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**Doped biphasic calcium phosphate: synthesis and structure**

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**ABSTRACT**

Hydroxyapatite, tricalcium phosphate, and a mixture of these, i.e. biphasic calcium phosphate (BCP), are widely employed as ceramic materials in hard tissue engineering, despite their poor mechanical and functional properties. The method of ionic substitution inside their lattice structures has been examined extensively by researchers in their long efforts to develop materials that closely resemble natural hard tissues. The presence of dopants has a deep impact on the phase assemblage, structural, and functional behaviors of BCP. In this context, the goal of the current article is to cover different aspects of ongoing research on doped biphasic calcium phosphate. Apart from providing brief descriptions of different synthesis routes for producing ion-modified BCPs, the limitations of each technique are also discussed. In addition, particular emphasis has been given to describing the key experimental results, which elucidate the structural changes occurring due to doping. In particular, the preferable substitution sites of different dopant ions and the resulting crystallographic changes are depicted quite elaborately. Finally, the effects of substitution on biological and mechanical properties of BCP are briefly mentioned. In summary, the present review focuses on the ionic substitutions in BCP systems and their collective effects on material behaviors.

**Keywords**

Biphasic calcium phosphate; hydroxyapatite; tricalcium phosphate; synthesis; ionic substitution; doping

**1. Introduction**

The World Health organization (WHO) has recognized musculoskeletal diseases resulting from trauma, osteoporosis, osteoarthritis or surgical intervention, as the second largest contributor to disabilities worldwide [1]. According to recent statistics, around 2.2 million patients require bone grafting procedure annually to improve the quality of life or to rectify bone defects [2]. Moreover, about 1.2 million people have lost their lives because of the lack of proper bone replacement facilities [3,4]. Both biological and synthetic bone graft materials are clinically used for hard tissue replacement therapy. Biological bone graft materials can be broadly classified into three categories: autografts, allografts, and xenografts [5]. While biological materials closely resemble natural bone, they are at high risk of immunorejection and microbiological contamination, which often leads to revision surgery and implant removal [5]. A limited supply of biological materials is another major drawback for such grafting. Hence, the search for synthetic bone replacement materials has been driving significant activity in the field of biomaterials.

Synthetic bone graft/implant materials can be distinctly traced to three generations (Figure 1) [4]. While the first-generation materials (Ti or stainless steel) are bioinert in nature and initiate a minimum foreign body response, the second-generation materials, which are able to form chemical bonds with living tissue, facilitate the formation of strong tissue-implant interfaces [4]. Second-generation implants can also undergo controlled degradation in vivo. The third-generation materials, on the other hand, can stimulate cellular response at the molecular level. It is noteworthy that materials of each generation have their own advantages and disadvantages. Calcium phosphate (CP)-based materials arguably belong to the second-generation biomaterials, because of their excellent osteoconductive and osteoinductive properties [6]. CPs can even induce osteoinduction in the absence of any osteogenic supplements [7].

Hydroxyapatite (Ca10(PO4)6(OH)2; HA), tricalcium phosphate (Ca3(PO4)2; TCP), tetracalcium phosphate (Ca4(PO4)2(OH)2; TTCP), biphasic calcium phosphate (BCP) and amorphous calcium phosphate (ACP) are some of the well-known CP-based bioceramics. Among these, the most-investigated calcium phosphate ceramic is undoubtedly HA. Two stable phases of HA are found in nature, and stoichiometric HA has a Ca/P ratio of 1.67. One belongs to the hexagonal (P63/m) symmetry and the other corresponds to the monoclinic P21/b symmetry [8]. The hexagonal structure is of great interest, because at nanoscale, natural bone is composed of hexagonal HA nanocrystals, dispersed in a collagenous matrix [6]. The hexagonal HA unit cell has dimensions of a = b = 9.432 Å and c = 6.881 Å [9]. Two non-equivalent calcium sites, namely Ca(1) and Ca(2), are present in the HA structure (Figure 2) [10]. Although both are six-fold coordinated, the first coordination shell of Ca(1) consists of three O(1)
and three O(2) atoms, while four O(3), one O(2) and one O_{-H} atom are present in that of Ca(2) \([10]\). Many authors described the Ca(1) site as nine-fold coordinated and Ca(2) as seven-fold coordinated due to the presence of oxygen atoms almost inside the first coordination shell \([11] [12]\). Keeping non-equivalent crystal sites in mind, the chemical formulae of HA can be written as Ca(1)\(_4\)Ca(2)\(_6\)[PO(1)O(2)O(3)]\(_{26}\)[O\(_{_{-H}}\)H\(_2\)]. The hydroxyl ions are arranged in parallel with the “c” axis of the lattice, and together they form the ion channel \([13]\). The ion channel
columns pass through the centers of the Ca triangles, located on the mirror plane at \( z = 1/4 \) and \( z = 3/4 \) [14]. The successive triangles are rotated at 60° around the “c” axis [14].

TCP, which is another CP-based bioceramic, has three polymorphs, \( \beta \), \( \alpha \), and \( \alpha’ \) [15]. Among these, \( \beta \)-TCP is stable at room temperature and converts to \( \alpha \)-TCP at higher temperatures (~1125°C), which converted back to \( \beta \)-TCP after cooling [16]. \( \alpha’ \)-TCP exists at the temperature ~>1470°C [17]. \( \beta \)-TCP has rhombohedral symmetry with space group R3\(_c\), having unit cell parameters, \( a = 10.3961 \) Å and \( c = 37.3756 \) Å [18]. The crystal structure of \( \beta \)-TCP consists of two distinct columns, “A” and “B”, parallel to the “c” axis, with five non-equivalent Ca sites (Figure 3). While the “A” column has the form of \( \cdots P(1)O_4 \) \( Ca(4)O_3 \) \( Ca(5)O_6 \) \( P(1)O_4 \cdots \), the structure of the “B” column can be described as \( \cdots P(3)O_4 Ca(1)O_7 \) \( Ca(3)O_8 \) \( Ca(2)O_8 \) \( P(2)O_4 \) \( P(3)O_4 \cdots \) [19]. One “A” column is surrounded by six “B” columns, whereas a “B” column is surrounded by two “A” and four “B” columns (Figure 3) [19]. On the other hand, \( \alpha \)-TCP and \( \alpha’ \)-TCP have monoclinic space group P2\(_1\)/a and hexagonal space group, P6\(_3\)/mmc, respectively [20]. The unit cell of \( \alpha \)-TCP has the following lattice parameters: \( a = 12.8592 \) Å, \( b = 27.3542 \) Å and \( c = 15.2223 \) Å. By contrast, the unit cell of \( \alpha’ \)-TCP is characterized by \( a = 5.3507 \) Å and \( c = 7.6841 \) Å [21].

Figure 3. Lattice structure of \( \beta \)-Tri Calcium Phosphate, viewed (a) from “c” axis and (b) along “c” axis [24].

BCP is a mixture of HA and \( \beta \)-TCP and is widely accepted as a better biocompatible material than its constituent phases [22] [23]. The properties of BCP depend on the phase fraction of HA/TCP. In general, the osteoinductive potential of BCP is almost equivalent to that of HA in the presence of osteoinductive growth factors, but it is higher than both HA and TCP in the absence of any supplements [7]. Despite being good osteoconductive and osteoinductive in nature, the main downside of BCP or its constituent phases is their poor functional and mechanical properties. The isomorphous substitution of different ions inside the HA and TCP lattice structure is one of the most explored methods of overcoming this drawback. Apart from this, it is a well-known fact that bone mineral contains different kinds of ions such as \( Na^+ \), \( Mg^{2+} \), \( CO_3^{2-} \), etc., apart from \( Ca^{2+} \). Hence, it has been hypothesized previously that ion-substituted, non-stoichiometric HA/TCP or a mixture of these may better mimic natural bone. This hypothesis prompted the interest of the scientific community in testing different kinds of doping inside the apatite or TCP crystal lattice. HA has the potential to tolerate severe lattice distortion and it can also retain its crystal symmetry in spite of being highly Ca-deficient (up to a Ca/P ratio of 1.3) [13]. This characteristic allows the HA structure to be doped
with appropriate dopants. Like HA, TCP also can hold its structural integrity against foreign ion substitution [24].

Against this backdrop, the present review article aims to discuss some of the key results related to doped BCP and its components (HA and TCP). The overall article is structured as follows. In the first section, an overview of different synthesis techniques along with their advantages and limitations is described. The next section is devoted to presenting the experimental findings about the structural changes in different kinds of doped HA/TCP. This is followed by concluding remarks. In summary, this review intends to provide a broad idea about different aspects of the current progress in the development of next-generation calcium phosphate-based bioceramics.

2. Different synthesis techniques for biphasic calcium phosphate

As discussed above, biphasic calcium phosphate is a mixture of HA and β-TCP. It is generally produced by mixing HA and TCP or by different chemical routes [25]. There are several diverse methods of synthesizing HA/TCP. As the Ca/P ratios of both the phases are very close to each other (1.67 for HA, 1.50 for TCP), a mixture of the two phases, i.e. BCP, is often obtained as the end product. Existing synthesis methods can be broadly classified into four categories (Figure 4), namely the dry method, wet chemical method, high-temperature technique and synthesis from biogenic sources [26]. Among these, the dry and wet methods are mainly used for the synthesis of doped HA/TCP/BCP. Each of these methods has its own advantages and disadvantages. In the present section, different synthesis techniques will be summarized.

2.1. Chemical synthesis in dry state

In the dry method, precursors are mixed without a solvent. The chemical compositions of the end products of the dry method do not depend greatly on the processing parameters; making it suitable for mass production. Among different types of dry methods, solid-state synthesis and the mechanochemical process are used mainly to produce HA/TCP.

2.1.1. Solid-state reaction

In a typical solid-state synthesis procedure, precursors are first mixed by milling and then calcined at a high temperature (~1000°C) [27]. Different types of salts are used as precursors, which serve as the source of calcium and phosphate ions. Due to the high temperatures used for calcination, the end products almost always show a well-crystallized structure. This is the major advantage of the solid-state synthesis technique. On the other hand, heterogeneity of the chemical composition is often observed in powders produced by solid-state reaction as the diffusion coefficients of ions are very small within the solid phase [28] [29]. Apart from this, the large size distribution of obtained particles is another major concern of the solid-state synthesis method.

Apart from the pure HA phase [27], different types of doped HA/TCP have also been prepared by means of solid-state reactions. Acros et al. [30], synthesized Si-substituted HA powder, for example, by high-temperature solid-state reaction of Ca$_2$P$_2$O$_7$, CaCO$_3$, and SiO$_2$ in the stoichiometric ratio. On the other hand, Enderle et al. [31] synthesized Mg-doped β-TCP by the solid-state reaction route, starting from CaCO$_3$, MgO, and (NH$_4$)$_2$HPO$_4$. Despite these reports,
little work has been done on the synthesis of HA/TCP by the solid-state synthesis route. This is probably due to the fact that it is very difficult to obtain a pure phase of HA/TCP by solid-state reaction.

2.1.2. Mechanochemical route

The mechanochemical method is used to fabricate nanocrystalline metals and ceramics [32]. In this process, the precursors are ground inside a planetary ball mill, keeping the molar ratio fixed at the stoichiometric ratio [33] [34]. In contrast to the solid-state synthesis route, the mechanochemical method usually produces products with a well-defined chemical structure due to enhanced reactions (kinetic and thermodynamic) among the reagents [35] [36]. This particular method is advantageous with respect to the solid-state reaction method, because of its better reproducibility and its greater suitability for mass production. Apart from the type of reagents, milling medium, milling duration, milling atmosphere, rotation speed, type and diameter of the balls, regent-to-ball mass ratio, etc., must be optimized in order to obtain the desired products through the mechanochemical route [37] [38,39].

There are several reports in the literature on the mechanochemical synthesis of pure and doped HA [37,40,41,42]. One such study was carried out by Nasiri-Tabrizi et al. [43] They synthesized HA nanorods and nanogranules via the mechanochemical route. The obtained particle size was 13 ± 7 nm and 15 ± 8 nm for two distinct sets of reagents. Besides this, Suchanek et al. synthesized Mg-substituted HA powder by the mechanochemical hydrothermal route with a median particle size of 102 nm–1.2 μm [44]. A few papers have reported the synthesis of carbonated HA using the mechanochemical synthesis method [45,46]. This method is favorable for mass production of fluorapatites, in particular [42,47,48]. Fathi and Zahraei fabricated 100% fluoride-substituted HA by the mechanochemical route using CaF₂ as a source of F⁻ ions [42]. According to their results, the obtained particle size was 35–65 nm and, in addition, the synthesized powder was suitable to be used as biomaterial as per ASTM standards.

2.2. Wet chemical method

Despite the fact that the dry method is suitable for mass production, powder particles obtained through this route are in general, irregular in shape and size. The wet method is particularly suitable for obtaining nanosized particles. Several kinds of wet methods are reported in the literature. Some of these will be discussed in the present section.

2.2.1. Chemical precipitation

The chemical precipitation method is the simplest route to obtaining HA/TCP/BCP powder. The synthesis of HA via the chemical precipitation method is based on the principle that, at pH 4.2, HA is the most stable phase in aqueous solutions under ambient conditions [49]. In the chemical precipitation method, different calcium and phosphate containing reagents are used as the sources of Ca and phosphate ions. In general, the dropwise addition of one reagent to the other under continuous stirring is followed in the chemical precipitation method. The resultant precipitate is washed, filtered, and dried; it is sometimes aged under atmospheric pressure [50] [51]. The desired yield of the reaction depends on the mixing rate, reagent concentration, drying method, etc. [52,53]. The molar ratio of the ions is kept fixed during the reaction [54]. Usually, non-stoichiometric and low-crystallized particles are obtained through the chemical precipitation route [55]. This probably occurs due to the complex crystal structures of calcium phosphate materials, vacancies in the crystal lattice, interactions among the particles, the presence of other phases, etc. [48,56].

Several alternative routes have been proposed in order to overcome this drawback. One of them is to use a temporary template for nucleation [57] [58]. Co-polymers were the initial candidates for this purpose [59]. Recently, macromolecules, which have a tendency to form micelles in aqueous solutions, have been used as nucleating centers to enhance the crystallinity of the obtained powder [60]. CTAB is the most popular choice for the synthesis of HA [61]. The synthesis of HA nanorods (50–80 nm diameter, 0.5–1.2 μm in length) in the presence of CTAB has been reported in the literature [62]. Apart from CTAB, PEG and Tween-80 are the other popular choices [47].

Other than macromolecules, small organic molecules have also been used to enhance the crystallinity of the precipitated powder. It is reported that more crystallite HA powder can be accomplished using citric acid as a chelator [63]. Apart from pure HA, the precipitation method has been employed to incorporate different kinds of dopants, namely carbonate [64,65], fluoride [66], chloride [67], metal ions (Na⁺, Sr²⁺, Zn²⁺, Ti⁴⁺, Fe²⁺/Fe³⁺, Mg²⁺, etc.) [68–75] inside the HA and TCP crystal lattices. This method has also been successfully used to substitute more than one dopant inside the lattice structure [76, 77].

2.2.2. Sol-gel synthesis

Sol-gel is one of the most widely used wet chemical methods for synthesis of inorganic compounds. The general synthesis framework consists of the following steps [78]:

(a) preparation of a 3D networked structure in an aqueous or organic medium
(b) gelation and drying of the gel
(c) calcination
This particular method allows molecular-level mixing of the precursors, resulting in improvement of the chemical homogeneity of the resultant products [79] [80,81]. Calcination is generally carried out below 1000°C, and this step is critical to controlling the chemical composition of the end product. Very often, a secondary phase is generated in the sol-gel synthesis route. Therefore, this method is useful for chemical production of BCP. In general, a certain pH (~10) is maintained throughout the chemical reaction [81]. The rate of gelation and the pH value strongly affect the yield [26]. However, a sol-gel technique without the need for maintaining pH has also been developed [82].

Bose et al. [80] successfully synthesized nanosized (30 nm–50 nm) HA particles using the sol-gel route. They used calcium nitrate and ammonium hydrogen phosphate as calcium and phosphorous precursors, respectively. Sucrose was used as the template material. Feng et al. [83] reported the aging time-dependent size distribution of sol-gel-derived HA particles. The particle size increased with increments in the aging time (10–15 nm after 4 h aging; whereas 50–80 nm particles were obtained after 72 h aging) [83]. Kaygili et al. employed the sol-gel synthesis method extensively to fabricate different types of emulsion, namely oil-in-water emulsion [84,85]. In almost all cases, they found β-TCP as a secondary phase [85]. Kalita et al. [89] reported usage of the sol-gel synthesis technique to obtain nanosized (2–10 nm) HA particles, modified with Mg and Zn. Ti-substituted HA with a particle size of ≤100 nm has also been produced via the sol-gel route [90]. In addition, several reports can be found on the synthesis of carbonate, fluoride, and silicate-doped HA [91,92,93]. Recently, our group has synthesized Sr/Fe co-doped BCP via sol-gel synthesis technique with a large particle size distribution (20 nm to >100 nm) [94,95].

2.2.3. Emulsion Technique

The emulsion method is arguably the most efficient technique for producing particles with controlled sizes and morphologies [96]. A microemulsion is a metastable dispersion of two immiscible liquids, formed in the presence of surfactants [97]. On the other hand, a nanoemulsion is ultrafine emulsion droplets, with typical size ranges from 20 nm to 200 nm [98]. Three types of surfactants are mainly used to form a microemulsion: ionic, nonionic, and co-polymers of different molecular weights [99]. The nature of the end product of the emulsion method depends on the type and concentration of surfactants [100] [101].

The emulsion process can be accomplished by forming three types of emulsion, namely oil-in-water emulsion, water-in-oil emulsion and water-in-oil-in-water double emulsion [97]. Among these, water-in-oil emulsion is mainly used for the synthesis of HA [26]. Researchers have synthesized HA particles with different shapes and sizes using the emulsion technique. Pradeesh et al. [96] fabricated HA microspheres by emulsion route, for example, using PVA as a stabilizer. On the other hand, Lim et al. [102] prepared nanocrystalline HA powders by means of the emulsion technique. They used a nonionic surfactant (KB6ZA) as a stabilizer. Apart from undoped HA, substitution of different ions inside the crystal lattice has also been done through the emulsion method. Zhou et al. [103] synthesized carbonated HA nanospheres with an average size of 10–30 nm, for example, through nanoemulsion method, even without a surfactant.

2.2.4. Hydrothermal Method

In the hydrothermal method, the reagents react among themselves at high temperature and pressure [104]. Powder obtained from the hydrothermal method is, in general, well-crystallized and stoichiometric in nature [105]. The pH and temperature are the most significant parameters for controlling the morphology of the synthesized powder [106] [107]. The major disadvantage of this method is that it is very hard to control the particle size and morphology [108]. One such noteworthy example is the synthesis of HA whiskers with a large size distribution (0.7 to 3.0 μm) [108]. Such limitations of hydrothermal method can be overcome by the use of organic modifiers. Two types of modifiers are used, chelating agents and organic surfactants. EDTA is reported to be the most popular surfactant for use in the hydrothermal method [109] [110,111]. Zhu et al. [112] established the fact that EDTA affects the reaction in two ways. First, it controls the speed of HA growth via interaction with the Ca²⁺ ions. Secondly, it enhances growth along the “c” axis, providing the grown crystal with a prism-like morphology. Lin et al. [113] synthesized trace elements (Na, Mg, K, F, Cl, and CO₃²⁻)-co-doped HA via the hydrothermal process without the use of any surfactant. The preparation of zinc-substituted hydroxyapatite (Zn-HA) by the hydrothermal method using Ca(NO₃)₂, (NH₄)₂PO₄, and Zn(NO₃)₂ as reagents has been reported [114]. Rod-shaped particles 50–60 nm in length and 20 nm in width were obtained. The hydrothermal method together with the mechanochemical route was used to prepare carbonated apatite, as well [46].

Besides the above-mentioned procedures, there are many other types of wet chemical routes that are suitable for the synthesis of undoped and doped HA/TCP. The sonochemical method is one of these. In this particular technique, reagents are activated using ultrasonic radiation [115]. A mixture of 10–20 nm × 20–50 nm short rod-like and spherical 10–30 nm in diameter HAP nanoparticles were synthesized via ultrasound-mediated precipitation [116]. The preparation of needle-shaped HA with an aspect ratio up to 80 via ultrasound radiation was also reported [117]. Taken together, it can be said
that wet chemical methods provide a vast opportunity to synthesize HA/TCP/BCP with different morphologies and crystallinity.

2.3. High-temperature processing

High-temperature methods use elevated temperature to burn or partially burn the precursors. Pyrolysis and combustion are the two major high-temperature processing techniques. The pyrolysis method is capable of producing highly crystalline HA [118]. The temperature and concentration of the precursors are two important parameters for controlling the composition of the end product [118]. The main disadvantage of pyrolysis is the formation of secondary agglomeration, which can be avoided by the addition of specific salts to the precursor solution [119]. On the other hand, in the solution combustion method, a rapid exothermic and self-sustaining redox reaction between the oxidants is used to synthesize the products [120]. A suitable organic fuel is required to carry out the reaction [121]. The chemical homogeneity of the obtained powder makes it advantageous over other synthesis techniques [122]. In the case of HA synthesis, Ca(NO$_3$)$_2$ is generally used as a precursor, and urea, citric acid, glycine, sucrose, etc., are used as fuel [123] [124]. Ghosh et al. reported preparation of HA nanocrystals through combustion method [125]. Besides this, an article on the synthesis of nano-structured fluorine and chlorine-substituted HA particles with the diameters ranging from 50 nm to 100 nm via the solution combustion route can also be found [126]. Sr-substituted close-packed hexagonal HA crystals, with primary particle sizes of 15 to 70 nm in length and 5 ± 1 nm in diameter, have also been obtained using this method [127]. In another interesting study, Narayan et al. [128] synthesized Ag-doped HA with antimicrobial properties using a self-sustained combustion reaction. Against the above-mentioned backdrop, it can easily be said that different high-temperature synthesis techniques have an excellent capability of producing pure and varied kinds of substituted HA.

Finally, HA/TCP can also be produced from different biogenic sources, such as bovine bone, fish scale, fish bone, sea-shell, coral and eggshell, etc. [129]. This method is of particular interest because of its economic and environmental advantages. Products obtained via this route closely resembles the bioapatite and are found to be more bioactive than synthetically obtained BCP [130]. This technique is especially useful for obtaining carbonated HA from eggshell waste [131]. In recent years, control over the morphologies of the HA particles obtained from biogenic sources has also been achieved employing eggshell and bamboo membrane [132] [133].

Extensive research is still continuing to explore different synthesis techniques. Researchers are now combining two or more distinct methods together to achieve better control over the chemical homogeneity, crystallinity, and morphology of the synthesized powders and to overcome the limitations of the individual routes. Innovation of alternate synthesis techniques, which can provide nanoparticles with new characteristics, remaining an open question to date that can be addressed in the future.

3. Structural changes due to doping

As stated in section 1, HA has the ability to retain its crystal structure after ionic substitution. Almost half of the elements in the periodic table can be incorporated into the HA crystal lattice structure without much distortion [134]. Cations usually substitute for Ca$^{2+}$ ions, and anions replace OH$^-$ or PO$_4^{3-}$ groups of the HA crystal. Both kinds of substitution lead to contraction or expansion of the lattice parameter(s). It is generally perceived that doping of larger ions leads to the expansion of lattice parameter “a”. This is not always true, particularly when a monovalent cation replaces a bivalent cation, as this may create additional vacancies [135].

Maintenance of charge neutrality is an essential criterion for any bulk material. The replacement of Ca$^{2+}$ ions with bivalent cations (Sr$^{2+}$, Mg$^{2+}$, Zn$^{2+}$, etc.) does not cause any charge imbalance in the crystal lattice, but this does occur in cases of monovalent ion (Na$^+$, K$^+$) substitution. This imbalance is neutralized either by the creation of supplementary vacancies [136], or through simultaneous substitution of cations and anions [137]. As for the trivalent ions, they are usually incorporated into the lattice structure as lower valence metal hydroxide ions [138]. On the other hand, monovalent anions (Cl$^-$, F$^-$) replace OH$^-$ groups of apatite crystal without compromising the electroneutrality. Bivalent anions substitute the phosphate groups while also generating both calcium and hydroxide vacancies, whereas tetravalent anions (SiO$_4^{4-}$) create hydroxide vacancies [135].

A brief discussion of two distinct Ca sites (Ca(1) and Ca(2)) of HA has already been presented in the introduction. The Ca(1) site is smaller in volume than the Ca(2) site [139]. This fact may lead to the incorrect conclusion that larger ions prefer the Ca(2) site for substitution. Substitutional preferences depend on the charge of the cations, nature of the anions present in the ion channel and the strength of the bonds between the ions and the surrounding atoms [135]. The Ca(1) site can also accommodate large ions, because of its longer ion-oxygen bond distance. With the increment of substituted ions in Ca(1), the c’ axis becomes elongated due to the mutual repulsion, which gets partially restrained by the accommodation of ions at the Ca(2) site [140].

Like HA, TCP also offers a cation site with octahedral coordination suitable for smaller ion substitution [141]. It has five distinct Ca sites, namely Ca(1) to Ca(5), along
with a vacancy for Ca(4) [24]. According to Yoshida et al. [24], monovalent atoms can substitute for Ca(4) sites including VCa(4) (Figure 5). The upper limit of monovalent ion substitution is ~9 mol%. On the other hand, bivalent cations replace Ca in the Ca(4) and Ca(5) sites, with a maximum substitution limit of 14 mol%. The substitution model for trivalent ions is quite different from those for mono/divalent ions. Three Ca\(^{2+}\) ions are substituted by two trivalent ions, and they do not simply substitute for Ca(4) or Ca(5) sites. Research is currently underway to determine the exact location of trivalent ions inside β-TCP lattice structure. However, the following substitution process has been proposed for trivalent cations (Figure 5) [24].

\[
2M^{III} = 3Ca^{2+} + V_{Ca(4)}
\]

Considering the above substitution model, the possible maximum substitution of trivalent cations inside the β-TCP structure would be ~9 mol%. In the present section, a brief description of the structural changes (lattice parameters) of HA and TCP due to different kinds of substitution will be depicted.

### 3.1. Anionic substitution

Among the various types of anionic substitution, carbonates, silicates, fluorides, and chlorides are the most studied. When substituted, each of these shows different effects on the apatite crystal lattice, which will be summarized in the present sub-section. The most abundant anionic substitute in bioapatite is carbonate. Carbonate ions can replace two groups in apatite crystal lattice, namely the hydroxy (type A) and the phosphate (type B) groups.

The substitution mechanisms are proposed to be as follows [142]:

1. A type: \(2OH^- \rightarrow CO_3^{2-} + V_{OH}\)
2. B type: a) \(Ca^{2+} + PO_4^{3-} + OH^- \rightarrow V_{Ca} + CO_3^{2-} + V_{OH}\)
   b) \(Ca^{2+} + 2PO_4^{3-} \rightarrow V_{Ca} + 2CO_3^{2-}\)
   c) \(PO_4^{3-} \rightarrow CO_3^{2-} + OH^-\)

A-type substitution is preferred for low carbonate content (<4 wt.%), whereas B-type substitution dominates at higher content [143]. The reports on mixed substitution (AB type) are also available [144]. Lattice parameter “a” increases and parameter “c” decreases in A-type substitution. The opposite trend is followed by type B substitution [135]. Several experimental strategies have been employed to determine the exact location of carbonate ions inside the crystal structure. According to one study, \(CO_3^{2-}\) groups randomly occupy the six equivalent positions around the “c” axis, keeping their triangular plane parallel to it [145]. In another study, the authors report that carbonate ions are arranged along the ion channel of the apatite crystal [146]. As for B-type substitution, in one of the proposed structures, carbonate ions are randomly distributed on the side face of the phosphate tetrahedron [147]. Leventouri et al. [148] used Rietveld refinement to obtain the exact position of the \(CO_3^{2-}\) groups in the case
of B-type substitution and best fit was obtained when the carbonate groups were placed in the mirror plane of the phosphate tetrahedron.

Fluorine and chlorine are two very important monovalent anions, which can substitute OH\(^{-}\) group inside the HA crystal lattice. Substitution of F\(^{-}\) inside the lattice structure improves the chemical stability of the HA phase [149]. Due to the smaller size of fluorine, the lattice parameter “a” contracts with increments in the fluorine content. However, an increase in the “c” axis, which is an order of magnitude smaller than the change in the “a” axis, has also been observed [66]. Overall, the substitution of fluorine leads to a compact unit cell structure [150]. It also affects the crystallization temperature and rheological properties. Both the viscosity and contact angle increase with increases in the amount of F\(^{-}\) substituted. In particular, the contact angle changed from 55.34° ± 0.35° (undoped) to 60.34° ± 0.46° in 100% F\(^{-}\) substituted HA [150]. On the other hand, the substitution of chlorine results in a significant increase in both the lattice parameters and unit cell volume [126]. This occurs due to the larger size of Cl\(^{-}\) ion. Unlike F\(^{-}\), substitution of Cl\(^{-}\) destabilizes the HA structure and leads to formation of BCP [67].

Silicates are closely associated with different metabolic functions. Hence, it is quite natural that several efforts have been made by researchers to study silicate-substituted HA systems. According to these reports, silicates replace the phosphate groups in the HA crystal and create additional hydroxide vacancies. The upper limit of Si incorporation inside the HA structure is found to be 5 wt.% [151]. Although Si substitution has an insignificant effect on the lattice parameters, it significantly (~0.2%) distorts the angle between the oxygen in the phosphate tetrahedron and phosphorus/silicon atom [152]. It has been found that 0.4 wt.% Si substitution imposes a very small (~0.005%) contraction in lattice parameter “a” and a relatively large (~0.1%) amount of expansion in lattice parameter “c” [153]. Doping of silicate ions also inhibits the crystal growth of Si-substituted HA, resulting in a reduction of the crystallite size [154].

Apart from the aforementioned anions, limited studies have been carried out on the substitution of sulfur and selenium oxyions inside the HA crystal lattice. Like silicate, both of these substitute phosphate groups and create hydroxide vacancies. Due to their large size, the substitution of SO\(_{4}^{2-}\) ions results in an increment in the lattice parameters and unit cell volume, while decreasing the structural integrity [155]. As for selenium oxyions, these can substitute inside the HA lattice in two forms: selenate (SeO\(_{4}^{2-}\)) and selenite (SeO\(_{3}^{2-}\)). While selenite has a slightly larger diameter than the phosphate group, that of selenate is almost identical to the phosphate group. Se substitution has a negative impact on the thermal stability of HA [156]. While selenate-substitution does not affect the lattice parameters, selenite-substitution significantly expands the lattice parameter “a”, without affecting the “c” axis [157]. The effect of selenite-doping on the “a” axis can be attributed to its flat trigonal pyramidal geometrical shape, which is quite different from the tetragonal structure of phosphate ions. This result is quite contradictory since a couple of other studies did not report any remarkable trend in changes in the “a” axis with the incorporation of selenite, while lattice parameter “c” decreased [158] [159]. Another recent study reported an increment of “a” and a decrease in the “c” axis with increases in selenite content [160]. The same discrepancy remains with respect to crystallinity as well. While Kolmas et al. [157] found no significant change in crystallinity with increments in selenate/selenite ion content, Ma et al. [158] reported a decline for the very same. In a later report, Kolmas et al. also noted a decrease in the crystallinity index with the incorporation of selenite groups inside the apatite lattice structure [161]. Such contradictions will necessitate further in-depth investigation.

3.2. Cationic substitution

As mentioned above, HA/TCP has a unique ability to incorporate a large number of metal ions inside its crystal lattice. In the present sub-section, crystallographic changes due to substitution of monovalent, divalent, and trivalent ions inside the HA/TCP structure will be discussed with some oft-cited examples.

3.2.1. Monovalent cations

Na\(^{+}\), K\(^{+}\), and Li\(^{+}\) are well-known monovalent metallic ions. They are of particular interest because of their vast range of role in different biological processes. Na\(^{+}\) and K\(^{+}\), for example, play central roles in generating action potential during neurotransmission. Li, on the other hand, is an essential trace element that is used to treat bipolar disorder [162]. Their substitution inside the HA/TCP lattice has been extensively studied. Li-substituted HA was prepared by Kaygili et al. [163], who found increments in both the crystallite size and crystallinity with increases in the amount of lithium along with transformation of the HA crystal structure from hexagonal to trigonal. Another study recorded an insignificant change in the “c” axis with a slight increase in “a” axis in different Li-HA samples [164].

Potassium is incorporated inside the HA structure with the creation of additional vacancies in the ion channel [165]. Contraction of the lattice parameter “a” takes place as a result of the presence of these created additional hydroxide vacancies. However, another study reported increments in both lattice parameters with the addition of K [166].
higher ionic radius (1.33 Å), it might be expected that K+ would prefer the Ca(2) site for substitution, but the experimental findings show the opposite trend [167]. Potassium substitution increases the thermal stability of the HA phase up to 1300°C [165]. It has also been found that the presence of potassium in the chemical solution during synthesis reinforces the formation of β-TCP, resulting in the formation of BCP [165].

As far as the sodium ion is concerned, substitution of Na+ ions in the Ca(2) site also leads to formation of supplementary vacancies in the crystal lattice [68,139]. Only a slight increase in lattice parameter "c" and the unit cell volume is observed with the addition of sodium ions inside the apatite crystal lattice [68]. Sodium ions are also capable of replacing calcium ions from the β-TCP lattice structure. Substitution of Na+ into β-TCP causes expansion of the unit cell [168]. The lattice parameter "α" expands while the "c" axis contracts in a linear manner with increments in the sodium content inside the β-TCP crystal structure. The incorporation of sodium also improves the mechanical properties, such as the compressive strength of β-TCP [169]. Like potassium, sodium also increases the thermal stability and hinders the transformation of β-TCP to α-TCP up to 1200°C [68].

### 3.2.2. Divalent and trivalent cations

Among the various divalent and trivalent cations, the substitutional effects of only a few will be briefly described in the present sub-section.

Magnesium is one of the most useful trace elements. All enzymes related to synthesis of ATP require Mg to function normally. A deficiency of Mg inhibits skeleton metabolism and bone growth [170]. Mg-doped HA and TCP are reported to modulate osteoblast and osteoclast activity. Using the Rietveld refinement method, Bigi et al. [171] found the Ca(2) site to be the preferred substitution site due to metal-oxygen interactions, whereas another study found the Ca(1) site to be favorable [172]. Some studies found a significant dimensional reduction only in HA lattice parameter "c" with increases in the Mg content [173]. Expansion of the "α" axis has also been reported [174]. The sites occupied by Mg2+ depend strongly on the synthesis technique, which leads to such discrepancies in the results. Mg-doped HA tends to have lower crystallinity than its undoped counterparts [173], and solubility increases with the amount of Mg [175]. The synthesized doped material becomes completely amorphous in nature when the Mg content reaches above 35 atom% [172]. On the other hand, Mg-substitution favors thermal conversion of HA into β-TCP [176]. Zyma et al. [177] explored the mechanical properties of Mg-doped HA, and found a decline in its compressive strength and microhardness, together with an increment in fracture toughness.

Enderle et al. [31] successfully synthesized Mg-doped β-TCP with different dopant contents. According to their findings, up to a 10 mol% concentration, Mg2+ occupied a six-fold coordinated Ca(5) site, which resulted in contraction of both the lattice parameters. At above 10 mol%, Mg2+ replaced Ca2+ ions on the nine-fold coordinated Ca(4) sites and the "c" axis began to expand. Shrinkage of the unit cell volume of β-TCP due to the Mg-substitution was also observed [178]. Mg-doping inside the β-TCP lattice also raised the β-TCP → α-TCP conversion temperature. For example, the conversion temperature was found to be 1540°C for 8 mol% Mg-doped β-TCP as opposed to the well-known transformation temperature of 1150°C [31].

Strontium is another essential trace element that is known for its beneficiary effect on bone growth [179]. It prevents bone resorption by inhibiting osteoclast activity and reinforces bone growth by promoting osteoblast activity and preosteoblastic division [179] [180]. In the present day, Sr is even used in drugs to prevent osteoporosis [181]. Hence, it is quite natural that the properties of Sr-doped HA have been investigated quite extensively. It has been found that, although the Ca(1) site is preferable for Sr substitution at low concentrations (~1 atom%), doping on Ca(2) sites occurs dominantly as the concentration increases [182]. At an ~5 atom% concentration, the ideal substitution ratio (Sr(2)/Sr(1) = 1.5) is achieved [182]. The lattice constants of HA increase monotonically with increases in the substituted Sr content [140] [183]. Sr substitution is known to stabilize the HA phase and to hinder the formation of the TCP phase at high temperatures [127] [184]. By contrast, the incorporation of larger amounts of Sr2+ inside the HA crystal structure facilitates incorporation of the HPO4 2- and CO3 2- groups, thus reducing the crystallinity [185]. The larger ionic radius of Sr2+ also induces distortion of the crystal structure, increasing its solubility [186]. Another study has shown that the porous Sr-substituted HA has compatible compressive strength (4.5 ± 1.4 MPa, for 1.15 mol% substitution) with natural bone [187]. Another noteworthy finding is that the addition of Sr-doped whisker-shaped HA to calcium phosphate cement can increase its compressive strength by almost two-fold [188]. Due to all of these interesting features, Sr-doped HA has emerged as an important material for hard tissue replacement treatment in recent years. On the other hand, Sr-doped β-TCP was studied by Bigi et al. [189], who found linear increases in both the lattice parameters, just as with HA.

Due to the antimicrobial effect of Zn, Zn-doped HA and TCP have been studied by the scientific community. Due to the smaller size of Zn2+ (0.77 Å), a progressive decline in lattice parameter "c" of the HA phase was found with increases in the Zn fraction [190]. Lattice parameter "α" initially decreased up to 10 mol% of the Zn content, and then began increasing [191]. The presence of a larger volume of adsorbed water played a central role in the expansion of the "α" axis [190]. Tas et al. [192] fabricated Zn-doped β-TCP and found that 4100 ppm Zn-doped β-TCP had the highest bulk density. Combining different
The structure and properties of iron-doped HA have been analyzed in the field of biomedical sciences to examine some unique characteristics of Fe-HA. Diamagnetic HA can be transformed into a para/superpara/ferromagnetic material via incorporation of iron [194]. This also improves the ionic conductivity of HA [85]. Fe-doped HA also exhibits hyperthermia effects, which make it a potential candidate for cancer therapy [195]. Iron may be substituted inside the HA lattice in two forms, ferrous (Fe²⁺) and ferric (Fe³⁺) ions. In the case of Fe²⁺ substitution, both the lattice constants decrease, whereas the “α” axis dilutes and the “c” axis contracts for Fe³⁺ incorporation [196]. In harmony with this, the HA unit cell also expands and contracts with the increases in Fe²⁺ and the Fe²⁺ fraction, respectively. By combining experimental results with theoretical calculations, Jiang et al. [10] demonstrated that, the sixfold-coordinated Ca(2) site was favorable for Fe²⁺ substitution, whereas non-stoichiometric Fe³⁺ substitution occurred on the Ca (1) site. Doping of iron is known to destabilize the HA crystal structure, as is evident from the progressive decline in crystallinity [195]. Recently, Gomes et al. [197] described the temperature-dependent Fe³⁺ doping mechanism in BCP. According to their observations, at below 600°C, BCP was primarily composed of the HA phase with physisorbed iron-doping cations on the surface. At intermediate temperatures, iron is incorporated inside the β-TCP structure with ferric cations located in the poorly crystallized shells; while at temperatures above 1000°C, BCP samples were again composed of iron-doped HA, with some of the ferric cations located on the poorly crystallized surface.

The structures of Ti, Ag, and Mn-doped HA are also of great interest. It has been found that Ag⁺ ions replace Ca²⁺ ions on Ca(1) sites and that both the lattice constants expand [198]. Ti⁴⁺ substitution also causes dilution of the crystal axes [72]. In the case of Mn²⁺ doping, substitution in the Ca(1) positions is preferred with resulting rotation of the phosphate groups [199]. Mn²⁺ also favors thermal conversion of HA to β-TCP. In aqueous solutions, Mn⁷⁺ ions prevent the formation of crystallite of HA from the precursors [200] [201]. Apart from the above-mentioned cations, doping of several other ions inside the HA/TCP crystal lattice has also been explored by researchers and many of these exhibit interesting behavior. Lanthanide-doped HA possesses luminescence properties, for example, and may be a useful material for biomedical imaging [202] [203]. The luminescence efficiency and color of the emitted light depend on the lanthanide element used and the degree of crystallinity [204]. Among lanthanides, Eu³⁺ usually prefers the Ca(2) site for substitution, but doping at Ca(1) sites has also been reported [205] [206]. Moreover, Eu-doped HA has the potential for use as a bio-probe and drug carrier [203] [204]. The substitution of other lanthanides (Ln, Ce, Pr, Nd, Sm) in HA was found to affect the particle size and morphology [207]. Lattice parameter “c” also tends to increase slightly in Ce-doped HA [84]. Rare earth elements such as Yttrium have also been incorporated into HA to enhance its mechanical properties [208] [209]. Kaygili et al. [210] synthesized Al³⁺-doped HA and found a dramatic decrease in crystallinity with increases in the Al fraction. Melnikov et al. [211] prepared Ga-doped HA but could not find any significant change in the lattice parameters. Lattice constant “a” and the degree of crystallinity are also reported to be reduced in Ni-doped HA [212]. By contrast, Cr²⁺/Cr³⁺ ion incorporation increases the crystallinity of apatites along with contraction of the “c” axis [213]. In the light of the above discussion, it can be stated that the vast diversity in structural properties among different kinds of doped HA/TCP enables us to tune the microstructure, morphology and functional properties of synthesized materials to develop better candidates for biomedical applications.

4. Effects of doping on biological and mechanical properties

Apart from affecting the lattice structure, ionic substitutions inside the HA/TCP crystal lattice also profoundly influence various material behaviors. In the present section, the effects of doping on the biological and mechanical properties of HA/TCP will be briefly described.

As mentioned above, carbonate and fluoride are the two most abundant anionic dopants, and the cytocompatibility of fluorapatite and carbonated apatite is well known [214] [215]. In vivo experiments were also carried out on these materials to evaluate their efficacy for hard tissue engineering with promising outcomes [216] [214]. Besides carbonate and fluoride, incorporation of silicate ions inside the apatite structure was also reported to enhance the metabolic activity of human osteosarcoma cells [217]. At the same time, different cationic substitutions also positively influence cell viability. For example, 3–7 atom% of Sr in the HA structure exhibited better cytocompatibility compared to undoped HA when tested with MG63 cell line [183]. Similarly, enhanced cell viability was achieved in the case of Mg, Mn, and Zn-doped HA/TCP [218] [219,220]. In another study, iron-doped HA was found to support osteoblast-like
cell (MG63) cell proliferation. Moreover, the hemo-
compatibility of Fe-doped HA was also confirmed
[221]. In almost in all cases, however, an upper thresh-
old of ion concentration existed, above which adverse
effects on cell viability were observed.

Ag, Zn, and Cu substitution inside the HA/TCP
lattice structure is known to induce antibacterial prop-
erties in BCP. The mechanism of antibacterial activity
is not quite clear, but the following three proposed
mechanisms can be found in the literature (Figure 6)
[222,223]:

(a) Penetration of ions inside bacterial cells and
hampering of the DNA replication process via
interference with ATP production.
(b) Accumulation of ions on bacterial cell mem-
branes, changing their permeability. This ulti-
mately leads to the destruction of the
membranes.
(c) Through the formation of reactive oxygen spe-
cies (ROS).

Ag is the most widely used antimicrobial agent. It inter-
acts with the thiolic (-SH) groups of protein to form S-Ag
bonds, which result in inactivity of proteins [224]. It was
reported that 0.2 wt.% of Ag-doped HA can inhibit the
growth of K. pneumoniae and C. krusei [225]. On the
other hand, activity of E. coli was reduced at a 0.5 wt.%
Ag concentration [225]. Much higher (~1 wt.%) content
of Ag dopant was required to inhibit S. aureus and
S. epidermidis growth [226]. Like Ag, Cu also forms
bonds with thiolic, imidazole, amine, and carboxylic
groups of proteins, causing structural changes, mem-
brane transport dysfunctions and cell death [223]. In
addition, it can also cause damage to DNA and RNA by
forming bonds with amide and amino groups, resulting
in inhibition of bacteria growth [227]. When tested
against the E. coli strain, it was noted that HA with a
~3.3 wt.% Cu concentration was able to inhibit bacte-
rial growth completely [227]. However, Cu is not particu-
larly effective against gram-positive bacteria. Besides Ag
and Cu, Zn ions also possess antimicrobial properties,
and their bacterial inhibitory mechanisms are quite simi-
lar to those of Cu. Thian et al. [228] reported the reduc-
tion of S. aureus viability in the presence of 1.6 wt.% Zn-
doped HA. Zn-doped HA also proved to be effective
against oral pathogens such as Aggregatibacter actino-
mycetemcomitans and S.mutans [229]. Considering all
these facts, it can be easily understood that an effective
fight against post-surgical infections without compro-
mising cell viability can be accomplished by tuning
different dopant contents in BCP-based hard tissue
implants.

Another important material aspect that is signifi-
cantly affected by ionic doping is mechanical behavior. It has
been previously noted that the incorporation of sodium
ions into a β-TCP structure linearly increased its compres-
sive strength from ~10MPa (undoped sample) to 32.2
MPa (10 mol% Na-doped sample) [168]. Interestingly, as
mentioned in section 3, the doping of Mg caused a
reduction in the microhardness (from 510 Pa in the
undoped sample to 190 Pa in 3 wt.% Mg-doped HA)

Figure 6. Probable mechanisms of antimicrobial activity of ions [222].
and compressive strength (from 500 Pa in undoped sample to 400/Pa in 3 wt.% Mg-doped HA) [177]. On the other hand, the diametrical strength of HA was reported to increase with the Y content in Y-doped fluorapatite [230]. Similar enhancement was obtained in the case of Si-doped carbonated HA [231]. Some other studies reported an increment in the microhardness values in 5 mol% Ag⁺ and 1 mol% F⁻ co-doped HA, compared to an undoped sample [232]. However, negative effects on the mechanical properties were observed in the case of Al³⁺ doping [233]. Uysal et al. [234] stated that ~2 mol% Zn²⁺ substitution in HA caused an increase in the Vickers hardness value, and further enhancement was achieved by Zn²⁺ and F⁻ co-substitution. Another possible way to increase the hardness of HA is to dope it with Ti⁴⁺. A recent study indicated an ~2-fold increase in hardness value in 0.8 atom% Ti-substituted HA compared to its undoped counterpart [235]. Doping of Sr also has a positive effect on the mechanical behavior of HA. Pal et al. [236] reported an increase in the Vickers hardness number from 492 ± 12 in pure HA to 602 ± 26 in Sr-doped HA with an Sr/Ca ratio of 1.79. Doping of Sr²⁺ alongside other ions (Fe³⁺ and Zn²⁺) in HA also helped in enhancing the microhardness value [237] [238]. Taken together, the mechanical properties of HA/TCP/BCP can be easily tailored by ionic doping, which thus provides an efficient technique for mimicking the mechanical behavior of natural bone more effectively.

5. Closing statement

In the field of biomaterials and tissue engineering, calcium phosphate-based materials such as HA/TCP/BCP have been of great interest for the last few decades. The ease of ion substitution inside apatite and TCP lattice structures and the ability to tailor their functional and biological properties has been investigated by the researchers in order to develop next-generation bioceramics for biomedical applications. The present review summarizes some of the facets of multi-directional research on doped HA/TCP. Different synthesis routes for the preparation of ion-substituted BCP have been introduced along with their limitations. A considerably detailed depiction of experimental results concerning the crystallographic structures of different ion-substituted BCP have also been penned along with the effects of doping on their biological and mechanical behaviors.

Despite the large volume of experimental works, challenges remain to be overcome. From the synthesis perspective, it can be commented that, although different synthesis techniques have been innovated, only a few of them can provide satisfactory performance economically and scientifically. Phase impurity of the synthesized particles and complex and expensive synthesis procedures are inevitably associated with almost every fabrication technique. Scalability, or the transfer from lab scale to the industrial scale, is another major challenge for any of these synthesis methods. Unfortunately, there seems to be very little effort toward technology transfer and industrial-academic collaboration. To address this issue, new synthesis techniques at the industrial level with more satisfactory performance should be established. The future research direction can be molded in order to address the above-mentioned limitation to accelerate the development of bioceramics with multifunctional properties even at the industrial level.

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