Int. J. Bio-Inorg. Hybr. Nanomater., 8(1): 5-25, Spring 2019

A Review of the properties, synthesis and application of Nano Hydroxyapatite

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Received: 15 October 2018; Accepted: 18 December 2018

ABSTRACT: Nano-Hydroxyapatite (nHAP) is a very valuable mineral that is widely used in tissue engineering as well as bone and dental repair. Moreover, it is a major component of bone, enamel and dentin that can interact effectively with healing tissues due to its high biocompatibility. It is important to note that the purpose of its medical application can be identified based on the structure and synthesis of HAP. This study aimed to efficiently review all the previously conducted studies on synthesis and application of nHAP over the years of researchers' efforts and present the results for optimizing biocompatible material synthesis.

Keywords: *Bone Regeneration, Interaction, nHAP, Preparation Methods, Structure.*

INTRODUCTION

It is great to know that most of our bones are made up of minerals, especially calcium, and all the efforts of physicians to treat diseases such as osteoporosis, osteoarthritism and fracture healing, have led to the replacement of these precious minerals. Bone consists of bone cells and the underlying proteins or bone matrix that fills the cartilage cell space. Bone cells are made through a process called bone formation. This process is dependent on the balance of osteoblast cells. Osteoblasts are responsible for the synthesis of a collagen material that deposits bone minerals on them. Osteoblasts are either cubic or multifaceted cells and are located in the ossification site as a single cell layer [1-4]. Osteoclasts absorb bone cells to be replaced by new cells during the osteogenesis process. Osteoclasts absorb bone cells to be replaced by new cells during the osteogenesis process. In fact, bone morphogenetic proteins (BMP), as important growth factors, Wnt proteins, fibroblast growth factor (FGFs) along with bone minerals are essential for regeneration and repair of bone [5, 6] and. The Wnt proteins have key role in osteogenesis and osteocell differentiations [7]. Bone minerals are composed of calcium phosphates that the majority (65%) is nano-hydroxyapatite [7]. Hydroxyapatite, which forms the major structure of bone, enamel, and dentin, has the molecular formula of $Ca_5(PO_4)_3OH$ (Fig. 1) [4]. It is important to note that its crystals have different unit

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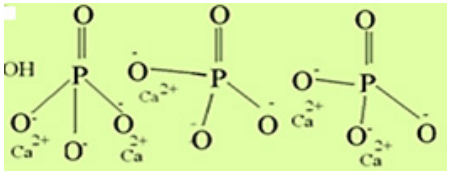


Fig. 1. the Structure of Hydroxyapatite

cells in bone and teeth.

Furthermore, it has a hexagonal structure in the bone in which four calcium ions are surrounded by nine oxygen atoms and the other six are surrounded by hydroxyl (OH) [8]. Fig. 2obtained from studies conducted by Guo [9] and Ikoma [10] , shows the cell structure of the HAP unit. As can be seen, there are respect there are 2 HAP units in each cell [11] often, referred to $Ca_{10}(PO4)_6OH_2$. In the enamel, HAP appears in the monoclinic structure. However, there are two HAP units in each cell; therefore, it has the same chemical composition of bone [12-15].

The hexagonal form of OH is present on the side edges of the single cell, and this form makes it easy for functional groups to access it. On the other side, it is very suitable for substitution with anions such as carbonate. Apatite crystals in enamel are larger than dentin and bone. In fact, this is one of the reasons that make enamel the hardest part of the body. The hydroxyl groups occupy different positions in two structures. Synthetic nHAP is also available in two forms, namely hexagonal and monoclinic. Hexagonal form is usually synthesized by deposition at temperatures below 100 °C and converted to monoclinic by heating [10, 13, 16-18].

In fact, what makes synthetic HAP, and especially synthetic nHAP, is very prominent in medical studies. Its biocompatibility, especially compatibility with bone and tooth tissue, is bioactive, non-toxic to the body, capable of forming and growing bone cells on it, and is non-inflammatory. The bioactivity of a substance indicates the ability of that substance to bind to living tissue. The HAP direct chemical bond to hard tissues through its functional groups and due to the similar bone and tooth structure, it can be a good replacement for these tissues. The nHAP is slightly and completely soluble in water and an acidic medium, respectively [19-21]. However, its dissolution increases in the presence of proteins, amino acids, enzymes, and

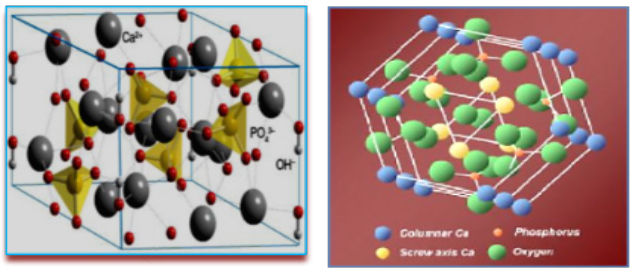


Fig. 2. Structure of Unit Cell of Hydroxyapatite [9, 10].

calcium-substituted ions [22].

In the body, there are osteoclast bone cells that absorb bone tissue and destroy old bone tissue to be produced and replaced by other cells called osteoblasts. Osteoclasts create an acidic environment that dissolves calcium and phosphate ions and results in the deposition of HAP on collagen and bone production [16, 23, 24]. Due to the structure of HAP, sodium, magnesium, and carbonate ions are substituted for calcium and phosphate ions, and this process leads to the bone enrichment of minerals that occurs during bone development through different life stages.

Why do we synthesize nHAP in different ways and use it in bone repair? Or why do not use natural nHAP isolated from hard bone tissue?

The answer to this question is in the structure and stoichiometry of natural and synthetic nHAP. Nano-sized HAP is present in the body and the Ca/P ratio is about 1.2-2. If this ratio is 1.67 it is called stoichiometry, otherwise it is non-stoichiometric. Non-stoichiometric HAP, known as calcium-deficient HAP, has carbonate and is less resistant to load bearing, and since cations can easily replace calcium ions, they are also called non-stoichiometers with calcium deficiency. However, synthetic HAP is often at a ratio of 1.67, which improves its strength and durability. Interestingly, non-stoichiometric and stoichiometric nHAPs are often in hexagonal and monoclinic forms, respectively [12, 24-27].

Identification and history of Hydroxyapatite use

The HAP was first introduced by Posner in 1892 with the chemical formula of, $Ca_{10}(PO4)_6OH_2$. Nonetheless, its crystal structure remained unknown until the discovery and application of X-radiation. In 1938, De Jong conducted a study on X-ray diffraction patterns and introduced the only identifiable bone mineral

Table 1. Lists some of the properties of natural and synthetic Hydroxyapatite [14, 25, 32, 34].

Synthesis	Natural
Harder than enamel	Low hardness, low mechanical stability
Thermal stability even at temperatures above 1300 ° C	Above 800 ° C it is converted into two phases, hydroxyapatite and calcium phosphate
High strength against cracking and moisture	Low strength against cracking and moisture
Variable solubility depending on the synthesis conditions	Low solubility
Density between 3-3.6 g / cm^3 depending on the synthesis conditions	Density about 3.08 g / cm^3
It varies depending on the raw materials and coatings given	The presence of carbonate, fluoride, sodium, potassium, magnesium, zinc, etc. in the network structure

phase known as apatite [28]. This led to the opening of a new chapter in material and biomaterials studies. Moreover, in 1958 Posner introduced the size of HAP network parameters as a = b = 9.432 and c = 6.88, which had a hexagonal structure [29-32]. In 1973, the monoclinic structure of HAP was examined by Elliott et al [33] which led to determination of its parameters (i.e., a = 9.421%, b = 2a, c = 6.881). Moreover, the Ca/P ratio was obtained at 1.67 in both structures. It is worth mentioning, that there have been several studies since then on bone structure and HAP.

The nHAP synthesis was first performed by Tai-Gang Nieh and Ping Luo [35]. Due to the structural similarity of HAP to the bone mineral, the researchers were interested in its application in bone replacements [36-48]. In 1969 Levitt reported the first dental prosthesis by HAP, and subsequently, the pelvic bone prosthesis was successfully coated with HAP[49,50].

Recent studies on the application of nano Hydroxyapatite

Due to its good biocompatibility and bioactivity, HAP has been used in both scientific and medical studies as a bone repair agent and a carrier for restorative and palliative care in bone defects and fractures. Nabipour et al synthesized nanocomposites from HAP and polymer and transported ibuprofen to bone repair [51]. In this regard, drugs, such as Methylprednisolone acetate, Triamcinolone Acetate, Teriflunomide + Methotrexate, Ibuprofen, Lovastatin and vancomycin hydrochloride have been studied [51-57]. Tissue engineering is a field in which artificial organs are constructed using materials, cells, and growth factors. Bone tissue engineering provides medical methods to reconstruct and regenerate bone tissue by constructing 3D scaffolds that can be implanted in cells. Scaffolds are porous materials in which cells grow, nourish, and multiply. At present, it is of great interest to use HAP for the manufacturing of bone scaffolds [58-61]. Sun et al. examined the parameters affecting the Ce/HAP nanoparticle properties as nano-scaffold for bone regeneration [62].

Similarly, Wang et al. designed a hybrid of HAP/nanofiber peptide that could act as a scaffold for HAP growth and nuclearization. Moreover, they have shown that it boosts bone marrow proliferation and is effective in tissue engineering[63]. Scaffolds can be made from organic polymers with HAP, which helps maintain their stability in the body and improve their mechanical properties. Hydrogels with nHAP can also be used as 3D scaffolds in bone tissue engineering due to the high biocompatibility, porosity and nontoxic that causes cell proliferation. [61, 64-66]. Chitosan, collagen, heparin, alginate and fibrin are some of injectable natural hydrogels that are more commonly used in tissue engineering [66-69]. Xu et al. reported HAP-peptide hybrid hydrogels as a 3D scaffold to accelerate differentiation of osteoblasts MC3T3-E1 cells [6]. Peptide hydrogel is obtained by dissolving Nap-$GFFY_p$ peptide in a Tris solution with a pH of about 6. This peptide was obtained by modifying NapGFFY peptide with the phosphate group for better hydroxyapatite interaction in to hydrogel scaffold.

Priya et al. reported nanocomposite hydrogel made of chitin and poly (butylene succinate) (PBSu) loaded with fibrin nanoparticles (FNPs) and magnesium-

doped bioglass (MBG). Their study showed that fibrin nanoparticles increase blood vessels in damaged bone, which improves the transfer of oxygen and nutrients to the bone [70]. PBSu, a synthetic polymer, improved the mechanical properties of hydrogel and promotes the proliferation and growth of bone cells. MBG is bioactive glass that can induce differentiation of stem cells into osteoblasts through chemical bonding with hydroxyapatite [70, 71].

3D nano scaffolds can be much more effective in osteogenesis and differentiating bone cells [7]. Because of, they provide wider dimensions for the activity of growth and skeletal factors. Medical 3D printing technology enables bone grafting or transplantation. This technique provides the production of various implant structures in damaged bone tissue with the help of a computer [72-75]. The HAP-polymer composite scaffolds (i.e., polycaprolactone and polypropylene fumarate) with 3D printing in in vitro and in vivo experiments showed bone healing [76]. In a study, Jakus et al. synthesized hyperplasic 3-D printed bone containing 90% HAP and 10% polycaprolactone. They revealed easy interactions between hard particle and its good elastic mechanical properties which was capable of recovering any deformation [77]. However, Butscher et al. previously synthesized 3-D printing in their study [78].

The application of magnetic nHAP such as Fe-doped HAP, Mn and Fe-doped HAP and Gd-doped HAP by external magnetism has received much attention due to its ability to bind to antibodies, enzymes, proteins and drugs. These composites are also used to treat bone cancers [79-83].

In addition to the usual methods of synthesizing and functionalizing nHAP such as isobaric, sol-gel, microemulsion and hydrolysis, in recent years electrodeposition method has been used to form nano-HAP which is very effective [84-89]. In this process, electrodes are performed by galvanizing or potentiometry and sodium nitrate can be used to increase the ionic strength of the electrodes. The solution containing calcium and phosphate ions can precipitate high crystalline nanoparticles on the cathode [90]. Recently, HAP plasma sprayed method is one of the common methods for coating on the surface of nHAP. This method can apply a thin layer on the nanoparticles at low temperatures [18, 31, 91-95].

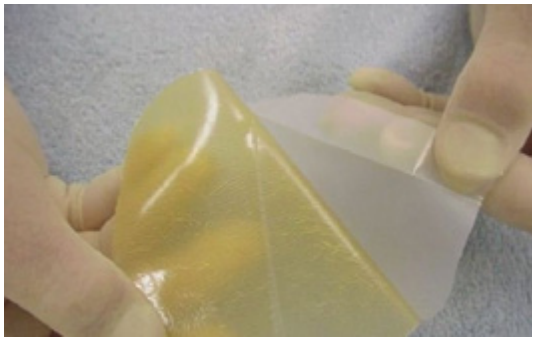


Fig. 3. Hydroxyapatite wound band

Canillas et al. produced dense nHAP in different sizes and morphologies using soluble combustion method. [96]. The purpose of this study was to increase the strength of nanoparticles. They found that the acidic environment reduces the porosity and size of the holes relative to water. This increases resistance and strength to the aquatic environment.

Effect of size and morphology and porosity of nano Hydroxyapatite on its application

It is worth noting that bone material as well as tooth biomolecules such as collagen can bind to minerals that are predominantly calcium phosphates, especially HAP, with hydrogen and electrostatic bonds. This binding affects the size, morphology, and mechanical properties of natural HAP [97]. The size of the HAP is about 50 nm [97-100], and the morphology of nHAP differs slightly in bone and tooth structure since they are more spherical in the bone and are rod- shaped in the tooth. Zhang et al. synthesized rod-shaped nHAP and controlled the size of nanomaterials with the help of polyvinylpyrolidone (PVP). In fact, PVP acted as a coating agent that could control the nucleation and growth of crystals, in such a way that the nanotubes become shorter in length. On the other hand, the functional group is similar in PVP and collagen, which improves the binding to nHAP [101].

In their study, Shi et al. investigated the effect of nHAP size on the apoptosis of osteoid cells [102]. They synthesized spherical nHAP at 20 and 80 nm and examined their effect on MG-63 cell growth over 5 day and found that the number of cells at 20 nm was greater than 80 nm. That is, cell proliferation is inversely proportional to the size of nHAP. The Trans-

mission Electron Microscopy analysis in cells affected by 20 nm and 80 nm nanoparticles showed that the nucleus was deformed at 80 nm and was not observed at 80 nm nHAP cell and membrane. This indicates that nHAP does not cross or cross 80 nm through the cell membrane. On the other hand, the percentage of apoptotic cells increases with increasing size. The size, morphology, and crystallinity of the particles can produce different results. Various forms (i.e., rod, pin, and spherical) can be seen in the nHAP extracted from natural sources such as mammalian bone morphology [25, 103].

In the same vein, Li et al. synthesized the micro- and nano-rod HAP particles by the deposition method with the presence of citric acid as a surfactant and synthesized an elliptical-like HAP using an oil-in-water [O/W] emulsion method (Fig. 4). In this study, they investigated the effect of HAP morphology on the growth of cancer cells [104].

Studies have shown that spherical nHAP are more stable than stretched nanotubes even at higher temperatures. Interestingly, pH can affect the morphology of the nanoparticles. On the other hand, it may change due to the morphology remaining, from a needle-shaped to a rod-like morphology change [101, 105]. Furthermore, Rao et al. showed that the morphology of nHAP affected the renal epithelial cell toxicity [106]. These nanoparticles can produce calcium oxalate in the kidney, which is a kidney stone. In several studies, spherical nanoparticles were more toxic than other nanoparticles, and plate nanoparticles were less toxic, compared to the others. Since the surface area of the spherical nanoparticles is greater than the needle, rod, and plate, the length-to-width ratio is also effective.

Moreover, studies have shown that increased crystallinity of nHAP increased proliferation and growth of osteoblast cells compared to amorphous samples. In synthetic methods, nHAP can be synthesized in a porous or dense manner. The amount of porosity in porous form is lower, and it is synthesized at high temperatures by heating HAP nanorods [102, 107, 108]. This type of nHAP is most commonly used for bone regeneration, and condensation occurs at higher temperatures. In fact, calcination at high temperatures helps improve the crystallinity of the nanoparticles, and density causes increased strength. Furthermore, porous nHAP can be used as a scaffold for bone defects [109-111]. Interestingly, it is necessary for the growth, repair and improvement of bone tissue in a normal morphology. These nanoparticles can hold water because of their porosity, and can also be a good adsorbent for metals that are almost similar to calcium and carry the appropriate drug [112, 113].

The optimum size for cellular uptake is about 27-30 nm with spherical morphology; however, the increasing size can decrease cellular uptake [114, 115]. Zhao et al synthesized spherical and rod-shaped nHAP of the same size and investigated the effect of morphology on osteoblast growth. Moreover, they, showed that spherical nanoparticles acted more efficiently than rods in the growth of osteoblasts [116] (Fig. 5).

Different methods of powder production also affect the final mechanical properties since the application of different methods will result in differences in grain size and chemical composition. For instance, smaller grain size leads to higher fracture toughness. Mechanical properties of condensed HAP are higher than those obtained for bone and tooth [117, 118].

The same as, other nanoparticles, the effective size of nHAP in clinical trials is between 100-30 nm to have longer blood circulation in the body since smaller particles are rapidly excreted by the kidneys and larger particles are invaded by phagocytic cells [119-121].

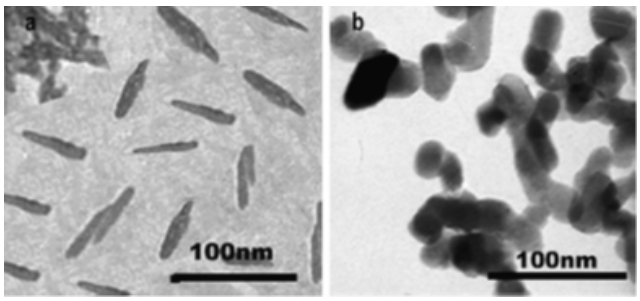


Fig. 4. TEM images of nanoparticles a) HAP rod b) elliptical.

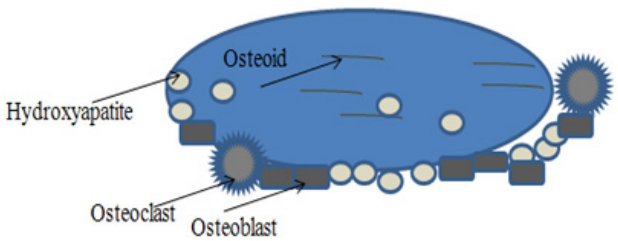


Fig. 5. The effect of Hydroxyapatite on Osteoblast growth

Synthetic methods

The synthesis of nHAP is extracted both from natural [109,122-128] and chemical sources. The bone of mammals like cattle, bones, aquatic shells, or egg shells are natural sources for HAP preparation. Natural HAP contains elements Na^{+}, Zn^{2+}, Mg^{2+}, K^{+}, Si^{2+}, Ba^{2+}, F^{-}, and CO_3^{2-}, which substitute for calcium and phosphate ions in HAP [8,129,130]. In synthetic HAP, cations replace calcium ions, whereas anions, especially carbonates and inorganic phosphates occupy the phosphate site in the network [131]. Natural bone contains 4-6% by weight of carbonate in its HAP structure which replaces phosphate ions [132-134]. By substituting carbonate ions for phosphate, the negative charge deficiency is compensated by the loss of part of the calcium network or substitution by monovalent cations such as sodium [135].

These elements are essential for bone regeneration and increase the dissolution of HAP. On the other hand, natural HAP has poorer mechanical properties such as resistance to pressure, fatigue and lower stiffness, whereas synthetic HAP can improve these mechanical properties [16, 17, 136-138].

Wet chemical methods including co-precipitation, sol-gel, sonochemical and emulsion and reverse micelles are common methods for the preparation of nHAP. Table 2 lists some of their advantages and disadvantages. The reverse micellar method (microemulsion of W/O) in which the surfactant plays a major role in the preparation and stability of the nanoparticles has been studied in recent years. To overcome the difficulties of this method, [Table2], the researchers used water-soluble polymers [polyelectrolytes] in emulsion droplets, including Na-Polyacrylate, an anionic polyelectrolyte that acts as a template for the formation of nanoparticles [139].

As mentioned in the Table 2, the co-precipitation method is a common method for the preparation of nHAP due to its simplicity, low cost, and low contamination; however, particle aggregation and agglomeration are high in this method. As a result, the nanoparticle surface can be modified with polymer to prevent confusion and aggregation and stability in different environments [65,140-142]. To reduce the size of nanoparticles , ultrasonic method was used [3, 143].

Lowe et al., with the help of nHAP prepared from salmon and by lyophilization, were able to obtain a scaffold from HAP-chitosan-fucoidan and show that cell proliferation is highly toxic in bone marrow mesenchymal stem cells (PMSCs). These scaffolds have 90% porosity, which are suitable for nutritional supplement and growth factor. On the other hand, porosi-

Table 2. The advantages and disadvantages of some of the nHAP synthesis methods [8, 89, 144-151]

Methods	Advantages	Disadvantages
Sol-gel	Control of size and morphology - Porosity control - Low toxicity - Good coating and strong adhesion to substrate	Need for high temperatures for drying - need for high pH - need for alkoxide
Co-Precipitation	Simple - Low Cost - Available Materials - Low Pollution - Morphological Control with Reactive Changing - Suitable for Industrial Production	High potential for particle aggregation and clumping - Need for nanoparticle surface coating - Need for high pH - High particle size range
Hydrothermal	High level of product, easy control of reaction conditions, environment friendly, high crystallinity, morphological diversity with pH control	Requires high temperature
Microemulsions and reverse micelles	Size Control and Prevention of aggregation -Often Needle Shaped	Need for organic solvent and surfactant, limited particle size inside emulsion droplets, and surfactant stability in reaction medium
Electrical deposition	Inexpensive materials and electrodes, thin film control	Effective for coating on substrates such as metals

ty increases the water absorption capacity of scaffolds to repair bone damage since water absorption and retention are effective for application in tissue regeneration [109]. It is worth noting that in some applications high-density nHAP powders and low inter particle distances are required to enhance mechanical properties. In these cases the combustion synthesis method and the sintering step play an important role in the final particle size [96, 144].

Sol-gel method

Sol is the distribution of colloidal particles in a fluid having a diameter of about 10 –1000 angstroms and the colloidal particles measuring 1–100 nm. As the condensation increases, the sol becomes a gel. This method is very useful in the preparation of metal oxides and nano-oxides due to the formation of condense with the formation of alkoxide bonds. The sol-gel method allows controlling the composition and structure at the atomic level. In the preparation of nHAP by sol-gel method, the precursors of calcium (nitrate, carbonate, and diethoxide) and phosphorus (triethylphosphate, phenyl dichlorophosphate, and pentoxide) are mixed leading to the production of uniform nanoparticles [140, 152] (Fig. 6).

Recently, sol-gel methods have been developed for the synthesis of nHAP, which have certain advantages such as lowering the synthesis temperature and not requiring high pH compared to other methods [152]. However, the use of alkoxide and the high reaction steps to obtain pure HAP as well as impurities such as CaO are major disadvantages of this method [153].

In this regard, studies have been conducted on the simple sol-gel method that does not require alkoxide by reacting with calcium nitrate and potassium pentoxide. However, this method requires high temperatures [144]. Rajabi et al. also applied a simple alkaline-free sol gel method to synthesize nHAP. Nonetheless, they have eliminated the need for high temperatures and prepared it at room temperature [144].

In a similar way, Hosseini et al. investigated the effect of different temperature, retention time and calcination temperature on nHAP using the sol-gel method. They showed that higher temperatures in the sol stage resulted in amorphous intermediate formation and stoichiometric HAP with Ca/P=1.67 [154]. Time

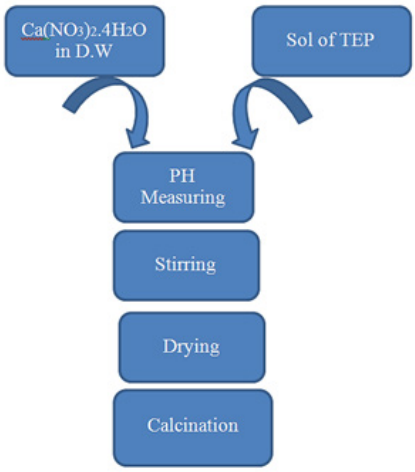


Fig. 6. The steps of preparation of nHAP by sol-gel method

changes the color of the solution, reduces the pH, and decreases CaO. Moreover, an increase the calcination temperature increases the crystallinity of the particles. However, the presence of coating agents such as citric and alginic acid can cause Ca^{2+} complexation and decrease CaO formation [145, 146, 154-161].

Co-precipitation method

This method, which is the simplest, cheapest and fastest way to make nHAP powders, is very common in nHAP synthesis. In this method, calcium sources include carbonate, chloride, nitrate, and calcium hydroxide. Moreover, phosphate sources include calcium hydrogen phosphate, phosphoric acid and other hydrogen phosphate salts that react with aqueous solutions[162]. The Ca / P ratio is approximately 1.67, and due to the solubility of nHAP in acidic environment, pH should be basic (Fig. 7). For this purpose, sodium or ammonia can be used [1,54,163,164]. The reaction is as follows:

$$10Ca(OH)_2+6H_3PO_4+NH_4OH\rightarrow Ca_{10}(PO_4)_6(OH)_2+18H_2O$$

In this method, the reaction temperature, pH, time and rate of mixing are adjusted to obtain a controlled size of the nanoparticles [116, 147]. On the other hand, the morphology of the nanoparticles can be changed by changing the molar ratio of the reactants [148].

It is important to note that due to the high tendency of the HAP nanoparticles to agglomerate, the nHAP must be coated with polymer or other agents other-

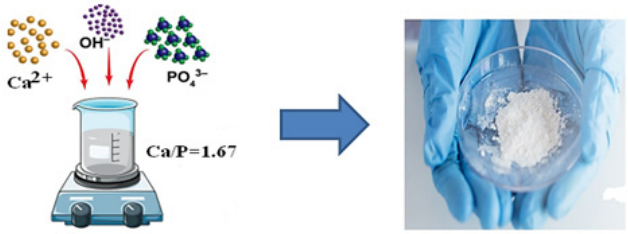


Fig. 7. Schematic of the formation of nHAP by Co-precipitation method.

wise coagulation method could be improved with ultrasound methods [110, 165]. In a study conducted by Qiu et al., the clogging was prevented with surfactants, and stable suspension of homogeneous nanoparticles was formed using an ultrasonic step [3]. Wang et al reported the effect of sodium phosphate on agglomeration controlling of nHAP without toxic effects [166]. On the other hand, ultrasonic coupling method affects particle size, morphology and homogeneity. In the sonochemical method, the particles have a high degree of crystallinity and spherical shape but a smaller surface area.

What is certain is that calcium phosphate deposition in the form of HAP occurs at high physiological conditions. As a result, HAP synthesis should also be high in PH [167-169]. Sarig et al. used microwave- coupling method in nHAP synthesis. The advantage of this method is the synthesis of small spherical nanoparticles with loose clusters that remain unchanged even for a long time [169]. Furthermore, Abidi et al. synthesized the HAP nanoparticles using the coupling method and showed that increasing the calcination temperature affected the size enhancement and improved the crystallinity of the nanoparticles [170].

Hydrolysis and hydrothermal methods

The hydrolysis method uses calcium carbonate as a calcium source and calcium phosphate or calcium hydrogen phosphate as a source of hydrogen in the presence of alkali at temperatures below 100 °C [136,171,172]. In the hydrothermal method, water is used as the reaction medium at high temperatures [149,150,173,174]. The advantage of hydrothermal co-precipitation over just co-precipitation is the variation of morphology with the aid of pH change [175,176].

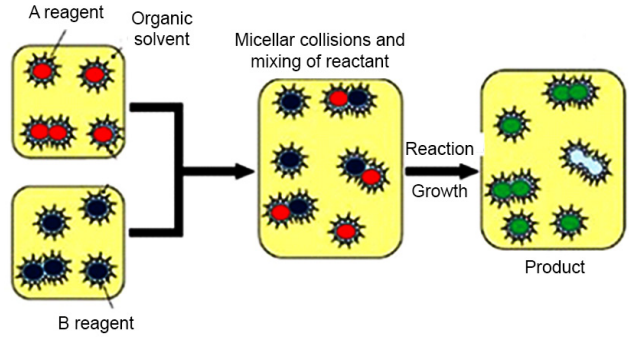


Fig. 8. Microemulsion Processes

Microemulsion and reverse micelle method

The emulsion is composed of two immiscible liquids (usually oil and water), one of which is dispersed in tiny droplets (Fig. 8). The great advantage of a microemulsion is that it acts as a solvent, dissolving polar and non-polar substances in its droplets, concentrating and separating the reactants. In addition, microemulsion may be used to overcome the problems of solvability and increase the rate of reaction. Water-insoluble drugs in drug doses have caused many problems due to their severe limitation in choosing the right solvent for oral and topical use [177]. Oil droplets sprayed with oil microemulsion in water provide a potential solvent for such drugs.

Due to the immiscibility of two-phase oil and water, amphiphilic molecules are used with hydrophilic head and hydrophobic tail. These molecules, which are called surfactants, can be formed at the interface of two phases and form a structure called micelles. In fact, micelles are colloidal surfactant molecules in a colloidal solvent that act as reagents for the synthesis of nanoparticles. However, the electrostatic effects of ionic surfactants can lead to further growth of nanoparticles. For surfactants with large polar heads, the cosurfactants, such as n-Butanol, n-Pentanol and n-Hexanol alcohols, are used. The names and structures of some surfactants are mentioned in Table 3 and

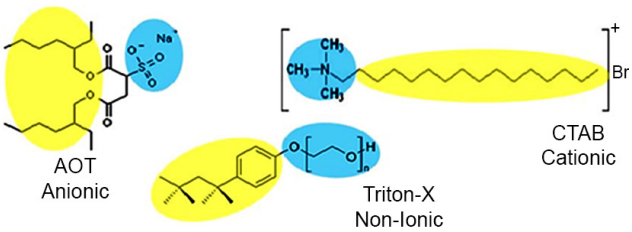


Fig. 9. The structure of anionic, cationic and non-ionic surfactants.

Fig. 9 [178, 179].

Organic solvents are used in the microemulsion methods (i.e; W/O and O/W). Reverse micelles are actually microemulsions of water in the oil that form nanoparticles in water droplets dispersed in organic solvents. Accordingly, it is necessary to have stable microemulsion with specific droplet size to control the size of the nanoparticles. To achieve this, surfactants and polyelectrolytes (water- soluble polymers) can be effective [151, 180, 181].

Li et al., prepared rod nHAP using co-precipitation and freeze-dried methods and prepared ellipse-like nanoparticles by emulsion method and examined their effect on cancer cell proliferation compared to HAP microparticles. In this study, the identification methods concluded that nHAP inhibited the growth and proliferation of cancer cells in both morphologies more than micro-percent [104].

Futhermore, different Ca/P ratios were obtained by mixing calcium carbonate and calcium hydrogen phosphate as the reaction raw materials and hydrolyzing with a benefit at pH = 13. On the other hand, it has been suggested that at high temperatures sodium ions can replace some of the calcium ions in the network, and the size of the nanoparticles increase in Ca/P ratio from 1 to 1.67 [182].

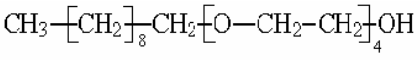
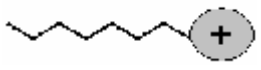
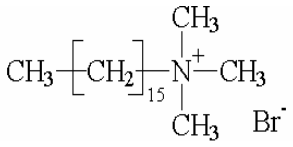
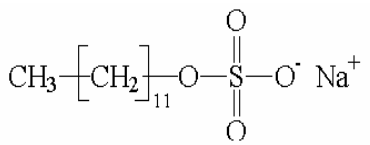
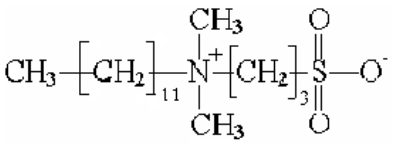
For the first time, Jahan et al. obtained nHAP from the eggshell using the reverse micellar method and used Triton X100 non-ionic surfactant to achieve maximum surface area and reduce the environmental cost with low nanoparticle absorption [151].

Investigation of the interaction between Hydroxyapatite and Bone

Given the fact that HAP binds to serum proteins and cellular integrin receptors to bind to osteoblastic cells, it is important to use nanoparticles in their in vivo work to interact with cells and somehow be absorbed by cells. This interaction is affected by the size, shape and morphology as well as surface charges of nanoparticles. Since the surface of the charged cell is negative, the positively charged surface nanoparticles are absorbed faster and more easily, and the negatively-charged nanoparticles are repelled by the cell surface. However, high positive charge makes this adsorption difficult and the closer it is to the neutral, the easier it is due to the zeta potential of the adsorption [106,183].

In a study performed by Motskin et al., they applied citrate coating on nHAP to negatively charge the nanoparticle surface. Since the level of negative charge was low, they showed a very favorable cellular uptake [163]. The purpose of this coating is to repel

Table 3. Some of common surfactants and their structures

Type of surfactant	shape	structure
Neutral		
Cationic		
Anionic		
Bipolar		

nHAP for greater colloidal stability. In the synthesis method they became rod-like nanoparticles that had better adsorption than the spherical shape.

Surface coatings on HAP not only prevent the accumulation of nanoparticles but also, bind to various factors on the surface, affecting cell proliferation and absorption.

Chen et al., investigated the effect of surface charge on nanoparticles, cell proliferation, and uptake using different carboxylic acid compounds with amino, carboxylic and methyl functional groups. They found that HAPs were more easily absorbed by bone cells [1, 163]. In addition to surface charge, crystallinity, solubility as well as surface roughness can affect cell adhesion. Therefore, high crystallinity and low solubility can improve cell attachment. Interestingly, both cellular binding is affected by the roughness of the nanoparticle surfaces and the surface roughness itself [16, 184].

In their study, Eliaz et al. demonstrated the efficacy of hydrophilic surface, temperature, pH use of acidic solution and role of osteoblast adhesion [185, 186]. According to the results, they chose the titanium base for the response of osteoblast cells to the surface of nHAP and noted that even the angle of implantation of titanium could be effective in cell attachment ($\theta = 30$). However this is not true for porous HAP.

The interesting thing about the structure of HAP is the presence of hydroxyl groups. As mentioned earlier (Fig. 2) it was found that the O-H hexagonal form on the side edges of the single cell made it easy for the functional groups to access it. On the other hand, it is very suitable for substitution with anions such as carbonate. The interesting thing about the structure of HAP is the presence of hydroxyl groups.

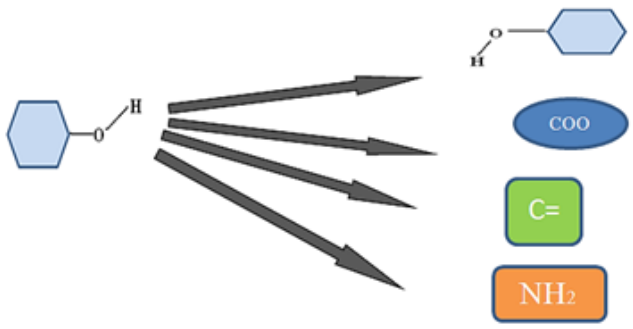


Fig. 10. Interaction of the hydroxyl group with the Hydroxyl, Carboxyl, Carbonyl and Amine groups

Fig. 10 Interaction of the hydroxyl group with the Hydroxyl, Carboxyl, Carbonyl and Amine groups previously mentioned (Fig. 2), it appears to exist in the O-H hexagonal form on the side edges of the single cell, which makes it easy for the functional groups to access it. On the other hand, it is very suitable for substitution with anions such as carbonate. The hydroxyl group, due to their electron pair, can first repel other nanoparticles and, on the other hand, can act as Lewis base and interact with Lewis acids such as alumina and titania [101, 150, 187-189]. This type of interaction improves the stability and mesoporosity of the nanoparticles. The HAP/Titania composites have a special place in medical engineering because of their favorable biological and mechanical properties. Adding titanium nanoparticles to the HAP structure, while improving the mechanical properties of apatite ceramics due to the superior mechanical properties of Titania compared to HAP will also increase the implant adhesion strength to the hard tissue, thereby helping to stimulate cell growth.

The presence of hydroxyl groups also binds to many molecules and surface coating agents of the nanoparticles and can bind to their carboxyl, amine and oxide groups. In fact, the main factor is the interaction of nHAP with collagen and other molecules and even the coating agents of the hydroxyl group. The nHAP can act as an electron donor and acceptor. It is worth noting that this interaction can be investigated with FT-IR techniques. The involvement of the hydroxyl group in bonding with oxygen or nitrogen causes the tensile bond peak (13575 cm-1) and flexural (1630 cm-1) displacement of the hydroxyl group. However, the rate of displacement depends on the atom attached to the hydroxyl group [10, 190]. Nevertheless, the presence of Ca2+ ions also interacts with functional groups such as carboxyl (COO-) in amino acids, proteins and carbonyl (C=O) with Nhap. In addition the phosphate group can also interact with functional groups, such as NH2. It should be noted that three oxygens in the phosphate ion have a negatively charged and have an equilibrium effect with the calcium cation and other cations [191]. Interestingly, many of the polymers used to coat the nHAP surface in the co-deposition method can affect the size and shape of the nanoparticles by binding Ca^{2+} ions to the polymer functional

groups. On the other hand, water also helps to bond nanoparticles together. However, loss of water at high temperatures makes this bond stronger [3, 64, 192].

Why is Hydoxyapatite used in bone regeneration?

Undoubtedly, it is essential for successful bone marrow transplantation and bone regeneration to create an effective interaction between bone and implant. One of the factors affecting the biocompatibility of the material is corrosion and toxicity. The use of metal alloys such as titanium as implants in the body can cause toxicity and inflammation problems due to metal release [50, 192, 193]. Fortunately, nHAP can easily bind to bone and cause bone growth and regeneration due to its structural similarity to bone and non-toxicity as a biocompatible material. In fact, the ability of HAP to bind to bone tissue is the most important reason for its use as a bone substitute. On the other hand, when implanted in the body, there are no toxic effects, swelling, infection, and a negative or excretory response from the body [101]. As mentioned earlier, the hydroxyl group can interact with functional groups of biomolecules, and this effective binding to collagen and other molecules has made it a viable option in bone regeneration. Nanometer-sized HAP increases the adhesion of bone marrow cells and fibroblast cells compared to traditional bio-ceramics. The adhesion of implant coated with HAP mineral with bioactive properties will gradually build up in the body tissue. Several studies have been conducted in recent decades to improve and enhance the mechanical properties of HAP [194]. When the HAP ceramics are implanted in the body, a HAP containing carbonate groups is formed on the surface and attaches a stronger HAP to the living bone. On the other hand, it has a short recovery after planting and its biodegradability and degradability properties make it efficient to use. This property, in addition to bone repair, can be used to transport drugs in bone therapy. Some HAP or HAP coated drugs are trademarked.

Fig. 11. Some of the most common hydroxyapatite drugs on the market

CONCLUSIONS

This study attempted we have attempted to introduce a new perspective on the application of nHAPs in bone repair by investigating how nHAP interacts with bone surface since the way bone interacts with the alternative affects the body's response. Moreover, the nHAP can be a good option for bone treatments because of its very good structure and biocompatibility. It is worth noting that the method and conditions of synthesis, type of coating and size, as well as the morphology of nanoparticles are very effective in their application.

ACKNOWLEDGMENT

The author would like to thank Dr. Kobra Akhavan for her contribution. Special thanks to Mazandaran University of Medical Sciences Sari, Iran and Islamic Azad University Science and Research Branch.

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