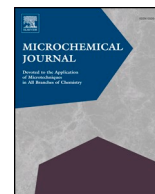




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Review article

Co-doped hydroxyapatites as potential materials for biomedical applications

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ABSTRACT

Hydroxyapatite (HA) is a synthetic biomaterial resembling the composition of mammalian hard tissue and thus, it is widely employed as a bone graft material, hard tissue engineering scaffold and coating layer for metallic substrates. Biological apatite is non-stoichiometric in nature. It is composed of small crystals and characterized by poor crystallinity and relatively high solubility with respect to stoichiometric HA. Chemical compositions of these crystals consist of Ca, P and trace amounts of various ions, such as Mg^{2+} , Zn^{2+} , Sr^{2+} , Ag^+ , Cl^- and F^- which are more prominent as dopants or adsorbed on the crystal surface. However, these ions play an important role in the metabolism of hard tissues. Synthetic HA is a stoichiometric material with a Ca/P ratio of 1.67, which lacks the presence of valuable trace ions regularly present in natural hard tissue. Thus, the structure of synthetic HA is partially incorporated by these ions to mimic the chemical composition of the biological apatite structure. Ionic substitutions have been planned as a tool to enhance the biological role of HA based materials. As single dopant frameworks have indicated great outcomes, it makes sense that various dopants can be utilized to further build the valuable impacts of each, within the constraints of the material stability of HA. This review is focused on co-ionic substitutions in HA system and their combined effects on related biomedical characteristics.

1. Introduction

Every year, nearly 2.2 million patients are hospitalized worldwide to undergo a bone grafting procedure to repair bone defects, or to alleviate suffering or to combat bone related diseases [1]. Bone grafting is a surgical procedure that involves the replacement of defected bone with biological or synthetic bone grafts. Various categories of biological bone graft materials are in use, such as autografts, allografts and xenografts. However, the utilization of biological materials is associated with numerous disadvantages, for instance simultaneous second surgical procedure, increased blood loss, limited supply, extra morbidity to the patient, risk of the transfer of microbiological contaminants and adverse immunological responses [1–5]. The drawbacks of biological bone grafts have prompted extraordinary interest in the development of improved synthetic alternatives. The development of synthetic bone graft substitutes is considered as a particularly important step to overcome the intrinsic limitations of biological bone grafts. Owing to the increasing demand of bone graft materials, their synthesis has received great attention and researchers are working towards introducing new materials with better quality and biological properties, so that the convalescence period of the patient can be shortened after the bone grafting procedure.

Bioceramics can be defined as biocompatible ceramic materials that are used for the repair and reconstruction of diseased or damaged parts of tissues. They can be bioinert, biodegradable bioactive and designed to stimulate specific cellular responses at the molecular level like any other biomaterial. Bioceramics can be manufactured in porous or dense, amorphous, or crystalline forms and applied as coatings, cements, scaffolds, and nano-particles. They also differ in their chemical compositions. The main group of bioceramics is calcium phosphate (CaP) family and the others are zirconia (ZrO_2), alumina (Al_2O_3), carbon, some silicates, phosphate families of glasses and glass-ceramics. There are many calcium orthophosphates with Ca/P molar ratios ranging between 0.5 and 2.0 [6]. Table 1 summarizes the names and formulas of the existing members of CaP family.

Most currently available biomaterials for hard tissue replacement and regeneration therapies are synthetic osteoconductive bone graft materials. Hydroxyapatite [$Ca_{10}(PO_4)_6OH_2$] is an osteogenic, osteoconductive and osteoinductive bioceramic. HA is very popular as an implant coating material and it is often used as a synthetic cement-less bone substitute in hip, knee, and other implants mainly due to its ability to promote bone ingrowth. Another particularly popular application of HA is being a drug carrier of chemotherapeutics and antibiotics.

It is possible to tailor the material properties of HA based on the

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Table 1
The names and formulas of existing calcium orthophosphates [7].

Ca/P molar ratio	Compound	Formula
0.5	Monocalcium phosphate monohydrate (MCPM)	$\text{Ca}(\text{H}_2\text{PO}_4)_2 \cdot \text{H}_2\text{O}$
0.5	Monocalcium phosphate anhydrous (MCPA or MCP)	$\text{Ca}(\text{H}_2\text{PO}_4)_2$
1.0	Dicalcium phosphate dihydrate (DCPD), mineral brushite	$\text{CaHPO}_4 \cdot 2\text{H}_2\text{O}$
1.0	Dicalcium phosphate anhydrous (DCPA or DCP), mineral monelite	CaHPO_4
1.33	Octacalcium phosphate (OCP)	$\text{Ca}_8(\text{HPO}_4)_2(\text{PO}_4)_4 \cdot 5\text{H}_2\text{O}$
1.5	α -Tricalcium phosphate (α -TCP)	$\alpha\text{-Ca}_3(\text{PO}_4)_2$
1.5	β -Tricalcium phosphate (β -TCP)	$\beta\text{-Ca}_3(\text{PO}_4)_2$
1.2–2.2	Amorphous calcium phosphates (ACP)	$\text{Ca}_x\text{H}_y(\text{PO}_4)_z \cdot n\text{H}_2\text{O}$, $n = 3\text{--}4.5$; 15–20% H_2O
1.5–1.67	Calcium-deficient hydroxyapatite (CDHA or Ca-def HA)*	$\text{Ca}_{10-x}(\text{HPO}_4)_x(\text{PO}_4)_{6-x}(\text{OH})_{2-x}$ ($0 < x < 1$)
1.67	Hydroxyapatite (HA, HAp or OHAp)	$\text{Ca}_{10}(\text{PO}_4)_6(\text{OH})_2$
1.67	Fluorapatite (FA or FAp)	$\text{Ca}_{10}(\text{PO}_4)_6\text{F}_2$
1.67	Oxyapatite (OA, OAp or OXA)**	$\text{Ca}_{10}(\text{PO}_4)_6\text{O}$
2.0	Tetracalcium phosphate (TTCP or TetCP), mineral hilgenstockite	$\text{Ca}_4(\text{PO}_4)_2\text{O}$

* Occasionally, it is called “precipitated HA (PHA)”.

** Existence of OA remains questionable.

crystal structure that allows a wide variety of substitutions and ion doping. HA has been doped with dozens of different ions in search for the promotion of bone remodeling and tissue regeneration, imparting magnetic properties, adding antibacterial activity, enhancing bio-integration etc. There are only a few examples of translation of the researches about doped HAs to the global medical market, such as a doped HA/collagen graft for dental applications. On the other hand, the future of clinical applications is shaping towards the design and synthesis of multifunctional systems having high biocompatibility. Co-doping of various anions and cations into the structure of HA is relatively a new concept which aims to use the synergistic effect of multi-element dopants.

The number of research articles with the keywords ‘co-doped’ + ‘hydroxyapatite’ published in the journals indexed by Science Direct since 2000 together with the trend in number of research articles with the keywords ‘doped’ + ‘hydroxyapatite’ are shown in (Fig. 1). The trend was very similar when the keyword ‘substituted’ is used instead of ‘doped’. The rapidly increasing number of research articles is the proof of how interesting ion-doped HAs are in the scientific community due to the influence of patient demands. Besides, the number of research articles on binary, ternary and mixed ion doping into the structure of HA is limited. This is because the effects of incorporation of each ion separately continue to be a subject of research and synergistic effects of ions are creating more complex systems. This review aims to give a comprehensive insight into the literature on co-doping of various

ions into the structure of HA.

2. Biological apatite

Biological apatite is the biomineral component of the hard tissues of vertebrates and consists of nonstoichiometric carbonated HA with poor crystallinity and small crystal dimensions. Human hard tissues, such as; enamel, dentine and bone are composite materials that has both organic and inorganic materials. The inorganic part is mainly composed of biological hydroxyapatite (BHA) blended with trace amounts of different ions. The organic phase is mainly composed of collagen and a small proportion of non-collagenous proteins, such as fibronectin, osteopontin, osteocalcin and bone sialoprotein [8]. The flexibility of bone is provided by collagen, whereas the stiffness is maintained by addition of mineral to the collagen network. Therefore, when the mineral content is removed from the bone, the tissue would be very flexible like tendons and ligaments. Conversely, when the organic content is removed, bone would be a brittle material with very low tensile strength. The hierarchic structure of human bone and the arrangement of HA crystals along the collagen fibrils of bone is given in Fig. 2. The crystals can be found both on the surface and within gaps between the collagen fibrils.

In addition to providing stiffness to bone, the inorganic matrix, which contributes approximately ~65–70% of the wet weight of bone, serves as an ion reservoir. Approximately 99% of total body calcium,

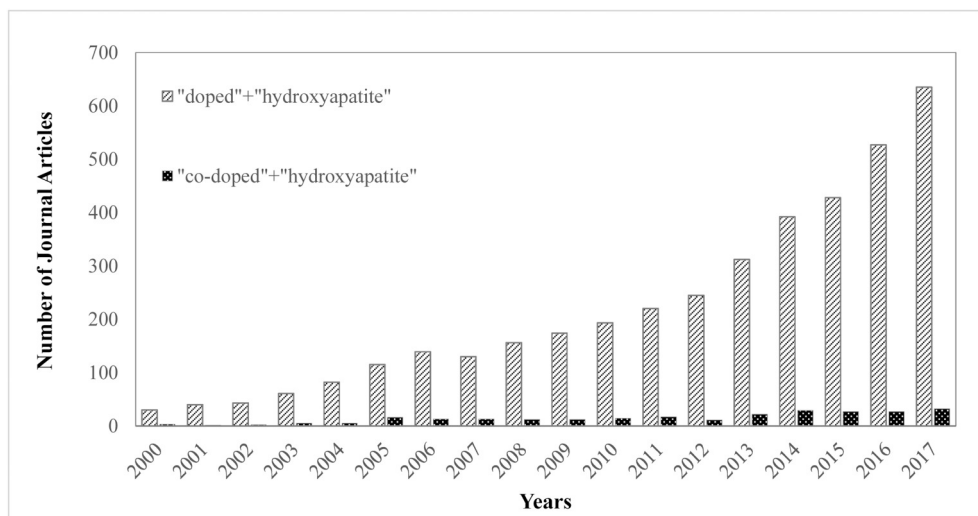


Fig. 1. Annual number of articles on doped HA and co-doped HA reported in Science Direct over the 2000–2017 period. Data source: scencedirect.com

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