precipitation rate and wash for multiple times, improve the purity [61]. Studies have shown that nano HAP with ideal Ca/P ratio, purity and grain size can be prepared by controlling the temperature, pH, drop acceleration of phosphate solution and applying other strengthening conditions (such as ultrasonic, adding surfactant, etc.) [62]. And some researchers have obtained nano-hap, which is similar to the hydroxyapatite structure in human bones in shape and size by precipitation method, with good dispersivity and shape stability, and still disperse well and does not grow at 600℃ [63,64].

And homogeneous precipitation method need to control the precipitant concentration in the solution to increase slowly, and control the supersaturation in the appropriate range, make the solution in the precipitation in balance, and avoiding the phenomenon of uneven concentration. The precipitation can appear uniformly in the whole solution, so as to obtain nano HAP particles with high purity and uniform particle size. It is one of the many methods of sedimentation extension.

When preparing HAP by homogeneous precipitation method, the preparation conditions and properties obtained are similar to hydrothermal and solvothermal methods. However, in order to form precursor precipitate, namely colloidal HAP precipitation, certain pH, temperature and solution conditions are often required.

And when preparing HAP whisker with acetamide (AA) as raw material, its nucleation can be formed at about 120℃, while the whisker precipitates with good stable growth can only be formed at more than 140℃, which has the same crystallographic characteristics as ordinary HAP crystals, and no other phases are detected. Compared with urea, an additive commonly used to increase pH value to promote nucleation and growth of HAP crystals, acetamide hydrolyzes at a lower rate under the required hydrothermal conditions, so AA’s slow hydrolysis provides a more stable and continuous growth environment compared with the widely used wet chemical route. Its low supersaturation can promote the rapid growth of HAP whiskers directly from hydrothermal solution without interference from other phases, and the whiskers are short of calcium, Ca/P= 1.6-1.65, and the whiskers grow spiraling in the direction of c-axis in preference, and the length and width of whiskers are determined.
by the concentration of calcium ions and other solution conditions. The structure, crystallinity and
growth habit of acetamide were not affected by the concentration of acetamide. During heat treatment
in air, HAP whiskers undergo obvious phase transition at about 1200℃, that is, HAP whiskers have
stable morphology at high temperature below 1200℃. The thermal stability of HAP whisker is related
to chemical composition and crystallinity. Such whiskers are beneficial to improve bone binding and
biological activity, as well as their mechanical properties, and also serve as a reinforcing material for
dense hyaluronic acid ceramics and porous hyaluronic acid ceramics. [23, 65, 66]

In addition, Wang et al. [67] found that in water system, acicular hydroxyapatite crystals
strengthened for biomedical materials can be synthesized from the precursor of dicalcium phosphate -
dicalcium phosphate hydrate and octacalcium phosphate crystals. M. Jevtić et al. [68] synthesize nano-
flake hydroxyapatite by ultrasonic field homogeneous precipitation method. These internal structures
of these plate-like structures consist of oriented and transversely connected nanorods. Through careful
observation of the microstructure of a single nanorod, it is found that it has highly regular, defect-free
lattice structure and unique crystal surface orientation, and the resulting structure is related to the
effect of ultrasound on the growth mechanism. In order to analyze the effect of temperature on the
morphology of hydroxyapatite crystals, Luo and his team [69] prepared hydroxyapatite crystals by
homogeneous co-precipitation with calcium nitrate and diammonium phosphate as raw materials and
urea as buffer. It was found that when the reaction temperature was increased from 70℃ to 95℃, the
crystal phase composition was changed from tricalcium phosphate and ocalcium phosphate to
hydroxyapatite single crystal, and the shape of hydroxyapatite crystal was changed from nodular
whisker to perfectly dense needle whisker.

6. Conclusion
HAP material, with its particularity, plays an irreplaceable role in medical bone repair and replacement
materials. Therefore, it has a broad research and application prospect in the field of materials and
biomedicine. In recent years, the research of hydroxyapatite and its composite materials has made
great progress and even been applied in clinic. However, most of these studies fundamentally fail to
improve their strength and toughness to meet clinical needs while maintaining their superior
properties. Moreover, the interfacial binding force of HAP complexes is not strong enough, and the
mismatch of degradation rate and new bone formation rate of related materials after implantation of
human body are still troubling the vast number of workers in the field of materials and biomedicines.
While many natural polymer including polysaccharide (cellulose, starch, chitin, chitosan and heparin,
etc.) and protein (collagen, gelatin, vegetable protein and keratin etc.), can composite with
hydroxyapatite. After that, their mechanical properties and biological activity can be improved, and at
the same time can maintain the biocompatibility of the natural polymer composite materials. [70] As a
result, natural polymer /HAP composites can be widely used in biomedicine, carrier, absorption and
separation and other fields. So, the author thinks that scientific research workers should be constantly
optimized and study some new preparation methods to improve the HAP own strength at the same
time, constantly improve the composite processing technology, use existing or synthetic polymer
materials, obey the principle of bionics, accurately control the microstructure of the composite
material with bone material structure similarity, research synthesis new bionic materials to meet the
requirements of clinical use.

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