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Review

Biphasic, triphasic and multiphasic calcium orthophosphates

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ABSTRACT

Biphasic, triphasic and multiphasic (polyphasic) calcium orthophosphates have been sought as biomaterials for reconstruction of bone defects in maxillofacial, dental and orthopedic applications. In general, this concept is determined by advantageous balances of more stable (frequently hydroxyapatite) and more resorbable (typically tricalcium orthophosphates) phases of calcium orthophosphates, while the optimum ratios depend on the particular applications. Therefore, all currently known biphasic, triphasic and multiphasic formulations of calcium orthophosphate bioceramics are sparingly soluble in water and, thus, after being implanted they are gradually resorbed inside the body, releasing calcium and orthophosphate ions into the biological medium and, hence, seeding new bone formation. The available formulations have already demonstrated proven biocompatibility, osteoconductivity, safety and predictability in vitro, in vivo, as well as in clinical models. More recently, in vitro and in vivo studies have shown that some of them might possess osteoinductive properties. Hence, in the field of tissue engineering biphasic, triphasic and multiphasic calcium orthophosphates represent promising biomaterials to construct various scaffolds capable of carrying and/or modulating the behavior of cells. Furthermore, such scaffolds are also suitable for drug delivery applications. This review summarizes the available information on biphasic, triphasic and multiphasic calcium orthophosphates, including their biomedical applications. New formulations are also proposed.

1. Introduction

Calcium orthophosphates are of special significance for humans because they represent the inorganic part of normal (bones, teeth and deer antlers) and pathological (i.e. those appearing due to various diseases) calcified tissues in mammals [1,2]. Therefore, due to chemical similarity to biological calcified tissues the majority of artificially prepared calcium orthophosphates possess remarkable biocompatibility and bioactivity. Materials scientists use this property to construct artificial bone grafts that are either entirely made of or surface coated by biologically relevant calcium orthophosphates [3,4]. The available calcium orthophosphates, with the chemical formulae, standard abbreviations and solubility data, are listed in Table 1 [5–8]. As can be seen from Table 1, the solubility values of individual calcium orthophosphates vary over a wide range.

It has been known since the mid 1980s that the existing calcium orthophosphates listed in Table 1 might form biphasic [9,10], triphasic and multiphasic (polyphasic) combinations, in which the individual components frequently cannot be separated from each other. Obviously, the individual phases in such formulations are homogeneously and intimately "mixed" at the submicron (<1 μm) level and, therefore, are strongly integrated with each other. Nevertheless, the presence of each individual phase is easily seen by X-ray diffraction (XRD) (Fig. 1), which clearly indicates that they remain unchanged. However, the sharp and well-defined diffraction peaks show that the dimensions of particle of the individual phases of hydroxyapatite (HA) and β-tricalcium phosphate (β-TCP) in such formulations exceeds ~50 nm (otherwise the diffraction peaks become broader). Thus, roughly speaking, biphasic, triphasic and multiphasic calcium orthophosphates consist of the individual phases with particle dimensions between 50 and 500 nm.

Concerning the properties of such biphasic, triphasic and multiphasic calcium orthophosphates, as a rule of a thumb one can say that, in general, they are between of those of the constituent phases and depend on the relative amounts of the ingredients. Furthermore, by changing the ratio of more stable and more soluble calcium orthophosphates it is possible to prepare biphasic, triphasic and multiphasic formulations possessing adjustable properties. Such bioceramics can be applied to large bone defects, in some load bearing areas and as customized pieces which will maintain their shape over long periods of time [13,14].

The main biomedical idea behind the biphasic, triphasic and multiphasic calcium orthophosphate formulations is a proper balance of more stable calcium orthophosphate phases and more soluble ones [15,16] such that the major biomedical properties

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Table 1
Existing calcium orthophosphates and their major properties [5–8].

Molar ratio (Ca/P)	Compound	Formula	Solubility at 25 °C		pH stability (range)
			$-\log K_s$	g l^{-1}	
0.5	Monocalcium phosphate monohydrate (MCPM)	$Ca(H_2PO_4)_2{\cdot}H_2O$	1.14	~18	0.0–2.0
0.5	Monocalcium phosphate anhydrous (MCPA or MCP)	$Ca(H_2PO_4)_2$	1.14	~17	[a]
1.0	Dicalcium phosphate dihydrate (DCPD), mineral brushite	$CaHPO_4{\cdot}2H_2O$	6.59	~0.088	2.0–6.0
1.0	Dicalcium phosphate anhydrous (DCPA or DCP), mineral monetite	$CaHPO_4$	6.90	~0.048	[a]
1.33	Octacalcium phosphate (OCP)	$Ca_8(HPO_4)_2(PO_4)_4{\cdot}5H_2O$	96.6	~0.0081	5.5–7.0
1.5	α-Tricalcium phosphate (α-TCP)	α-$Ca_3(PO_4)_2$	25.5	~0.0025	[b]
1.5	β-Tricalcium phosphate (β-TCP)	β-$Ca_3(PO_4)_2$	28.9	~0.0005	[b]
1.2–2.2	Amorphous calcium phosphates (ACP)	$Ca_xH_y(PO_4)_z{\cdot}nH_2O$, n = 3–4.5, 15–20% H_2O	[c]	[c]	~5–12[d]
1.5–1.67	Calcium-deficient hydroxyapatite (CDHA or Ca-def HA)[e]	$Ca_{10-x}(HPO_4)_x(PO_4)_{6-x}(OH)_{2-x}$ ($0 < x < 1$)	~85	~0.0094	6.5–9.5
1.67	Hydroxyapatite (HA, HAp or OHAp)	$Ca_{10}(PO_4)_6(OH)_2$	116.8	~0.0003	9.5–12
1.67	Fluorapatite (FA or FAp)	$Ca_{10}(PO_4)_6F_2$	120.0	~0.0002	7–12
1.67	Oxyapatite (OA, OAp or OXA)[f]	$Ca_{10}(PO_4)_6O$	~69	~0.087	[b]
2.0	Tetracalcium phosphate (TTCP or TetCP), mineral hilgenstockite	$Ca_4(PO_4)_2O$	38–44	~0.0007	[b]

[a] Stable at temperatures above 100 °C.
[b] These compounds cannot be precipitated from aqueous solutions.
[c] Cannot be measured precisely. However, the following values were found: 25.7 ± 0.1 (pH 7.40), 29.9 ± 0.1 (pH 6.00), 32.7 ± 0.1 (pH 5.28). The comparative extent of dissolution in acidic buffer is: ACP >> α-TCP >> β-TCP > CDHA >> HA > FA.
[d] Always metastable.
[e] Occasionally referred to as "precipitated HA" (PHA).
[f] The existence of OA remains questionable.

(necessary levels of bioactivity, bioresorbability, osteoconductivity and osteoinductivity) of such formulations can be adjusted by changing the ratios between the phases. Compared with both α- and β-TCP, HA is a more stable phase under physiological conditions, as it is less soluble (Table 1) in aqueous media and thus has slower resorption kinetics. Therefore, due to the higher biodegradability of the α- or β-TCP component, the reactivity of biphasic formulations of HA with any type of TCP increases with increasing TCP/HA ratio. Thus the in vivo bioresorbability of such formulations can be adjusted through the phase composition [17]. Similar conclusions are also valid for biphasic formulations of α-TCP and β-TCP (in which α-TCP is the more soluble phase), as well as for triphasic (HA, α-TCP and β-TCP) formulations, in which α-TCP appears to be the most soluble phase, while HA is the most inert phase. The biodegradability properties of biphasic formulations of HA with β-TCP are well documented [18,19].

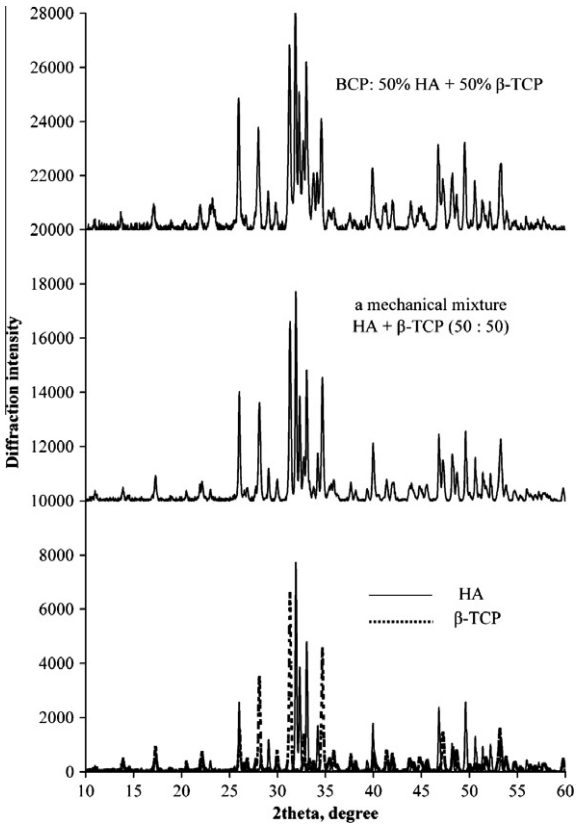

Fig. 1. XRD patterns: (bottom) the patterns of pure HA and β-TCP printed together; (middle) mathematical summation of the HA and β-TCP patterns; (upper) biphasic calcium phosphate (BCP) consisting of 50% HA and 50% β-TCP. Reprinted from Dorozhkina and Dorozhkin [11] and Dorozhkin [12] with permission.

This manuscript reviews the current state of the art knowledge on biphasic, triphasic and multiphasic calcium orthophosphates starting from the preparation techniques and ending with their biomedical applications.

2. General definitions and knowledge

Prior to providing information on biphasic, triphasic and multiphasic calcium orthophosphates one must define the basic terminology. According to Wikipedia, the free encyclopedia, in the physical sciences a phase is a region of space throughout which all physical and chemical properties of a material are essentially uniform. Examples of such properties include density, refractive index, chemical composition, crystal structure, etc. A phase is also a region of a material that is chemically uniform and physically distinct, which might be mechanically separable. Further, one should note that, in addition to the aforementioned definitions the term phase is often used as a synonym for a state of matter, such as gas, liquid or solid. For example, in a system consisting of ice and water, solid blocks of ice represent one phase, liquid water is a second phase and humid air over the water is a third phase (http://en.wikipedia.orgwiki/Phase_(matter)/). Since all available calcium orthophosphates are solids under ambient conditions, which are either thermally unstable (monocalcium phosphate monohydrate (MCPM), anhydrous monocalcium phosphate (MCPA), dicalcium phosphate dihydrate (DCPD), anhydrous dicalcium phosphate (DCPA), octacalcium phosphate (OCP), amorphous calcium phosphates (ACP), calcium-deficient hydroxyapatite (CDHA)) or melt at very high temperatures with partial decomposition (α-TCP, β-TCP, HA, oxyapatite (OA), fluorapatite (FA), tetracalcium phosphate (TTCP)), the latter definition is not applicable to the subject of this review.

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