



Review

Nanoscale hydroxyapatite particles for bone tissue engineering

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ABSTRACT

Hydroxyapatite (HAp) exhibits excellent biocompatibility with soft tissues such as skin, muscle and gums, making it an ideal candidate for orthopedic and dental implants or components of implants. Synthetic HAp has been widely used in repair of hard tissues, and common uses include bone repair, bone augmentation, as well as coating of implants or acting as fillers in bone or teeth. However, the low mechanical strength of normal HAp ceramics generally restricts its use to low load-bearing applications. Recent advancements in nanoscience and nanotechnology have reignited investigation of nanoscale HAp formation in order to clearly define the small-scale properties of HAp. It has been suggested that nano-HAp may be an ideal biomaterial due to its good biocompatibility and bone integration ability. HAp biomedical material development has benefited significantly from advancements in nanotechnology. This feature article looks afresh at nano-HAp particles, highlighting the importance of size, crystal morphology control, and composites with other inorganic particles for biomedical material development.

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1. Introduction

Bone is a natural organic–inorganic ceramic composite consisting of collagen fibrils containing embedded, well-arrayed, nanocrystalline, rod-like inorganic materials 25–50 nm in length [1–3]. Structural order in bone occurs at several hierarchical levels and reflects the materials and mechanical properties of its components (Fig. 1). Hydroxyapatite (HAp) is chemically similar to the inorganic component of bone matrix – a very complex tissue with general formula $\text{Ca}_{10}(\text{OH})_2(\text{PO}_4)_6$. The close chemical similarity of HAp to natural bone has led to extensive research efforts to use synthetic HAp as a bone substitute and/or replacement in biomedical applications [4,5].

Tissue engineering is intensively researching solutions that have the potential to reduce the complications related to current treatment methods. Tissue engineering can be defined as an interdisciplinary field that applies the principles of engineering and life sciences to develop biological substitutes that restore, maintain or improve tissue function [6]. This concept involves three main strategies: the use of isolated cells or cell substitutes to replace limited functions of the tissue; utilization of tissue-inducing substances such as growth factors; and scaffolds to direct tissue development. An ideal scaffold for bone tissue engineering is a matrix that acts as a temporary substrate allowing cell growth and tissue development. This occurs initially in vitro and eventually in vivo. The scaffold should be able to mimic the structure and biological function of the native extracellular matrix (ECM) in terms of both chemical

composition and physical structure. Scaffolds used for tissue engineering applications should also be biocompatible; able to provide appropriate mechanical support; exhibit favorable surface properties such as promoting adhesion, proliferation and differentiation of cells; and provide an environment in which cells can maintain their phenotypes.

Recently, HAp has been used for a variety of biomedical applications, including matrices for drug release control and bone tissue engineering materials [8,9]. Since HAp has chemical similarity to the inorganic component of bone matrix, synthetic HAp exhibits strong affinity to host hard tissues. Chemical bonding with the host tissue offers HAp a greater advantage in clinical applications compared to most other bone substitutes such as allografts or metallic implants [10]. The main advantages of synthetic HAp are its biocompatibility, slow biodegradability in situ, and good osteoconductive and osteoinductive capabilities [1,11]. A study by Taniguchi et al. showed that sintered HAp exhibits excellent biocompatibility with soft tissues such as skin, muscle and gums. Such capabilities have made HAp an ideal candidate for orthopedic and dental implants or components of implants. Synthetic HAp has been widely used to repair hard tissues. Common uses include bone repair, bone augmentation, as well as coating of implants or acting as fillers in bone or teeth [12–18]. However, the low mechanical strength of normal HAp ceramics restricts its use mainly to low load-bearing applications. Recent advances in nanoscience and nanotechnology have reignited interest in the formation of nanosized HAp and the study of its properties on the nanoscale.

Nanocrystalline HAp powders exhibit improved sinterability and enhanced densification due to greater surface area, which may improve fracture toughness, as well as other mechanical

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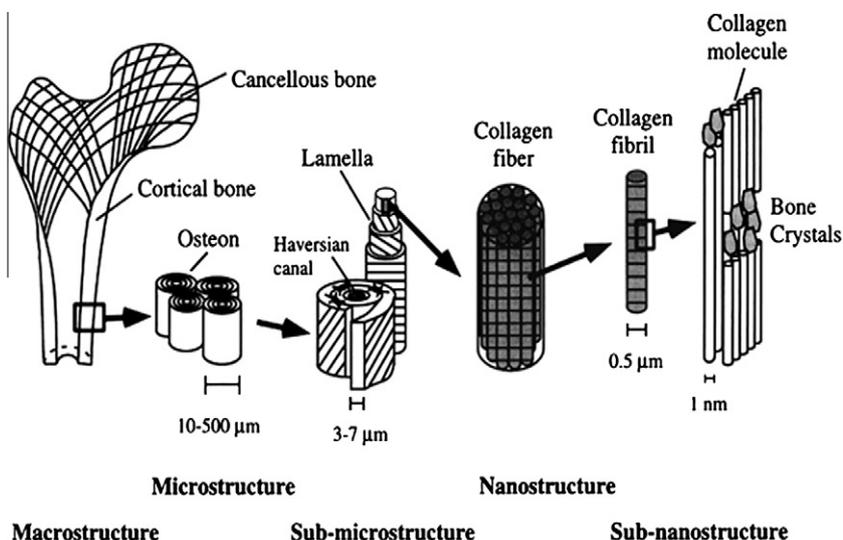


Fig. 1. The hierarchical structure of bone at its various length scales. The microstructure of cortical bone consists of osteons with Haversian canals and lamellae, and at the nanoscale, the structural units are collagen fibers composed of bundles of mineralized collagen fibrils. Copyright Elsevier and reproduced with permission [7].

properties [11]. Moreover, nano-HAp, compared to coarser crystals, is expected to have better bioactivity [19]. Thus, nano-HAp particles can be utilized for engineered tissue implants with improved biocompatibility over other implants. Nanotechnology has the potential to significantly benefit development of HAp biomedical materials. To our knowledge, several reviews of nanocrystalline calcium orthophosphates have been published in recent years. For example, Dorozhkin et al. [20,21] reviewed the current state of technology and recent developments of various nanosized and nanocrystalline calcium orthophosphates, involved in synthesis and characterization as well as biomedical and clinical applications. Moseke et al. [22] reviewed the synthesis and properties of tetracalcium phosphate (TTCP) in biomaterial applications such as cements, sintered ceramics and coatings on implant metals; Johnson et al. [18] reviewed the compression, flexural and tensile properties of calcium phosphate (CaP) and CaP-polymer composites for applications in bone replacement and repair; Tran et al. [23] summarized studies that have demonstrated enhanced *in vitro* and *in vivo* osteoblast functions (e.g. adhesion, proliferation, synthesis of bone-related proteins and deposition of calcium-containing mineral) on nanostructured metals, ceramics, polymers, and composites. After reviewing these feature articles to avoid any redundancy, we focus on calcium orthophosphate, and characterize its properties in the condition of nano-HAp with different morphologies and porous structures—materials that offer great promise as bone substitutes and/or replacements in biomedical applications. Moreover, we summarize how composites of HAp and other inorganic nanomaterials can enhance the bioactivity and biocompatibility of HAp – an area that has become the focus of recent research. The remainder of this feature article is organized into five sections. In the Section 2, the synthesis of morphologically different nano-HAps is introduced. Section 3 discusses the fabrication of the porous structure of nano-HAp. Section 4 reviews the bio-orthopedic properties of nanoscale HAp for application in bone tissue engineering. Section 5 introduces composites of HAp and other inorganic nanomaterials for enhancing the bioactivity and biocompatibility of HAp. Finally, in Section 6, we provide a summary and our own perspectives on this active area of research.

2. Synthesis of nanoscale HAp

HAp ($\text{Ca}_{10}(\text{OH})_2(\text{PO}_4)_6$) nano- and microcrystals with multiform morphologies (separated nanowires, nanorods, microspheres,

microflowers and microsheets) have been successfully synthesized by many powder processing techniques, including sol-gel synthesis [24–28], solid state reactions [29], co-precipitation [30], hydrothermal reactions [31], microemulsion syntheses [32] and mechanochemical synthesis [33].

2.1. HAp nanoparticles

From a practical application perspective, suitable nano- or micromaterials with specific morphologies not only need to be capable of being synthesized in large quantities with a desired composition, reproducible size and structure, but also of being prepared and assembled using environmentally responsible techniques. Recently, environmentally friendly synthetic methodologies, including molten-salt synthesis, hydrothermal processing, biomimic synthesis and template synthesis, have been implemented as viable techniques for the synthesis of a range of materials [34,35]. Nanosized HAp particles can be prepared by a variety of techniques such as mechanochemical synthesis [36], combustion preparation [37] and various wet chemistry techniques [38,39]. Among the most reported precipitation processes, chemical agents such as citric acid [40,41], amino acids [42] and ethylenediaminetetraacetic acid (EDTA) [43,44] have been used to mediate HAp nucleation and crystal growth. These modifiers exert significant control over crystal morphology due to affinity between the modifying agent and the HAp crystals. However, there has been less focus on the precipitation kinetics of nucleation and growth, which are related to the degree of supersaturation, S_{HAp} . This value can be calculated as follows:

$$S = \frac{\text{IAP}_{\text{HAp}}}{K_{\text{sp}}}, \quad (1)$$

where IAP_{HAp} is the ionic activity product expressed as:

$$\text{IAP}_{\text{HAp}} = [\text{Ca}^{2+}]^5 [\text{PO}_4^{3-}]^3 [\text{OH}^-] \gamma_{\text{Ca}^{2+}}^5 \gamma_{\text{PO}_4^{3-}}^3 \gamma_{\text{OH}^-}. \quad (2)$$

The brackets represent ion concentrations of the respective species and γ values are the activity coefficients of the ions. K_{sp} is the solubility product of HAp. With a higher degree of supersaturation, a greater driving force for precipitation, i.e. a faster precipitation rate, was expected with increasing IAP_{HAp} [45].

Biological mineralization (or biomineralization) is the process of *in vivo* inorganic material formation. The new theory of “aggre-

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