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A Brief Overview of Hydroxyapatite for Biomedical Uses

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ABSTRACT

In the treatment of critical-sized bone defects, calcium phosphates (CaPs), biocompatible and recyclable materials, have attracted a lot of attention for bone regeneration. They show potential as an alternative to allografts and autografts. One of the main reasons for their usefulness is their close similarity to the mineral component of genuine bone. Since hydroxyapatite (HA) is the main inorganic phase of bone tissue, it is particularly significant among the several CaPs. With a focus on fabrication methods and their impact on the mechanical characteristics of the final structures, this paper offers a thorough summary of both historical and contemporary advancements in the use of HA as a bone graft material. Material processing advancements have made it possible to produce HA-based grafts in a variety of shapes, meeting the needs of many clinical applications and producing promising results in both in vitro and in vivo investigations. Additionally, the increasing focus on developing three-dimensional porous grafts that approximate the trabecular structure of bone has created new challenges, particularly in acquiring mechanical properties suitable for potential use in load-bearing sites.

Keywords

Hydroxyapatite (HA), Allografts, Autografts, In vitro,In Vivo, calcium phosphates.

INTRODUCTION

Calcium phosphates (CaPs) have been of interest to the scientific community since the early 1900s as materials for the creation of bone replacements in biomedical applications. The first investigation was conducted in 1920 when CaPs were utilized as a filler to heal rabbits' critical-size bone fractures[1]. Due to their osteogenic potential in vitro and in vivo, as well as their physico-mechanical characteristics that resemble those of human bone[2].

CaPs are now widely used in several medical specialties, including otolaryngology, orthopedics, skull and maxillofacial reconstruction, spine surgery, treatment of osseous fractures and bone diseases, percutaneous implants, and dentistry/periodontal surgery[3]. According to an American study, around 1.3 billion dollars were spent solely on CaP-based bone substitutes in 2010[4]. The primary components of bone (~60 wt%) and dental enamel (~90 wt%) are CaPs[5]. and this is the primary reason for their research in bone regeneration and repair.

Their chemical characteristics and crystalline structure are very comparable to those of bone apatite[6] and outstanding biocompatibility with living cells[7,8]. It is generally established that CaPs, in any form (e.g., coating, powder, bulk, or porous scaffolds), have osteoconductive qualities that allow bone cells to adhere, proliferate, and migrate. It has also been observed that soluble and/or nano-sized CaPs have osteoinductive qualities, actively encouraging the development and regeneration of new bone[9,10].

The majority of CaPs can partially dissolve in bodily fluids while they are permanently present

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in the human body. The supersaturation of the biological environment and resulting formation of apatite nanocrystals on the material surface are determined by the local increase in Ca2+ and PO43− ions at the bone/implant interface[11]. The rate at which the surface apatite layer forms depends on the type of bioceramic used; hydroxyapatite takes 30 days, whereas β-tricalcium phosphate takes about 14 days[12]. Bioactive glasses, which react quickly with biological fluids, can generate a surface apatite layer within hours to days[13].

The time scale of response in vitro and in vivo clearly determines the difference between osteoconductive and osteoinductive biomaterials. Because of this, highly reactive materials like soluble CaPs or bioactive glasses are categorized to be in the latter group, However, a classic example of the former is non-porous hydroxyapatite, which has virtually little solubility[14].

Qui and Ducheyne have used an 11-step sequence to characterize the general responses that take place at the interface between CaPs and the biological environment[11].

1. Dissolution of CaPs
2. Precipitation from the solution on the surface of CaPs
3. Ion transfer and structural adjustment at the tissue/CaP interface
4. Dispersion from the boundary surface layer in the CaPs
5. Effects mediated by the solution on cell activity
6. Organic and mineral phase deposition without integration into the CaP surface
7. Deposition with integration of CaPs into the surface
8. Chemotaxis to the surface of CaPs
9. Cells attachment and proliferation
10. Differentiation of cells
11. ECM formation

In addition, CaPs are effective carriers of growth factors, bioactive peptides, and different cell types[4]. They affect the expression of osteoblastic differentiation markers such collagen type I (COL1), bone morphogenetic proteins (BMPs), and alkaline phosphatase (ALP) and help in the development of mesenchymal stem cells[3]. Growth factors from the surrounding fluids can be stored in the intrinsic micropores of CaP materials, which are created by sintering powders[15].

Osteoinduction is heavily influenced not just by porosity, which may accelerate solubility and stimulate interactions with cells and biomolecules. Other factors to consider are composition, crystallinity (more crystallinity means slower degradation), and surface area (granular product vs. bulk blocks). Higher degradation rates usually result in higher osteoinductivepotential[11].CaPs can be made more osteoinductive by including specific signaling molecules (extrinsic osteoinductivity) or by optimizing the material's chemical and structural properties.

Other factors that affect osteoinduction include composition, degree of crystallinity (high crystallinity indicates low degradation rates), and surface area in general (granular product vs. bulk blocks, for example). Porosity can also speed up solubility and encourage interactions with cells and biomolecules[16].

Better osteoinductive potential is usually associated with higher degradation rates[11].CaPs'osteoinductivity is sometimes enhanced by introducing specific osteoinductive molecules that signal (extrinsic osteoinductivity) or by optimizing the material's structure and/or chemistry (intrinsic osteoinductivity)[17].

The varied Ca/P ratios of the different kinds of CaPs result in distinct releases of calcium and phosphate ions, which are essential for bone mineralization[3,6,18].

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Changes in pH affect the chemical stability of CaPs in accordance with dissolving rate, and this can be controlled during the material's synthesis stage by adjusting the temperature, solvent type, pressure, and kind of precursors utilized[19].

A "technological" approach to dissolving control involves adjusting the sintering temperature in order to modulate the accessible surface area. The specific surface area will rise in tandem with the remaining inter-particle microporosity when the sintering temperature of CaPs is lowered. On the other hand, increasing the sintering temperature causes the micropores' volume and size to decrease, which lowers the specific surface area[11].

Because CaPs show a physical similarity to the mineral phase of bone, they have certain drawbacks, such as the absence of an organic phase (collagen, for example), which can be somewhat addressed by the creation of composites[20], They are unsatisfactory for load-bearing prosthetic applications, where harder metallic implants are usually used, because to their low mechanical strength and excessive brittleness.

Grain size determines strength in dense bioceramics; the smaller the crystals, the more durable the ceramic. Furthermore, when the crystalline phase grows and porosity reduces, the mechanical characteristics improve. CaPs will exhibit higher compressive and tensile strength as well as fracture toughness if the crystalline phase occurs over the amorphous component[4,10].

According to an estimation, it suggests to utilize 70% coarse powders and 30% fine powders to obtain maximum packing and minimal shrinkage after sintering, which would result in increased mechanical strength[4].

CaPs are brittle polycrystalline materials that closely depend on composition, crystallinity, grain size, and porosity. These mechanical properties are linked to solubility both in vitro and in vivo. The creation of multiphasic CaP compounds is a method for effectively modifying the mechanical characteristics of CaPs. Using this method, homogenous mixtures of two (biphasic), three (triphasic), or more (multiphasic) single phases of CaPs with varying solubility are prepared.

The primary CaPs utilized in biomedical applications are listed in Table 1 along with their key attributes. The solubility and dissolution rate of the most widely utilized CaPs are as follows: α-TCP > β-TCP > HA > FA.

Table 1. Existing CaPs and their key characteristics, taken from [4].

Material	Chemical Formula	Ca/P Molar Ratio	Solubility at 25 ◦C, g/L	**pH Stability Range in Aqueous Solutions (25 ◦C)**
Monocalcium phosphate monohydrate (MCPM)	$Ca(H_2PO_4)_2·H_2O$	0.5	~18	0.0–2.0
Dicalcium phosphate	$CaHPO_4·2H_2O$	1	~0.088	2.0–6.0

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dehydrate (DCPD), mineral brushite				
Octacalcium phosphate (OCP)	Ca8(HPO4)2(PO4)4·5H2O	1.33	~0.0081	5.5–7.0
α–Tricalcium phosphate (α-TCP)	α-Ca3(PO4)2	1.5	~0.0025	a
β–Tricalcium phosphate (β-TCP)	β-Ca3(PO4)2	1.5	~0.0005	a
Amorphous calcium phosphate (ACP)	CaxHy(PO4)z·nH2O, n = 3–4.5, 15–20% H2O	1.0–2.2 c	b	5.0–12.0
Hydroxyapatite (HA)	Ca10(PO4)6(OH)2	1.67	~0.0003	9.5–12.0
Fluorapatite (FA)	Ca10(PO4)6F2	1.67	~0.0002	7.0–12.0
Oxyapatite (OA)	Ca10(PO4)6O	1.67	~0.087	a
Tetracalcium phosphate (TTC)	Ca10(PO4)2O	2	~0.0007	a

[a] It is impossible for these substances to precipitate out of aqueous solutions. [b] It is impossible to test ACP's solubility exactly. Nevertheless, as stated in [6], log(K_s) values of 25.7 ± 0.1 (pH = 7.40), 29.9 ± 0.1 (pH = 6.00), and 32.7 ± 0.1 (pH = 5.28) were found. In an acidic buffer, the relative degree of dissolution is ACP >> α-TCP >> β-TCP >> HA > FA [6]. Under some experimental circumstances, [c] A Ca/P ratio less than 1 was reported.

CONCLUSION

Calcium phosphates—particularly hydroxyapatite (HA)—have emerged as highly promising materials for bone regeneration due to their close chemical and structural resemblance to the mineral phase of natural bone. Their excellent biocompatibility, osteoconductive properties, and potential osteoinductivebehavior make them suitable alternatives to conventional autografts and allografts in various biomedical applications.Advancements in material synthesis, processing techniques, and scaffold fabrication have enabled the development of HA-based grafts with controlled porosity, crystallinity, and mechanical strength. These improvements have significantly enhanced their in vitro and in vivo performance. However, limitations such as brittleness and low load-bearing capacity remain challenges, particularly for applications in high-stress environments.Future research should focus on optimizing multiphasic compositions, composite materials, and three-dimensional porous architectures to better mimic natural bone structure while improving mechanical reliability. With continued innovation, hydroxyapatite-based biomaterials are expected to play an increasingly vital role in orthopedic, dental, and reconstructive treatments.

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