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REVIEW ARTICLE

First detection, characterization, and application of amorphous calcium phosphate in dentistry

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Abstract *Background/purpose:* This literature review provides an overview of the first detection, structure, chemical composition, morphology characterization, phase transformation, and clinical application of amorphous calcium phosphate (ACP) to dentistry.
Materials and methods: ACP is the essential mineral phase formed in mineralized tissue and the first product to be used as artificial hydroxyapatite. ACP is unique among the calcium phosphates in that it lacks the long-range, periodic atomic scale order of crystalline calcium phosphates. Its X-ray diffraction patterns are broad and diffuse with a maxima at 25° 2θ, and no other different features compared with well-crystallized hydroxyapatite. Under electron microscopy, its morphologic form appears as small spheroidal particles of a few tenths of a nanometer in scale. In aqueous media ACP is easily transformed into crystalline phases such as octacalcium phosphate and apatite, due to the growth of the microcrystal.
Results: ACP has better osteoconductivity and biodegradability than tricalcium phosphate and hydroxyapatite *in vivo*. Moreover, it can increase alkaline phosphatase activity of mesoblasts, enhance cell proliferation activity, and promote cell adhesion. The unique role of ACP in the formation of mineralized tissues makes it a potentially useful candidate for use in materials for tissue repair and regeneration. The same properties may make ACP suitable as a potential remineralizing agent for dental applications.
Conclusion: Recently developed bioactive ACP-filled composites are potentially effective anti-demineralizing/remineralizing agents for the preservation and repair of teeth.

Introduction

Over the last decade, calcium phosphates have been of special interest to dentistry, the orthopedic industry, and

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medicine because of their excellent performance. This appears logical due to their similarity to the mineral phases of most hard tissues of human bones and teeth. Calcium phosphates of biological significance are summarized in Table 1.[1–5] Amorphous calcium phosphate (ACP) is the initial solid phase that precipitates from a highly supersaturated calcium phosphate solution, converting readily to stable crystalline phases such as octacalcium phosphate (OCP) or apatite products.

ACP is unique among the calcium phosphates. Its morphologic form, structural models, and X-ray diffraction patterns are typical of noncrystalline substances with short-range periodic regularity. ACP has been shown to have better *in vivo* osteoconductivity than hydroxyapatite (HAP) and better biodegradability than tricalcium phosphate (TCP). In addition, it has no cytotoxicity and good bioactivity. These excellent biocharacteristics explain why ACP has potential for wide application in oral biology, dentistry, orthopedic biomechanics, materials, and medicine. This review provides an account of the first detection, structure, composition, and morphologic characterization of ACP, as well as its phase transformation and biomedical applications, especially in dentistry.

First detection of ACP

Generally, it is believed that ACP was first described by Aaron S. Posner[6] in the mid 1960s. He obtained an amorphous precipitate by accident when mixing high concentrations (—30 mM) of calcium chloride and sodium acid phosphate (—20 mM) in buffer. X-ray diffraction revealed the pattern of this rapidly precipitated phase as showing only two very broad and diffuse peaks, with maxima at 25° 2θ with no features, and it was clearly not apatite. This diffraction pattern is typical for substances that lack long-range periodic regularity. Immediately after being mixed, the spontaneously formed precipitate was a noncrystalline, or amorphous, calcium phosphate with calcium-to-phosphorus molar ratio (Ca/P) of 1.50, while after several hours, upon aging, it could convert to poorly crystalline apatite. Afterward, this solid in contact with the precipitating solution converts slowly to crystalline apatite (Ca/P = 1.67) through an autocatalytic mechanism.

Actually, another report appeared in *Nature* in 1965, in which Eanes[7] identified ACP as a bone component. It seemed plausible to Posner that such an amorphous material called ACP was present in bone, and along with the apatite, might account for the broad diffraction pattern of bone mineral and for its variable composition. Posner and his staff[8,9] also described an age-dependent change in the ACP content of bone, with the proportion of ACP decreasing with age. In 1975, ACP was identified as the mineral in the hepatopancreas of the blue crab.[10] X-ray diffraction revealed that the mineralized cytoplasmic structure isolated from the hepatopancreas of the blue crab is very similar in short-range atomic structure to synthetic amorphous calcium phosphate.

Structural studies

After detection of amorphous calcium phosphate, further experiments focused on its structure. It was proposed that synthetic amorphous calcium phosphate particles, which appear as 300—1000 Å spheres in the electron microscope (Fig. 1),[6] the exact size depending on preparation conditions, consist of a random assembly of ion clusters 9.5 Å in diameter, dimensions consistent with the chemical composition $Ca_9(PO_4)_6$. The 15%—20% of water found in synthetic amorphous calcium phosphate was shown to be mostly in the interstices between, and not within, the individual $Ca_9(PO_4)_6$ clusters (Fig. 2).[6,11,12,13] Aggregated particles readily dissolve and crystallize to form apatite, a thermodynamically stable phase, because the binding effect of water is not strong. The typical radial distribution

Table 1 Summary of biologically significant calcium phosphates.[1–5]

Compound	Acronym	Formula	Ca/P molar ratio
Monocalcium phosphate, monohydrate	MCPM	Ca(H2PO4)2·H2O	0.5
Monocalcium phosphate, anhydrous	MCPA or MCP	Ca(H2PO4)2	0.5
Dicalcium phosphate dihydrate, mineral brushite	DCPD	CaHPO4·2H2O	1.0
Dicalcium phosphate anhydrous, mineral monetite	DCPA or DCP	$CaHPO_4$	1.0
Octacalcium phosphate	OCP	Ca8(HPO4)2(PO4)4·5H2O	1.33
α-tricalcium phosphate	α-TCP	α-$Ca_3(PO_4)_2$	1.5
β-tricalcium phosphate	β-TCP	β-$Ca_3(PO_4)_2$	1.5
Amorphous calcium phosphate	ACP	CaxHy(PO4)z·nH2O, $n = 3$—4.5; 15%—20% H2O	1.2—2.2
Calcium-deficient hydroxyapatite	CDHA or Ca-def HA	Ca10-x(HPO4)x(PO4)6-x(OH)2-x ($0 < x < 1$)	1.5—1.67
Hydroxyapatite	HA, Hap, or OHAp	$Ca_{10}(PO_4)_6(OH)_2$	1.67
Fluorapatite	FA or FAp	$Ca_{10}(PO_4)_6F_2$	1.67
Oxyapatite	OA, OAp, or OXA	$Ca_{10}(PO_4)_6O$	1.67
Tetracalcium phosphate, mineral hilgenstockite	TTCP or TetCP	$Ca_4(PO_4)_2O$	2.0