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Review Article

Synthesis and modification of apatite nanoparticles for use in dental and medical applications

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Summary Synthesised hydroxyapatite (HAp) exhibits excellent biocompatibility, making it an ideal candidate for use as a hard tissue substitute material. Nanoscale-size effects and surface phenomena impart HAp nanoparticles with unique properties compared to the conventional-sized HAp ceramics. Modification of HAp is also important for regulating its physiochemical properties. In this review, methods of HAp synthesis and modification, and various applications of HAp nanoparticles for dental and medical treatment are discussed.

Contents

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1. Introduction

Vertebrate hard tissues consist mainly of inorganic compounds (Table 1 [1]), collectively termed biological apatite. Apatite is a general term for crystalline minerals and can be represented by the formula $M_{10}(ZO_4)_6X_2$. Each component (M, ZO_4, and X) in the formula can be replaced by a large number of different ions listed below [2]:

M = Ca^{2+}, Mg^{2+}, Sr^{2+}, Ba^{2+}, Mn^{2+}, Fe^{2+}, Zn^{2+}, Cd^{2+}, Pb^{2+}, H^+, Na^+, K^+, Al^{3+}, etc.
ZO_4 = PO_4^{3-}, AsO_4^{3-}, VO_4^{3-}, SO_4^{2-}, CO_3^{2-}, SiO_4^{4-}, etc.
X = OH^-, F^-, Cl^-, Br^-, O^{2-}, CO_3^{2-}, vacancy, etc.

The most common apatite found in nature is calcium phosphate apatite, where M and ZO_4 are Ca^{2+} and PO_4^{3-}, respectively. When X is OH^- (*i.e.* $Ca_{10}(PO_4)_6(OH)_2$; stoichiometric Ca/P molar ratio is 1.67), the apatite is named hydroxylapatite [3], traditionally also called as hydroxyapatite (HAp).

Stoichiometric HAp belongs to a hexagonal crystal system [4] and has two major crystal planes: *a* plane and *c* plane (Fig. 1). It is widely believed that the *a* plane is rich in calcium ions and hence positively charged, whereas the *c* plane is rich in phosphate and hydroxide ions and hence negatively charged [7,8]. That is, HAp surfaces exhibit anisotropic characteristics such as anisotropic adsorption profiles for biomolecules [8]. Note that the surface ion composition (and hence, the surface charge) of HAp in aqueous medium varies according to the ion composition of the medium because of ion exchange [9] and gradual dissolution [10].

Synthetic HAp sintered ceramics (in dense, porous, and granular forms) have been used in dental and medical fields [2,11,12], and their applications include alveolar ridge reconstruction and augmentation [13], fillers for bone defects [14], and middle ear implants [15]. HAp is bioactive (osteoconductive); thus, HAp has the ability to encourage bone growth along its surface when placed in the vicinity of viable bone or differentiated bone-forming cells [16]. HAp is one of many types of calcium orthophosphates listed in Table 2 [17], and some other calcium phosphates that show higher solubility than HAp have been also used in dental and medical fields [17,18].

Table 1 Comparative compositions (wt%) of bone, dentine, and enamel [1].

	Bone	Dentine	Enamel
Ca	34.8	35.1	36.5
P	15.2	16.9	17.7
Na	0.9	0.6	0.5
K	0.03	0.05	0.08
CO_2	7.4	5.6	3.5
F	0.03	0.06	0.01
Total inorganics	65	70	97
Total organics	25	20	1.5
Water	10	10	1.5

Biological apatite is a non-stoichiometric form of HAp containing trace ions and deficient Ca^{2+}. The trace ions include positively charged ions (such as Mg^{2+}, Na^+, and K^+) and negatively charged ions (such as CO_3^{2-}, Cl^-, and F^-), and the most common substituting ion is carbonate (CO_3^{2-}), which can replace OH^- and PO_4^{3-}, respectively [4]. Depending on the hard tissue type, biological apatite exhibits different crystal morphologies. For example, in bone tissue, the *c* axes of crystallites (*ca.* 50 nm × 25 nm × 4 nm [19]) are parallel to the extending collagen fibres, resulting in the exposure of the *a* planes on the bone surface. In contrast, in tooth enamel, larger crystallites (*ca.* 100 μm × 25 nm × 70 nm [20]) form enamel prisms extending from the dentino-enamel junction, resulting in *c*-planes that are preferentially parallel to the enamel surface.

Nanoparticles (nanopowders, nanocrystals, or nanostructured particles) are microscopic particles with at least one dimension in the nanometer scale (usually, 100 nm or less). In general, nanoparticles offer improved properties compared with conventional-sized materials because of their large surface-to-volume ratio (specific surface area) [21]. To control the properties of HAp nanoparticles, it is important to control the particle morphology (the exposure of their *a* and *c* planes), which can be achieved by adjusting their synthesis methods. Modification of HAp is also important for the regulation of its physiochemical properties. This paper provides a summary of existing knowledge and recent progress on HAp nanoparticles, from synthesis and modification to dental and medical applications.

2. Synthesis methods for HAp nanoparticles

HAp nanoparticles can be synthesised *via* various methods that are categorised as solid-state and wet-state methods (Table 3).

2.1. Solid-state methods

Solid-state methods are solid-state reactions between raw material powders (*e.g.* $CaHPO_4$ and CaO) induced by thermal treatments, and they usually give stoichiometric and