Acta Biomaterialia 9 (2013) 6283–6321

Contents lists available at SciVerse ScienceDirect

Acta Biomaterialia

journal homepage: www.elsevier.com/locate/actabiomat

Review

New developments in polymer-controlled, bioinspired calcium phosphate mineralization from aqueous solution

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ARTICLE INFO

Article history:
Received 23 August 2012
Received in revised form 13 November 2012
Accepted 21 December 2012
Available online 3 January 2013

Keywords:
Calcium phosphate
Biomimetics
Mineralization
Polymers
Bioinspired

ABSTRACT

The polymer-controlled and bioinspired precipitation of inorganic minerals from aqueous solution at near-ambient or physiological conditions avoiding high temperatures or organic solvents is a key research area in materials science. Polymer-controlled mineralization has been studied as a model for biomineralization and for the synthesis of (bioinspired and biocompatible) hybrid materials for a virtually unlimited number of applications. Calcium phosphate mineralization is of particular interest for bone and dental repair. Numerous studies have therefore addressed the mineralization of calcium phosphate using a wide variety of low- and high-molecular-weight additives. In spite of the growing interest and increasing number of experimental and theoretical data, the mechanisms of polymer-controlled calcium phosphate mineralization are not entirely clear to date, although the field has made significant progress in the last years. A set of elegant experiments and calculations has shed light on some details of mineral formation, but it is currently not possible to preprogram a mineralization reaction to yield a desired product for a specific application. The current article therefore summarizes and discusses the influence of (macro)molecular entities such as polymers, peptides, proteins and gels on biomimetic calcium phosphate mineralization from aqueous solution. It focuses on strategies to tune the kinetics, morphologies, final dimensions and crystal phases of calcium phosphate, as well as on mechanistic considerations.

1. Introduction

Calcium phosphates are important materials in biology and biomaterials science. They have therefore been studied extensively [1–3]. In the form of substituted hydroxyapatite (HAP), calcium phosphate is the most common mineral in vertebrate tissues. It confers mechanical stability to bones and teeth, and is therefore a key component in human health. As a result, calcium phosphate powders, coatings, composites and ceramics have attracted interest from the academic and commercial sides [4–17]. Calcium phosphate has also been used as a stable, biocompatible, non-toxic and cheap inorganic material for nanoparticulate ingredients in cosmetics, organic/inorganic hybrid particles for drug delivery and microcontainers for pharmaceutical applications [18–24].

Biomimetic mineral formation avoids harsh conditions, such as high temperatures. It therefore, for example, enables the synthesis of calcium phosphate composites containing unstable calcium phosphate phases. Such materials may be interesting for drug delivery, bone or dental repair, or RNA delivery [25–27]. These synthetic approaches, however, rely on the control of multiple interactions between precursor ions, polymeric additives and all precipitating phases. If one intends to tailor a specific mineralization process or calcium phosphate/polymer combination for a specific application, these interactions need to be understood and quantified. Moreover, the thermodynamics and kinetics of precursor association, nucleation and crystal growth need to be known and controlled. This is a complex endeavor because, in both nature and technology, numerous parameters, such as pH, temperature, salt and polymer concentration, polymer molecular weight, polymer architecture or the presence of further compounds, affect nucleation and growth at different points in time and space [28]. Quantifying polymer-controlled mineralization is therefore a multi-time scale and multi-length scale problem, which in many cases makes the investigation of individual mineralization steps challenging. The situation is further complicated by the large number of different calcium phosphate phases (see Table 1).

The chances of understanding biomimetic mineralization will increase once sufficiently large datasets on the effects of polymers on nucleation and growth are available from the literature. However, it is important to realize that the understanding of, for example, calcium carbonate mineralization is also helpful to understand calcium phosphate mineralization. Calcium phosphate mineralization should therefore not be viewed as an isolated problem of a small community of biomimetics researchers; rather, it should be seen as a point in case centered around a very important

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http://dx.doi.org/10.1016/j.actbio.2012.12.027

Table 1
Calcium phosphate phases [8,70,71].

Phase[a]/Common name	Chemical formula/Crystal system	Synthesis from aqueous solution at ambient conditions	pH of formation	Precursor for	Typical shape	pK_L	Ca/P ratio
ACP[b]	$Ca_3(PO_4)_2{}^*nH_2O$ N/a	Yes	All	All crystalline phases[p]	Beads	32.7 (pH 5) 29.9 (pH 6) 32.7 (pH 7.4)	1.5
DCPD[c] Brushite	$CaHPO_4{}^*2H_2O$ Monoclinic, C2/c	Yes	<4–5	HAP Monetite	Large Plates	6.95	1
DCPA Monetite	$CaHPO_4$ Triclinic, P1	Yes	<4–5	Brushite Apatite	Plates	6.9	1
α-TCP[d] Whitlockite	$Ca_3(PO_4)_2$	No[n]	–[n]			25.5	1.5
β-TCP[e]	$Ca_3(PO_4)_2$	No[n]	–[n]			28.9	1.5
OCP[f]	$Ca_8H_2(PO_4)_6{}^*5H_2O$ Triclinic, P1	Yes	<5–6	HAP		96.6	1.33
HAP[g]	$Ca_5(OH)(PO_4)_3$ Hexagonal, P63/m[l] Monoclinic[m]	Yes	>7	OXA	Needles	116.8	1.6
ClAP	$Ca_5(Cl)(PO_4)_3$ Hexagonal, P63/m	Yes	>7		Needles		1.6
FAP[h]	$Ca_5(F)(PO_4)_3$ Hexagonal, P63/m	Yes	>7		Needles	120	1.6
TTCP Hilgenstockite	$Ca_4O(PO_4)_2$		Basic	HAP		38–44	2
OXA[i]	$Ca_{10}O(PO_4)_6$	No[n]	–[n]			69	
MCP[j]	$CaH_4(PO_4)_2$	No[o]	–[o]			1.14	0.5
MCPM[k]	$CaH_4(PO_4)_2{}^*H_2O$		Acidic			1.14	0.5

Table adapted from Ref. [49]. Note that the original table in Ref. [49] contains three errors: (i) the different calcium phosphate phases are not polymorphs but amorphous or crystalline phases; (ii) the Ca/P ratio of stoichiometric HAP is not 1.7 but 1.67; and (iii) the unit of the solubility product of OCP is $(mol\ l^{-1})^{14}$, not $(mol\ l^{-1})^8$. The current table lists the negative decadic logarithm (pK_L) instead of the solubility product for better clarity of the table. The pK_L values for calcium-deficient apatite, carbonated apatite, human enamel and dentin are 85.1, 111.5, 96.1–117.5 and 88.8–104.0, respectively [8,29]. A detailed study of the solubility products of OCP was performed by Tung et al. Carrodeguas and De Aza [63].

[a] ACP, amorphous calcium phosphate; DCPD, dicalcium phosphate dihydrate; DCPA, dicalcium phosphate anhydrous; TCP, tricalcium phosphate; OCP, octacalcium phosphate; HAP, hydroxyapatite; ClAP, chloroapatite; FAP, fluoroapatite; TTCP, tetracalcium phosphate; OXA, oxyapatite; MCP, monocalcium phosphate; MCPM, monocalcium phosphate monohydrate.
[b] Two discrete forms: ACP1 and ACP2.
[c] The large crystal face is 0 1 0.
[d] Widely used as bone substitute.
[e] Stabilized by magnesium ions.
[f] Layered structure (apatitic and hydrated layers).
[g] A major inorganic component in bone and teeth.
[h] Highly stable in acid, favored over HAP at pH < 6.
[i] Decomposition product of HAP, water soluble.
[j] Highly water soluble.
[k] Water soluble.
[l] Biological form.
[m] More stable than the biological form.
[n] High-temperature synthesis.
[o] High-temperature synthesis (>500 °C).
[p] ACP appears to be a precursor for DCPD, although there is little evidence of this in the literature [72,73].