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Review article

Development of the third generation of bioceramics: Doping hydroxyapatite with *s*-, *p*-, *d*-, and *f*-blocks cations and their potential applications in bone regeneration and void filling

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Abstract

The bioceramic market is expected to grow at a compound annual growth rate (CAGR) of about 7% within 2022–2027. In this regard, hydroxyapatite (HA) is highly recommended as a leading material for the development of the third generation of bioceramics due to its intrinsic osteoconduction, osteoinduction, and osteogenesis properties. However, the use of synthetic HA is currently limited due to the unfavourable mechanical and morphological issues on cell infiltration and interaction. To overcome these obstacles, various strategies have been proposed, especially through a wide range of cationic and anionic doping. Among them, cationic doping seems to have a set of significant benefits over pure HA due to the significant microstructural modifications, and thus this strategy represents a major step forward in improving the inherent drawback of bioceramic implants, i.e., their poor mechanical properties. Accordingly, this review aims to highlight candidates with potential for further clinical development of the third-generation bioceramics through doping HA with *s*-, *p*-, *d*-, and *f*-blocks cations and to explore their potential applications in bone regeneration and void filling. We first introduce the concept of bone grafting and its classifications, and then we discuss bioceramic-based bone grafting materials. Subsequently, mono-, dual-, and multi-cationic substitutions in HA and their performances, especially in biomedical applications, are

comprehensively reviewed. Finally, the challenges and prospects of ionic substitution in HA, particularly in lanthanoids- and actinoids-containing HA-based ceramics are proposed.

Graphical abstract

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Introduction

Over the past decades, developments in bioceramics have contributed dramatically to the growth of the modern health care industry and the quality of human life [[1], [2], [3]]. Calcium phosphates (CaPs) are major components of biological minerals, among them, the thermodynamically most stable phase, HA ($Ca_{10}(PO_4)_6(OH)_2$) and its based biomaterials, have received more attention in biomedical applications than other CaPs due to their bone mineral similarity, as well as intrinsic osteoconduction, osteoinduction, and osteogenesis properties [[4], [5], [6]].

Due to their similarities to natural bone and teeth, and superb biological behaviour in contact with body fluids, synthetic HA has also developed as synthetic bone grafts, which can be used as an alternative to auto- and allografts [7,8]. These materials are often used in biomedical applications, e.g., as a replacement for bony and periodontal defects [9], alveolar ridge [10], middle ear implants [11], tissue engineering systems [12,13], drug delivery agents [14], dental materials [6], and bioactive coating on metallic osseous implants [15]. These materials have also attracted much attention in non-medical applications, e.g., as a catalyst for chemical reactions [16], ion conductors [17], gas sensors [18], water treatment processes [19], and remediation of heavy metal polluted soils [20]. However, the HA brittleness and its adhesion to the surfaces of medical implants are probable restrictions when high shear forces are developing around the damaged tissue [21], where a commonly used strategy to overcome this concern is the modification of HA configuration through atomic doping [[22], [23], [24]]. Ionic substitutions in HA are expected to play a key role in bone metabolism and enhance the process of osteogenesis and bone remodelling, thereby improving biological ability compared to stoichiometric HA [25].

An ideal dopant should improve the physicochemical properties of HA, without compromising the biological performance of the doped structure. In addition, small amounts of dopant must provide an excellent combination of elastic modulus and strength to significantly increase HA fracture toughness. For this purpose, a variety of methods have been developed to prepare substituted HA, especially the hydrothermal method [26], solid-state reactions [27,28], sol-gel process [29], chemical precipitation [30], emulsion route [31], solution combustion [32], sonochemical synthesis [33], biogenic sources [34], microwave synthesis [35] and flame spray pyrolysis [36]. Each method possesses some advantageous characteristics that make it