Calcium Orthophosphates: Occurrence, Properties and Major Applications

Sergey V. Dorozhkin*

Kudrinskaja sq. 1-155, Moscow 123242, Russia

Abstract

The present overview is intended to point the readers' attention to the important subject of calcium orthophosphates. They are of the special significance for the human beings because they represent the inorganic part of major normal (bones, teeth and antlers) and pathological (i.e., those appearing due to various diseases) calcified tissues of mammals. Therefore, the majority of the artificially prepared calcium orthophosphates of high purity appear to be well tolerated by human tissues *in vivo* and possess the excellent biocompatibility, osteoconductivity and bioresorbability. These biomedical properties of calcium orthophosphates are widely used to construct bone grafts. In addition, natural calcium orthophosphates are the major source of phosphorus, which are used to produce agricultural fertilizers, detergents and various phosphorus-containing chemicals. Thus, there is a great significance of calcium orthophosphates for the humankind and, here, an overview on the current knowledge on this subject is provided.

Keywords: Calcium orthophosphates; Hydroxyapatite; Fluorapatite; Occurrence; Properties; Applications

Introduction

Due to the abundance in nature (as phosphate ores) and presence in living organisms (as bones, teeth, deer antlers and the majority of various pathological calcifications), calcium orthophosphates are the inorganic compounds of a special interest for human being. They were discovered in 1769 and have been investigated since then [1,2]. According to the databases of scientific literature (Web of knowledge, Scopus, Medline, etc.), the total amount of currently available publications on the subject exceeds 40,000 with the annual increase for, at least, 2000 papers. This is a clear confirmation of the importance.

Briefly, by definition, all calcium orthophosphates consist of three major chemical elements: calcium (oxidation state +2), phosphorus (oxidation state +5) and oxygen (reduction state -2), as a part of the orthophosphate anions. These three chemical elements are present in abundance on the surface of our planet: oxygen is the most widespread chemical element of the earth's surface (~ 47 mass %), calcium occupies the fifth place (~ 3.3 – 3.4 mass %) and phosphorus (~ 0.08 – 0.12 mass %) is among the first twenty of the chemical elements most widespread on our planet [3]. In addition, the chemical composition of many calcium orthophosphates includes hydrogen, as an acidic orthophosphate anion (for example, HPO_4^{2-} or H_2PO_4^-), hydroxide (for example, $\text{Ca}_{10}(\text{PO}_4)_6(\text{OH})_2$) and/or incorporated water (for example, $\text{CaHPO}_4 \cdot 2\text{H}_2\text{O}$). Regarding their chemical composition, diverse combinations of CaO and P_2O_5 oxides (both in the presence of water and without it) provide a large variety of calcium phosphates, which are differentiated by the type of the phosphate anion. Namely, ortho- (PO_4^{3-}), meta- (PO_3^-), pyro- ($\text{P}_2\text{O}_7^{4-}$) and poly- ($(\text{PO}_3)_n^{n-}$) phosphates are known. Furthermore, in the case of multi-charged anions (valid for orthophosphates and pyrophosphates), the calcium phosphates are also differentiated by the number of hydrogen ions attached to the anion. Examples include mono- ($\text{Ca}(\text{H}_2\text{PO}_4)_2$), di- (CaHPO_4), tri- ($\text{Ca}_3(\text{PO}_4)_2$) and tetra- ($\text{Ca}_2\text{P}_2\text{O}_7$) calcium phosphates. Here, one must stress that prefixes “mono”, “di”, “tri” and “tetra” are related to the amount of hydrogen ions replaced by calcium [4-6]. However, to narrow the subject, calcium orthophosphates will be considered and discussed only. Their names, the standard abbreviations, chemical formulae and solubility values are listed in Table 1 [7,8]. Since all of them belong to calcium orthophosphates, strictly speaking, all abbreviations in Table 1 are incorrect; however, they have been extensively used in literature for decades and, to avoid any confusions, there is no need to modify them.

In general, the atomic arrangement of all calcium orthophosphates is built up around a network of orthophosphate (PO_4) groups, which stabilize the entire structure. Therefore, the majority of calcium orthophosphates are sparingly soluble in water Table 1; however, all of them are easily soluble in acids but insoluble in alkaline solutions. In addition, all chemically pure calcium orthophosphates are colorless transparent crystals of moderate hardness but, as powders, they are of white color. Nevertheless, natural minerals of calcium orthophosphates are always colored due the presence of impurities and dopants, such as ions of Fe, Mn and rare earth elements [9,10]. Biologically formed calcium orthophosphates are the major component of all mammalian calcified tissues [11], while the geologically formed ones are the major raw material to produce phosphorus-containing agricultural fertilizers, chemicals and detergents [12-14].

Geological and Biological Occurrences

Geologically, natural calcium orthophosphates are found in different regions mostly as deposits of apatites, mainly as ion-substituted FA (igneous rocks), and phosphorites (sedimentary rocks) [13-15]. In addition, natural ion-substituted CDHA was also found [16] but it is a very rare mineral. Some types of sedimentary rocks can be formed by weathering of igneous rocks into smaller particles [17]. Other types of sedimentary rocks can be composed of minerals precipitated from the dissolution products of igneous rocks or minerals produced by biomineralization Figure 1 [18]. Thus, due to a sedimentary origin, both a general appearance and a chemical composition of natural phosphorites vary a lot [19,20]. It is a common practice to consider francolite (or carbonate-hydroxyfluorapatite regarded as its synonym) as the basic phosphorite mineral [15,21-24]. According to Henry [25], the name francolite was given by Mr. Brooke and Mr. Nuttall to a mineral from Wheal Franco, Tavistock, Devon, some years prior to 1850. A

*Corresponding author: Sergey V. Dorozhkin, Kudrinskaja sq. 1-155, Moscow 123242, Russia, E-mail: sedorozhkin@yandex.ru

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Ca/P molar ratio	Compound	Formula	Solubility at 25°C, -log(K _s)	Solubility at 25°C, g/L	pH stability range in aqueous solutions at 25°C
0.5	Monocalcium phosphate monohydrate (MCPM)	Ca(H ₂ PO ₄) ₂ ·H ₂ O	1.14	~ 18	0.0 – 2.0
0.5	Monocalcium phosphate anhydrous (MCPA or MCP)	Ca(H ₂ PO ₄) ₂	1.14	~ 17	[c]
1.0	Dicalcium phosphate dihydrate (DCPD), mineral brushite	CaHPO ₄ ·2H ₂ O	6.59	~ 0.088	2.0 – 6.0
1.0	Dicalcium phosphate anhydrous (DCPA or DCP), mineral monetite	CaHPO ₄	6.90	~ 0.048	[c]
1.33	Octacalcium phosphate (OCP)	Ca ₈ (HPO ₄) ₂ (PO ₄) ₄ ·5H ₂ O	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	[a]
1.5	β-Tricalcium phosphate (β-TCP)	β-Ca ₃ (PO ₄) ₂	28.9	~ 0.0005	[a]
1.2 – 2.2	Amorphous calcium phosphates (ACP)	Ca _x H _y (PO ₄) _z ·nH ₂ O, n = 3 – 4.5; 15 – 20% H ₂ O	[b]	[b]	~ 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) ₆ F ₂	120.0	~ 0.0002	7 – 12
1.67	Oxyapatite (OA, OAp or OXA) ^[f] , mineral voelckerite	Ca ₁₀ (PO ₄) ₆ O	~ 69	~ 0.087	[a]
2.0	Tetracalcium phosphate (TTCP or TetCP), mineral hilgenstockite	Ca ₄ (PO ₄) ₂ O	38 – 44	~ 0.0007	[a]

[a] These compounds cannot be precipitated from aqueous solutions.

[b] 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) [236]. The comparative extent of dissolution in acidic buffer is: ACP >> α-TCP >> β-TCP > CDHA >> HA > FA [107].

[c] Stable at temperatures above 100°C.

[d] Always metastable.

[e] Occasionally, it is called "precipitated HA (PHA)".

[f] Existence of OA remains questionable

Table 1: Existing calcium orthophosphates and their major properties [7,8].

cryptocrystalline (almost amorphous) variety of francolite (partly of a biological origin) is called collophane (synonyms: collophanit, collophanita, collophanite, grodnolite, kollophan) [26-28]. It occurs in natural phosphorites predominantly as fossil bones and phosphatized microbial pseudomorphs: phosphatic crusts of chasmolithic biofilms (or microstromatolites) and globular clusters with intra-particle porosities [29-32]. Natural phosphorites (therefore, francolite and collophane as well) occur in various forms, such as nodules, crystals or masses. Occasionally, other types of natural calcium orthophosphates are found as minerals, for example clinohydroxylapatite [33], staffelite (synonyms: staffelit, staffelita) belonging to carbonate-rich fluorapatites (chemical formula: Ca₅[(F,O)(PO₄CO₃)₃]) [34,35] and DCPD [36]. Furthermore, calcium orthophosphates were found in meteoric stones [37,38]. The world deposits of natural calcium orthophosphates are estimated to exceed 150 billion tons; from which approximately 85% belong to phosphorites and the remaining ~ 15% belong to apatites.

As minor constituents (< ~ 5%), natural calcium orthophosphates (both apatites and phosphorites) occur in many geological environments. Concentrations sufficient for economic use (> 15%) are also available. Namely, the largest world deposits of natural apatites are located in Russia (the Khibiny and Kovdor massifs, Kola peninsula [39,40]), Brazil and Zambia, while the largest world deposits of natural phosphorites are located in Morocco, Russia, Kazakhstan, USA (Florida, Tennessee), China and Australia [12-15]. In addition, they are found at seabed and ocean floor [41]. The majority of natural calcium orthophosphates occur as small polycrystalline structures (spherulitic clusters). Larger crystals are rare [42]. They usually have the crystal structure of apatites (hexagonal system, space group P6₃/m). Giant crystals including "a solid but irregular mass of green crystalline apatite, 15 feet long and 9 feet wide" [43] and a single euhedral crystal from the Aetna mine measuring 2.1 × 1.2 m with an estimated weight of 6 tons [44] were found. None of them is a pure compound; they always contain dopants of other elements. For example, ions of calcium might be partially replaced by Sr, Ba, Mg, Mn, K, Na, Fe; ions of orthophosphate may be partly replaced by AsO₄³⁻, CO₃²⁻ and VO₄³⁻ [45]; ions of hydroxide, chloride, bromide, carbonate and oxide may to a certain extent substitute fluoride in the crystal lattice of natural apatites [23]. Furthermore, organic radicals have been found in natural apatites [46,47]. In principle, the crystal structure of apatites can incorporate half the Periodic Chart in its atomic arrangement. In medicine, this property might be used as an antidote for heavy metal intoxication [48]. Ease of atomic substitution for apatite leaves this mineral open to a wide array of compositions. This might be related to the fact that the apatite structure type displays porous properties [49]. The substitutions in apatites are usually in trace concentrations but for certain dopants large concentrations and even complete solid solutions exist (e.g., F

and OH⁻). To make things even more complicated, some ions in the crystal structure may be missing, leaving the crystallographic defects, which leads to formation of non-stoichiometric compounds, such as CDHA. Figure 2 shows examples of polycrystalline and single-crystalline samples of natural FA.

Manufacturing of elementary phosphorus (white and red) [50,51], phosphoric acids [13,52-55], various phosphorus-containing chemicals, agricultural fertilizers (namely, superphosphate [56-58], ammonium orthophosphates [59] and detergents (principally sodium tripolyphosphate [60] are the major industrial applications of natural calcium orthophosphates. The annual consumption of a phosphate rock has approached ~ 150 million tons and about 95 percent of this production is utilized in the fertilizer industry [61,62].

In biological systems, many organisms, ranging from bacteria and isolated cells to invertebrates and vertebrates, synthesize calcium orthophosphates [18]. Formation of calcium orthophosphates in primitive organisms is believed to enable the storage and regulation of essential elements such as calcium, phosphorus and, possibly, magnesium. The morphology of precipitates in these organisms (small intracellular nodules of ACP often located in mitochondria) complies with the necessities for rapid mobilization and intracellular control of the concentration of these elements [63]. In vertebrates calcium orthophosphates occur as the principal inorganic constituent of normal (bones, teeth, fish enameloid, deer antlers and some species of shells) and pathological (dental and urinary calculus and stones, atherosclerotic lesions, *etc.*) calcifications [11,64-69]. Except for small portions of the inner ear, all hard tissue of the human body is formed of calcium orthophosphates. Structurally, they occur mainly in the form of poorly crystalline, non-stoichiometric, Ca-deficient, Na-, Mg- and carbonate-containing HA. It is often called “biological apatite” [70-72] (which might be abbreviated as BAp [73,74], bioapatite [75-78e] or dahllite. The latter was named in 1888 by Broeger and Bäckstroem [79] after the Swedish mineralogist brothers Tellef and Johan Martin Dahll.

The main constituents of human bones are calcium orthophosphates (~ 60 – 70 wt.%), collagen (~ 20-30 wt.%) and water (up to 10 wt.%) [68,75,80,81]. Detailed information on the chemical composition of the most important human normal calcified tissues is comprised in Table 2. One should note that the values mentioned in Table 2 are approximate; the main constituents can vary by a percent or more [82].

The Members of Calcium Orthophosphate Family

In the ternary aqueous system Ca(OH)₂ – H₃PO₄ – H₂O (or CaO – P₂O₅ – H₂O) [83-85] there are twelve known non-ion-substituted calcium orthophosphates with the Ca/P molar ratio ranging between 0.5 and 2.0 Table 1. An anhydrous phase diagram CaO – P₂O₅ at temperatures within 200-2200°C is shown in Figure 3 [86,87]. Table 3 comprises crystallographic data of the existing calcium orthophosphates [5,88,89]. The most important parameters of calcium orthophosphates are the ionic Ca/P ratio, basicity / acidity and solubility. All these parameters strongly correlate with the solution pH. The lower the Ca/P molar ratio is, the more acidic and water-soluble the calcium orthophosphate is [4-6]. One can see that the solubility ranges from high values for acidic compounds, such as MCPM, to very low values for basic compounds, such as apatites, which allow calcium orthophosphates to be dissolved, transported from one place to another and precipitated, when necessary. Crystallization, dissolution and phase transformation processes of different calcium orthophosphates under various experimental conditions have been reviewed [90]. Regarding applications, some of them might be used in food industry

and, according to the European classification of food additives, calcium orthophosphates of food grade quality are known as E341 additive.

Due to the triprotic equilibrium that exists within orthophosphate-containing solutions, variations in pH alter the relative concentrations of the four polymorphs of orthophosphoric acid Figure 4 [91] and thus both the chemical composition Figure 5 [92] and the amount of the calcium orthophosphates that are formed by a direct precipitation. The solubility isotherms of different calcium orthophosphates are shown in Figure 6 [5,6,84,85,93,94]. However, in 2009, the classic solubility data of calcium orthophosphates [5,6,84,85,93,94] were mentioned to be inappropriate [95]. According to the authors of the latter study, all previous solubility calculations were based on simplifications, which

Figure 2: Polycrystalline (a) and single-crystalline (b) FA of a geological origin. The single crystal has a grey-green color due to incorporated ions of transition metals.

Figure 3: Phase diagram of the system CaO – P₂O₅ (C = CaO, P = P₂O₅) at elevated temperatures. Here: C₂P₂ means 7CaO·5P₂O₅; other abbreviations should be written out in the same manner. Reprinted from Refs. [86,87] with permission.

Composition, wt%	Enamel	Dentine	Cementum	Bone	HA
Calcium ^[a]	36.5	35.1	~ 35	34.8	39.6
Phosphorus (as P) ^[a]	17.7	16.9	~ 16	15.2	18.5
Ca/P (molar ratio) ^[a]	1.63	1.61	~ 1.65	1.71	1.67
Sodium ^[a]	0.5	0.6	[c]	0.9	–
Magnesium ^[a]	0.44	1.23	0.5 – 0.9	0.72	–
Potassium ^[a]	0.08	0.05	[c]	0.03	–
Carbonate (as CO ₃ ²⁻) ^[b]	3.5	5.6	[c]	7.4	–
Fluoride ^[a]	0.01	0.06	up to 0.9	0.03	–
Chloride ^[a]	0.30	0.01	[c]	0.13	–
Pyrophosphate (as P ₂ O ₇ ⁴⁻) ^[b]	0.022	0.10	[c]	0.07	–
Total inorganic ^[b]	97	70	60	65	100
Total organic ^[b]	1.5	20	25	25	–
Water ^[b]	1.5	10	15	10	–
Crystallographic properties: Lattice parameters (± 0.003 Å)					
a-axis, Å	9.441	9.421	[c]	9.41	9.430
c-axis, Å	6.880	6.887	[c]	6.89	6.891
Crystallinity index (HA = 100)	70 – 75	33 – 37	~ 30	33 – 37	100
Typical crystal sizes (nm) [11]	100 μm ×50×50	35×25×4	[c]	50×25×4	200 – 600
Ignition products (800 °C)	β-TCP + HA	β-TCP+ HA	β-TCP+ HA	HA + CaO	HA
Elastic modulus (GPa)	80	23.8 ± 3.7	15.0 ± 3.6	0.34 – 13.8	10
Tensile strength (MPa)	10	100	[c]	150	100

^[a] Ashed samples.

^[b] Unashed samples.

^[c] Numerical values were not found in the literature but they should be similar to those for dentine.

Table 2: Comparative composition and structural parameters of inorganic phases of adult human calcified tissues. Due to the considerable variation found in biological samples, typical values are given in these cases [4,81].

Figure 4: pH variation of ionic concentrations in triprotic equilibrium for phosphoric acid solutions. Reprinted from Ref. [91] with permission

Figure 5: Various calcium orthophosphates obtained by neutralizing of orthophosphoric acid. Ca/P are reported in the figure. The solubility of calcium orthophosphates in water decreases drastically from left to right, HA being the most insoluble and stable phase. Reprinted from Ref. [91] with permission.

were only crudely approximate. The problem lies in incongruent dissolution, leading to phase transformations and lack of the detailed solution equilibria. Using an absolute solid-titration approach, the true solubility isotherm of HA was found to lie substantially lower than previously reported. In addition, contrary to a wide belief, DCPD appeared not to be the most stable phase below pH ~ 4.2, where CDHA was less soluble [95].

A brief description of all known calcium orthophosphates Table 1 is given below.

MCPM

Monocalcium phosphate monohydrate (Ca(H₂PO₄)₂·H₂O; the IUPAC name is calcium dihydrogen orthophosphate monohydrate) is both the most acidic and water-soluble calcium orthophosphate. Although acidic calcium orthophosphates in general were known by 1795 as “super-phosphate of lime” [96], their differentiation started in 1800-s. Namely, by 1807, researchers first prepared a calcium phosphate, which could be attributed to MCPM [97].

MCPM crystallizes from aqueous solutions containing dissolved ions of H₂PO₄⁻ and Ca²⁺ at the Ca/P ratio ~ 0.5 and solution pH below ~ 2.0. Besides, MCPM might be precipitated from aqueous solutions containing organic solvents [98,99]. At temperatures above ~ 100°C, MCPM releases a molecule of water and transforms into MCPA but at temperatures > ~ 500 °C MCPA further transforms into Ca(PO₃)₂ [100]. The results of the spectroscopic investigations of MCPM are available in literature [101].

Due to high acidity and solubility, MCPM is never found in biological calcifications. Moreover, pure MCPM is not biocompatible with bones [102]. However, in medicine MCPM is used as a component

Figure 6: Top: a 3D version of the classical solubility phase diagrams for the ternary system $\text{Ca}(\text{OH})_2 - \text{H}_3\text{PO}_4 - \text{H}_2\text{O}$. Reprinted from Ref. [94] with permission. Middle and bottom: solubility phase diagrams in two-dimensional graphs, showing two logarithms of the concentrations of (a) calcium and (b) orthophosphate ions as a function of the pH in solutions saturated with various salts. Reprinted from Ref. [384] with permission [385].

of several self-hardening calcium orthophosphate formulations [103,104]. In addition, MCPM is used as a nutrient, acidulant and mineral supplement for dry baking powders, food, feed and some beverages [105,106]. Coupled with NaHCO_3 , MCPM is used as a leavening agent for both dry baking powders and bakery dough. MCPM might be added to salt-curing preserves, pickled and marinated foods. In addition, MCPM might be added to tooth pastes and chewing gums [107]. Besides, MCPM might be added to ceramics and glasses, while agriculture is the main consumer of a technical grade MCPM, where it is used as a fertilizer, triple superphosphate [108].

MCPA (or MCP)

Monocalcium phosphate anhydrous ($\text{Ca}(\text{H}_2\text{PO}_4)_2$; the IUPAC name is calcium dihydrogen orthophosphate anhydrous) is the anhydrous form of MCPM. Although MCPM has been known since 1807 [1,2], MCPA was differentiated as “tetra-hydrogen calcium phosphate, $\text{H}_4\text{Ca}(\text{PO}_4)_2$ ” by 1879 [109]. It crystallizes under the same conditions as MCPM but at temperatures above $\sim 100^\circ\text{C}$ (e.g., from concentrated hot mother liquors during fertilizer production). In addition, MCPA might be prepared from MCPM by dehydration. Furthermore, it might be also prepared at ambient temperatures by crystallization in water-restricted or non-aqueous systems. Like MCPM, MCPA never appears in calcified tissues and is not biocompatible due to its acidity. There is no current application of MCPA in medicine. Due to the similarity with MCPM, in many cases, MCPA might be used instead of MCPM; however, highly hygroscopic properties of MCPA reduce its commercial applications [13,105].

DCPD

Dicalcium phosphate dihydrate ($\text{CaHPO}_4 \cdot 2\text{H}_2\text{O}$; the IUPAC name is calcium hydrogen orthophosphate dihydrate; the mineral brushite) has been known since, at least, 1804 [96]. As a mineral, brushite was first discovered in phosphatic guano from Avis Island (Caribbean) in 1865 [110] and named to honor an American mineralogist Prof. George Jarvis Brush (1831 – 1912), Yale University, New Haven, Connecticut, USA.

DCPD can be easily crystallized from aqueous solutions containing dissolved ions of HPO_4^{2-} and Ca^{2+} at the Ca/P ratio ~ 1 and solution pH within $\sim 2.0 < \text{pH} < \sim 6.5$. Other preparation techniques such as neutralization of H_3PO_4 and/or MCPM solutions by CaO, CaCO_3 or more basic calcium orthophosphates (α - or β -TCP, CDHA, HA, TTCP) are also known. Interestingly, that precipitation of DCPD by mixing a $\text{Ca}(\text{OH})_2$ suspension and a H_3PO_4 solution in the equimolar quantities was found to occur in five stages, being HA the first precipitated phase [111,112]. Besides, DCPD might be prepared in gels [113,114]. DCPD transforms into DCPA at temperatures above $\sim 80^\circ\text{C}$ and this transformation is accompanied by $\sim 11\%$ decrease in volume [115] and structural changes [116]. The value for $\Delta_r G^\circ$ for $\text{DCPD} \rightarrow \text{DCPA}$ transformation is -1.032 kJ/mol [116]. Briefly, DCPD crystals consist of CaPO_4 chains arranged parallel to each other, while lattice water molecules are interlayered between them [117]. The atomic structure of the {010} interface of DCPD with water was determined [118]. Recently, data on DCPD solubility have been updated by solid titration technique [119]. The optical properties of DCPD were described [120], while many additional data on DCPD including a good drawing of its atomic structure might be found in Ref. [121].

DCPD is of biological importance because it is often found in pathological calcifications (dental calculi, crystalluria, chondrocalcinosis and urinary stones) and some carious lesions [4,64-66]. It was proposed as an intermediate in both bone mineralization and dissolution of enamel in acids (dental erosion) [4,64,65]. In medicine, DCPD is used in self-setting calcium orthophosphate formulations [104] and as an intermediate for tooth remineralization. DCPD is added to toothpaste both for caries protection (in this case, it is often coupled with F-containing compounds such as NaF and/or $\text{Na}_2\text{PO}_3\text{F}$) and as a gentle polishing agent [107]. Other applications include a flame retardant [122], a slow release fertilizer, using in glass production, as well as calcium supplement in food, feed and cereals. In food industry, it serves as a texturizer, bakery improver and water retention additive. In dairy industry, DCPD is used as a mineral supplement. In addition, plate-like crystals of DCPD might be used as a non-toxic, anticorrosive and passivating pigment for some ground coat paints [105].

DCPA (or DCP)

Dicalcium phosphate anhydrous (CaHPO_4 ; the IUPAC name is calcium hydrogen orthophosphate anhydrate; the mineral monetite) is the anhydrous form of DCPD. Although DCPD has been known since, at least, 1804 [1,2], DCPA was differentiated as “mono-hydrogen calcium orthophosphate, HCaPO_4 ” by 1879 [107]. As a mineral, monetite was first described in 1882 in rock-phosphate deposits from the Moneta (now Monito) Island (archipelago of Puerto Rico), which contains a notable occurrence [123].

Due to the absence of water inclusions, DCPA is less soluble than DCPD Table 1. Like DCPD, DCPA can be crystallized from aqueous solutions containing Ca/P ratio ~ 1 at solution pH within $\sim 2.0 < \text{pH} < \sim 6.5$ but at temperatures $> \sim 90^\circ\text{C}$. In addition, DCPA might be

prepared by dehydration of DCPD. Furthermore, it might be also prepared at ambient temperatures in water-restricted or non-aqueous systems, such as gels [113], ethanol [124], as well as in the oil-in-water and water-in-oil systems [125]. DCPA is physically stable and resisted hydration even when dispersed in water for over 7 months in the temperature range of 4-50°C [126]. A calcium-deficient DCPA was also prepared. It might be sintered at ~ 300°C [127]. Unlike DCPD, DCPA occurs in neither normal nor pathological calcifications. It is used in self-setting calcium orthophosphate formulations [104]. Besides, DCPA might be implanted as bioceramics [128]. Other applications include using as a polishing agent, a source of calcium and phosphate in nutritional supplements (e.g., in prepared breakfast cereals, enriched flour and noodle products), a tableting aid [129] and a toothpaste component [107]. In addition, it is used as a dough conditioner in food industry [105].

OCP

Octacalcium phosphate ($\text{Ca}_8(\text{HPO}_4)_2(\text{PO}_4)_4 \cdot 5\text{H}_2\text{O}$; the IUPAC name is tetracalcium hydrogen orthophosphate diorthophosphate pentahydrate, another name is octacalcium bis(hydrogenphosphate) tetrakis(phosphate) pentahydrate) is often found as an unstable transient intermediate during the precipitation of the thermodynamically more stable calcium orthophosphates (e.g., CDHA) in aqueous solutions. To the best of my findings [1,2], OCP has been known since, at least, 1843, when Percy published a paper [130], in which he described formation of “a new hydrated phosphate of lime” with a chemical formula $2\text{CaO} + \text{PO}_5 + 6\text{H}_2\text{O}$, in which “1 equiv. water being basic and 5 constitutional”. However, according to Bjerrum [131], a calcium orthophosphate with the OCP composition was first described by Berzelius in 1836.

The preparation techniques of OCP are available in literature [132-135]. Briefly, to prepare OCP, Ca- and PO_4 -containing chemicals must be mixed to get the supersaturated aqueous solutions with the Ca/P ratio equal to 1.33. However, OCP might be non-stoichiometric and be either Ca-deficient (Ca/P=1.26) or include excessive calcium (up to Ca/P = 1.48) in the structure [135]. Furthermore, a partially hydrolyzed form of OCP with Ca/P molar ratio of 1.37 might be prepared [135,136]. The full hydrolysis of OCP into CDHA occurs within ~ 6 hours [134]. Ion-substituted OCP might be prepared as well [137,138]. Crystals of OCP are typically small, extremely platy and almost invariably twinned.

The triclinic structure of OCP displays apatitic layers (with atomic arrangements of calcium and orthophosphate ions similar to those of HA) separated by hydrated layers (with atomic arrangements of calcium and orthophosphate ions similar to those in DCPD) [4-6,135]. A similarity in crystal structure between OCP and HA [139,140] is one reason that the epitaxial growth of these phases is observed. It is generally assumed that, in solutions, the hydrated layer of the (100) face is the layer most likely exposed to solution. The water content of OCP crystals is about 20% that of DCPD and this is partly responsible for its lower solubility. New data on OCP solubility have been published recently [141].

OCP is of a great biological importance because it is one of the stable components of human dental and urinary calculi [142,143]. OCP was first proposed by W. E. Brown to participate as the initial phase in enamel mineral formation and bone formation through subsequent precipitation and stepwise hydrolysis of OCP [139,140,144]. It plays an important role in formation of apatitic biominerals *in vivo* [145]. A “central OCP inclusion” (also known as “central dark line”) is seen by transmission electron microscopy in many biological apatites and in synthetically precipitated CDHA [146-148]. Although OCP has not

been observed in vascular calcifications, it has been strongly suggested as a precursor phase to biological apatite found in natural and prosthetic heart valves [149,150]. In surgery, OCP is used for implantation into bone defects [151-154]. For the comprehensive information on OCP, the readers are referred to other reviews [135,142].

β -TCP

β -tricalcium phosphate ($\beta\text{-Ca}_3(\text{PO}_4)_2$; the IUPAC name is tricalcium diorthophosphate beta, other names are calcium orthophosphate tribasic beta or tricalcium bis(orthophosphate) beta) is one of the polymorphs of TCP. Although calcium orthophosphates with the composition close to that of TCP, CDHA and HA were known in 1770-s [1,2], α - and β - polymorphs of TCP were differentiated only by 1932 [155,156].

β -TCP cannot be precipitated from aqueous solutions. It is a high temperature phase, which can be prepared at temperatures above ~ 800°C by thermal decomposition of CDHA or by solid-state interaction of acidic calcium orthophosphates, e.g., DCPA, with a base, e.g., CaO. In all cases, the chemicals must be mixed in the proportions to get the Ca/P ratio equal to 1.50. However, β -TCP can also be prepared at relatively low temperatures (~ 150°C) by precipitation in water-free mediums, such as ethylene glycol [157,158]. Apart from the chemical preparation routes, ion-substituted β -TCP can be prepared by calcining of bones [159,160]: such type of calcium orthophosphates is occasionally called “bone ash” [161]. At temperatures above ~ 1125°C, β -TCP is transformed into a high-temperature phase α -TCP. Being the stable phase at room temperature, β -TCP is less soluble in water than α -TCP Table 1. Both ion-substituted [162-165] and organically modified [166-168] forms of β -TCP can be synthesized, as well. The modern structural data on β -TCP are available in Refs [169-171], those on Vicker's and Knoop microhardness studies might be found in Ref [172], while solubility data – in Ref [173]. Furthermore, an ability of β -TCP to store an electrical charge by electrical polarization was studied and this material was found to have a suitable composition and structure for both ion conduction and charge storage [174].

Pure β -TCP never occurs in biological calcifications. Only the Mg-substituted form ($\beta\text{-TCMP} = \beta\text{-tricalcium magnesium phosphate}$, $\beta\text{-(Ca,Mg)}_3(\text{PO}_4)_2$), which is often called whitlockite to honor Mr. Herbert Percy Whitlock (1868 – 1948), an American mineralogist, the curator of the American Museum of Natural History, New York City, New York, USA [175]. Since $\beta\text{-TCMP}$ is less soluble than $\beta\text{-TCP}$ [176], it is formed instead of β -TCP in dental calculi and urinary stones, dentine caries, salivary stones, arthritic cartilage, as well as in some soft-tissue deposits [4,64-66,177-180]. However, it has not been observed in enamel, dentine or bone. In medicine, β -TCP is used in the self-setting calcium orthophosphate formulations [104] and other types of bone grafts [159,181-185]. Dental applications of β -TCP are also known. For example, β -TCP is added to some brands of toothpaste as a gentle polishing agent [107]. Multivitamin complexes with calcium orthophosphate are widely available in the market and β -TCP is used as the calcium phosphate there. In addition, β -TCP serves as a texturizer, bakery improver and anti-clumping agent for dry powdered food (flour, milk powder, dried cream, cocoa powder). Besides, β -TCP is added as a dietary or mineral supplement to food and feed [186]. Occasionally, β -TCP might be used as inert filler in pelleted drugs. Other applications comprise porcelains, pottery, enamel, using as a component for mordants and ackey, as well as a polymer stabilizer [105]. β -TCP of a technical grade (as either calcined natural phosphorites or bone dust) is used as a slow release fertilizer for acidic soils [13].

α -TCP

α -tricalcium phosphate (α -Ca₃(PO₄)₂; the IUPAC name is tricalcium diorthophosphate alpha, other names are calcium orthophosphate tribasic alpha or tricalcium bis(orthophosphate) alpha) is another polymorph of TCP, which was differentiated by 1932 [155,156]. α -TCP is also a high temperature phase; therefore, it cannot be precipitated from aqueous solutions either. Thus, α -TCP is usually prepared by the same techniques as β -TCP (see the previous section) but, since the β -TCP $\rightarrow$ α -TCP transition temperature is $\sim 1125^\circ\text{C}$ [187], calcining is performed at temperatures above $\sim 1200^\circ\text{C}$ [188]. Consequently, α -TCP is often considered as a high temperature polymorph of β -TCP. However, data are available that α -TCP might be prepared at lower temperatures. Namely, at the turn of the millennium, the previously forgotten data that the presence of silicates stabilized α -TCP at temperatures of 800 – 1000°C [189] were rediscovered again. Such type of α -TCP is called “silica stabilized α -TCP” [190-192]. Furthermore, sometimes, α -TCP might be prepared at even lower temperatures ($\sim 700^\circ\text{C}$) by a thermal decomposition of low temperature ACPs [193].

Although α -TCP and β -TCP have exactly the same chemical composition, they differ by the crystal structure Table 3 and solubility Table 1. In the absence of humidity, both polymorphs of TCP are stable at room temperatures; however, according to a density functional study, stability of β -TCP crystal lattice exceeds that of α -TCP [170]. Therefore, of them, α -TCP is more reactive in aqueous systems, has a higher specific energy and in aqueous solutions it can be hydrolyzed to CDHA [194-196]. Milling was found to increase the α -TCP reactivity even more [197]. Although, α -TCP never occurs in biological calcifications, in medicine, it is used as a component of self-setting calcium orthophosphate formulations [104]. On the other hand, the chemically pure α -TCP has received not much interest in the biomedical field [183]. The disadvantage for using α -TCP is its quick resorption rate (faster than formation of a new bone), which limits its application in this area. However, the silicon stabilized α -TCP (more precisely as a biphasic composite with HA) has been commercialized as a starting material to produce bioresorbable porous ceramic scaffolds to be used as artificial bone grafts [190-192]. Upon implantation, α -TCP tends to convert to CDHA, which drastically reduces further degradation rate. Theoretical insights into bone grafting properties of the silicon-stabilized α -TCP might be found in Ref [198]. The structure of α -TCP is well described in literature [170,171], while the surface and adsorption properties are available in Ref [199]. Similar to β -TCP, α -TCP of a technical grade might be used slow release fertilizer for acidic soils [105].

To conclude, one should briefly mention on an existence of α' -TCP polymorph, which was discovered in 1959 [189]. However, this TCP polymorph lacks of any practical interest because it only exists at temperatures between $\sim 1450^\circ\text{C}$ and its melting point ($\sim 1756^\circ\text{C}$). It reverts to α -TCP polymorph by cooling below the transition temperature.

ACP

Amorphous calcium phosphates (ACPs) represent a special class of calcium orthophosphate salts, having variable chemical but rather identical glass-like physical properties, in which there are neither translational nor orientational long-range orders of the atomic positions. To the best of my findings [1,2], ACP was first prepared in 1845 [200]. Nevertheless, until recently [201], ACP has often been considered as an individual calcium orthophosphate with a variable chemical composition, while, in reality, ACP is just an amorphous

state of other calcium orthophosphates. Therefore, in principle, all compounds mentioned in Table 1 might be somehow fabricated in an amorphous state but, currently, only few of them (e.g., an amorphous TCP) are known [201]. Thus, strictly speaking, ACP should be excluded from Table 1. Furthermore, since ACPs do not have the definite chemical composition, the IUPAC nomenclature is not applicable to describe them.

Depending on the production temperatures, all types of ACP are divided into two major groups: low-temperature ACPs (prepared in solutions, usually aqueous ones) and high-temperature ACPs [201]. Low-temperature ACPs (described by the chemical formula Ca_xH_y(PO₄)_z·nH₂O, $n=3-4.5$; 15 – 20% H₂O) are often encountered as a transient precursor phase during precipitation of other calcium orthophosphates in aqueous systems. Usually, an ACP is the first phase precipitated from supersaturated solutions (the higher supersaturation, the better) prepared by rapid mixing of solutions containing ions of calcium and orthophosphate [5,201]. Such ACP precipitates usually look like spherical particles with diameters in the range 200 to 1200 Å without a definite structure. Generally, the ACP particles are smaller if prepared under conditions of high supersaturation and/or high pH, while for a given pH, higher temperatures give larger particles [202,203]. The freshly precipitated ACPs contain 10 – 20% by weight of tightly bound water, which is removed by vacuum drying at elevated temperature [204]. The amorphization degree of ACPs increases with the concentration increasing of Ca- and PO₄-containing solutions, as well as at a high solution pH and a low crystallization temperature. A continuous gentle agitation of as precipitated ACPs in the mother solution, especially at elevated temperatures, results in a slow recrystallization and formation of better crystalline calcium orthophosphates, such as CDHA [4,5]. In addition, other production techniques of ACPs are known [201].

The lifetime of ACPs in aqueous solutions was reported to be a function of the presence of additive molecules and ions, pH, ionic strength and temperature. Thus, ACPs may persist for appreciable periods and retain the amorphous state under some specific experimental conditions [203]. The chemical composition of ACPs strongly depends on the solution pH and the concentrations of mixing solutions. For example, ACPs with Ca/P ratios in the range of 1.18 (precipitated at solution pH = 6.6) to 1.53 (precipitated at solution pH = 11.7) [5,205] and even to 2.5 [4,64,65] were described. It should be noted that unsubstituted ACPs are unstable in aqueous solutions and even when stored dry they tend to transform into more crystalline calcium orthophosphates, such as poorly crystalline CDHA. The presence of poly(ethylene glycol) [206], ions of pyrophosphate, carbonate and/or magnesium in solutions during the crystallization promotes formation of ACPs and slows down their further transformation, while the presence of fluoride has the opposite effect [4-6,81,207]. In general, low temperatures ACPs heated to $\sim 550^\circ\text{C}$ (so that all volatiles have already escaped) remain amorphous, but further heating above $\sim 650^\circ\text{C}$ causes their transformation into crystalline calcium orthophosphates, such as α - or β -TCP, HA, mixtures thereof, depending on the Ca/P ratio of the ACP heated.

High-temperature ACPs might be prepared using high energy processing at elevated temperatures [201]. This method is based on a rapid quenching of melted calcium orthophosphates occurring, e.g., during plasma spraying of HA [87,208,209]. A plasma jet, possessing very high temperatures ($\sim 5000 - \sim 20000^\circ\text{C}$), partly decomposes HA. That results in formation of a complicated mixture of products, some of which would be ACPs. Obviously, all types of high-temperature

Compound	Space group	Unit cell parameters	Z ^[a]	Density, g cm ⁻³
MCPM	triclinic $P\bar{1}$	$a = 5.6261(5)$, $b = 11.889(2)$, $c = 6.4731(8)$ Å, $\alpha = 98.633(6)^\circ$, $\beta = 118.262(6)^\circ$, $\gamma = 83.344(6)^\circ$	2	2.23
MCPA	triclinic $P\bar{1}$	$a = 7.5577(5)$, $b = 8.2531(6)$, $c = 5.5504(3)$ Å, $\alpha = 109.87(1)^\circ$, $\beta = 93.68(1)^\circ$, $\gamma = 109.15(1)^\circ$	2	2.58
DCPD	monoclinic Ia	$a = 5.812(2)$, $b = 15.180(3)$, $c = 6.239(2)$ Å, $\beta = 116.42(3)^\circ$	4	2.32
DCPA	triclinic $P\bar{1}$	$a = 6.910(1)$, $b = 6.627(2)$, $c = 6.998(2)$ Å, $\alpha = 96.34(2)^\circ$, $\beta = 103.82(2)^\circ$, $\gamma = 88.33(2)^\circ$	4	2.89
OCP	triclinic $P\bar{1}$	$a = 19.692(4)$, $b = 9.523(2)$, $c = 6.835(2)$ Å, $\alpha = 90.15(2)^\circ$, $\beta = 92.54(2)^\circ$, $\gamma = 108.65(1)^\circ$	1	2.61
α -TCP	monoclinic $P2_1/a$	$a = 12.887(2)$, $b = 27.280(4)$, $c = 15.219(2)$ Å, $\beta = 126.20(1)^\circ$	24	2.86
β -TCP	rhombohedral $R3cH$	$a = b = 10.4183(5)$, $c = 37.3464(23)$ Å, $\gamma = 120^\circ$	21 ^[b]	3.08
HA	monoclinic $P2_1/b$ or hexagonal $P6_3/m$	$a = 9.84214(8)$, $b = 2a$, $c = 6.8814(7)$ Å, $\gamma = 120^\circ$ (monoclinic) $a = b = 9.4302(5)$, $c = 6.8911(2)$ Å, $\gamma = 120^\circ$ (hexagonal)	4 2	3.16
FA	hexagonal $P6_3/m$	$a = b = 9.367$, $c = 6.884$ Å, $\gamma = 120^\circ$	2	3.20
OA	hexagonal $P\bar{6}$	$a = b = 9.432$, $c = 6.881$ Å, $\alpha = 90.3^\circ$, $\beta = 90.0^\circ$, $\gamma = 119.9^\circ$	1	~ 3.2
TTCP	monoclinic $P2_1$	$a = 7.023(1)$, $b = 11.986(4)$, $c = 9.473(2)$ Å, $\beta = 90.90(1)^\circ$	4	3.05

^[a] Number of formula units per unit cell.

^[b] Per the hexagonal unit cell.

Table 3: Crystallographic data of calcium orthophosphates [5,88,89].

ACPs are definitively anhydrous contrary to the precipitated ACPs. Unfortunately, no adequate chemical formula is available to describe the high-temperature ACPs.

In general, as all amorphous compounds are characterized by a lack of long-range order, it is problematic to discuss the structure of ACPs (they are X-ray amorphous). Concerning a short-range order (SRO) in ACPs, it exists, just due to the nature of chemical bonds. Unfortunately, in many cases, the SRO in ACPs is uncertain either, because it depends on many variables, such as Ca/P ratio, preparation conditions, storage, admixtures, *etc.* Infrared spectra of ACPs show broad featureless phosphate absorption bands. Electron microscopy of freshly precipitated ACPs usually shows featureless nearly spherical particles with diameters in the range of 20 to 200 nm. However, there is a questionable opinion that ACPs might have an apatitic structure but with a crystal size so small, that they are X-ray amorphous. This is supported by X-ray absorption spectroscopic data (EXAFS) on biogenic and synthetic samples [210-213]. On the other hand, it was proposed that the basic structural unit of the precipitated ACPs is a 9.5 Å diameter, roughly spherical cluster of ions with the composition of $\text{Ca}_9(\text{PO}_4)_6$ Figure 7 [5,205,214,215]. These clusters were found experimentally as first nuclei during the crystallization of CDHA and a model was developed to describe the crystallization of HA as a step-wise assembly of these units [216] (see section 5.10. HA (or HAp, or OHAp) below). Biologically, ion-substituted ACPs (always containing ions of Na, Mg, carbonate and pyrophosphate) are found in soft-tissue pathological calcifications (*e.g.*, heart valve calcifications of uremic patients) [4,64-66].

In medicine, ACPs are used in self-setting calcium orthophosphate formulations [104]. Bioactive composites of ACPs with polymers have properties suitable for use in dentistry [107,201] and surgery [201,217]. Due to a reasonable solubility and physiological pH of aqueous solutions, ACPs appeared to be consumable by some microorganisms and, due to this reason, it might be added as a mineral supplement to culture media. Non-biomedical applications of ACPs comprise their using as a component for mordants and ackey. In food industry, ACPs are used for syrup clearing. Occasionally, they might be used as inert

filler in pelleted drugs. In addition, ACPs are used in glass and pottery production and as a raw material for production of some organic phosphates. To get further details on ACPs, the readers are referred to special reviews [201,215,218].

CDHA (or Ca-def HA)

Calcium-deficient hydroxyapatite ($\text{Ca}_{10-x}(\text{HPO}_4)_x(\text{PO}_4)_{4-6-x}(\text{OH})_{2-x}$ ($0 < x < 1$)) became known since the earliest experiments on establishing the chemical composition of bones performed in 1770-s [1,2]. However, the initial appropriate term “subphosphate of lime” appeared by 1819 [219]. Other chemical formulae such as $\text{Ca}_{10-x}(\text{HPO}_4)_x(\text{PO}_4)_{4-6-x}(\text{OH})_2$ ($0 < x < 2$), $\text{Ca}_{10-x-y}(\text{HPO}_4)_x(\text{PO}_4)_{4-6-x}(\text{OH})_{2-2x-2y}$ ($0 < x < 2$ and $y < x/2$), $\text{Ca}_{10-x}(\text{HPO}_4)_x(\text{PO}_4)_{4-6-x}(\text{OH})_{2-x}(\text{H}_2\text{O})_x$ ($0 < x < 1$), $\text{Ca}_{9-x}(\text{HPO}_4)_{1+2x}(\text{PO}_4)_{5-2x}(\text{OH})$, *etc.* were also proposed to describe its variable composition [5]. As seen from these formulae, Ca-deficiency is always coupled with both OH-deficiency and protonation of some PO_4 groups with simultaneous formation of the ionic vacancies in the crystal structure [220]. In addition, CDHA often contains tightly bound water molecules, which might occupy some of these ionic vacancies. For example, there is an approach describing a lack of the hydroxide vacancies in CDHA: to

Figure 7: A model of ACP structure. Reprinted from Ref. [214] with permission.

perform the necessary charge compensation of the missing Ca^{2+} ions, a portion of OH^- anions is substituted by neutral water molecules [221]. This water is removed by vacuum drying at elevated temperature. Concerning possible vacancies of orthophosphate ions, nothing is known about their presence in CDHA. It is just considered that a portion of PO_4^{3-} ions is either protonated (as HPO_4^{2-}) or substituted by other ions (e.g., CO_3^{2-}) [222]. Since CDHA does not have any definite chemical composition, the IUPAC nomenclature is not applicable to describe it.

CDHA can be easily prepared by simultaneous addition of Ca- and PO_4 -containing solutions in the proportions to get Ca/P ratio within 1.50 – 1.67 into boiling water followed by boiling the suspension for several hours (an ageing stage). That is why, in literature it might be called as “precipitated HA (PHA)” [223,224]. Besides, it might be prepared by hydrolysis of α -TCP [194-196]. Other preparation techniques of CDHA are known as well [225-228]. During ageing, initially precipitated ACPs are restructured and transformed into CDHA. Therefore, there are many similarities in the structure, properties and application between the precipitated in alkaline solutions ($\text{pH} > 8$) ACPs and CDHA. Some data indicated on a presence of intermediate phases during further hydrolysis of CDHA to a more stable HA-like phase [229]. In general, CDHA crystals are poorly crystalline and of submicron dimensions. They have a very large specific surface area, typically 25-100 m^2/g . On heating above $\sim 700^\circ\text{C}$, CDHA with Ca/P = 1.5 converts to β -TCP and that with $1.5 < \text{Ca/P} < 1.67$ converts into a biphasic composite of HA and β -TCP (see section 5.14. Biphasic, triphasic and multiphasic calcium orthophosphate formulations below) [230]. A solid-state transformation mechanism of CDHA into HA + β -TCP biocomposite was proposed [231,232].

The variability in Ca/P molar ratio of CDHA has been explained through different models: surface adsorption, lattice substitution and intercrystalline mixtures of HA and OCP [233]. Due to a lack of stoichiometry, CDHA is usually doped by other ions [63]. The doping extent depends on the counter-ions of the chemicals used for CDHA preparation. Direct determinations of the CDHA structures are still missing and the unit cell parameters remain uncertain. However, unlike that in ACPs (see section 3.8. ACP above), a long-range order exists in CDHA. Namely, the following lattice parameters were reported for CDHA with Ca/P = 1.5: $a = 9.4418(20) \text{ \AA}$ and $c = 6.8745(17) \text{ \AA}$ [228].

A systematic study of defect constellations in CDHA is available in literature [221]. As a first approximation, CDHA may be considered as HA with some ions missing (ionic vacancies) [234]. The more amount of Ca is deficient, the more disorder, imperfections and vacancies are in the CDHA structure [235]. Furthermore, a direct correlation between the Ca-deficiency and the mechanical properties of the crystals was found: calcium deficiency lead to an 80% reduction in the hardness and elastic modulus and at least a 75% reduction in toughness in plate-shaped HA crystals [236]. Theoretical investigations of the defect formation mechanism relevant to non-stoichiometry in CDHA are available elsewhere [237].

Unsubstituted CDHA (i.e., that containing ions of Ca^{2+} , PO_4^{3-} , HPO_4^{2-} and OH^- only) does not exist in biological systems. However, the ion substituted CDHA: Na^+ , K^+ , Mg^{2+} , Sr^{2+} for Ca^{2+} ; CO_3^{2-} for PO_4^{3-} or HPO_4^{2-} ; F^- , Cl^- , CO_3^{2-} for OH^- ; plus some water forms biological apatite – the main inorganic part of animal and human normal and pathological calcifications [4,63,64]. Therefore, CDHA is a very promising compound for industrial manufacturing of artificial bone substitutes [238], including drug delivery applications [239]. Non-biomedical applications of CDHA are similar to those of ACP and HA.

Interestingly that CDHA was found to possess a catalytic activity to produce biogasoline [240].

HA (or HAp, or OHAp)

Hydroxyapatite ($\text{Ca}_5(\text{PO}_4)_3(\text{OH})$), but is usually written as $\text{Ca}_{10}(\text{PO}_4)_6(\text{OH})_2$ to denote that the crystal unit cell comprises two molecules; the IUPAC name is pentacalcium hydroxide tris(orthophosphate)) is the second most stable and least soluble calcium orthophosphate after FA. Apatites were recognized as calcium phosphates by, at least, 1789 [1,2]. Here, it is worth noting that hydroxylapatite would be a more accurate abbreviation expansion of HA (perhaps, hydroxideapatite would be even better because it relates to calcium hydroxide) while by both the medical and material communities HA is usually expanded as hydroxyapatite.

Chemically pure HA crystallizes in the monoclinic space group $P2_1/b$ [241]. However, at temperatures above $\sim 250^\circ\text{C}$, there is a monoclinic to hexagonal phase transition in HA (space group $P6_3/m$) [5,89,205,242,243]. The detailed description of the HA structure was first reported in 1964 [244] and its interpretation in terms of aggregation of $\text{Ca}_3(\text{PO}_4)_2$ clusters, the so-called Posner's clusters, has been widely used since publication of the article by Posner and Betts [204]. In hexagonal HA, the hydroxide ions are more disordered within each row, when compared with the monoclinic form, pointing either upward or downward in the structure. This induces strains that are compensated for by substitutions or ion vacancies. Some impurities, like partial substitution of hydroxide by fluoride or chloride, stabilize the hexagonal structure of HA at ambient temperature. Due to this reason, hexagonal HA is seldom the stoichiometric phase and very rare single crystals of natural HA always exhibit the hexagonal space group. The crystal structure of HA is well described elsewhere [5,88,89], the detailed analysis of the electronic structure, bonding, charge transfer, optical and elastic properties are also available [245-248], while the readers interested in Posner's clusters are referred to other papers [249-251]. A shell model was developed to study the lattice dynamics of HA [252], while a cluster growth model was created to illustrate its growth [216]. Polarization characteristics [253,254] and pyroelectrical properties [255] of HA bioceramics have been investigated. First-principles calculations for the elastic properties of doped HA [256] and vacancy formation in HA [257] were performed. Computer simulations of the structures and properties of HA are well described in feature articles [258,259].

Several techniques might be utilized for HA preparation; they can be divided into solid-state reactions and wet methods [260], which include precipitation, hydrothermal synthesis and hydrolysis of other calcium orthophosphates. However, in all cases, Ca- and PO_4 -containing chemicals must be mixed to get the Ca/P ratio strictly equal to 1.67. Nevertheless, even under the ideal stoichiometric conditions, the precipitates are generally non-stoichiometric, suggesting intermediate formation of precursor phases, such as ACP and CDHA. Usually unsintered HA is poorly crystalline and often non-stoichiometric, resembling the aforementioned CDHA. However, well crystalline HA can be prepared from an aqueous solution [261]. HA with the Ca/P ratio > 1.67 (Ca-rich HA) might be prepared as well [262]. The detailed information on HA synthesis is available elsewhere [263-267]. In addition, there are good reviews on HA solubility, crystal growth and intermediate phases of HA crystallization [268], as well as on HA dissolution [269].

Pure HA never occurs in biological systems. However, due to the chemical similarities to bone and teeth mineral Table 2, HA is widely

used as coatings on orthopedic (e.g., hip joint prosthesis) and dental implants [107,270-274]. HA bioceramics is very popular as well [275-277]. Due to a great similarity to biological apatite, over a long time HA has been used in liquid chromatography of nucleic acids, proteins and other biological compounds [278-282] and for drug delivery purposes [283-287]. Also, HA is added to some brands of toothpaste as a gentle polishing agent instead of calcium carbonate [288,289]. Non-biomedical applications of HA include its using as an environmentally friendly filler for elastomers [290], a sorbent of poisonous chemical elements [291,292] and a carrier for various catalysts [293-295]. Furthermore, HA by itself might act as a catalyst for formaldehyde combustion at room temperature [296].

FA (or FAp)

Fluorapatite ($\text{Ca}_5(\text{PO}_4)_3\text{F}$, but is usually written as $\text{Ca}_{10}(\text{PO}_4)_6\text{F}_2$ to denote that the crystal unit cell comprises two molecules; the IUPAC name is pentacalcium fluoride tris(orthophosphate)) is the only ion-substituted calcium orthophosphate, considered in this review. Since the presence of 2.5% of fluorides in natural apatites was established by 1798 [297], this date might be accepted as the earliest hearing of FA.

FA is the hardest (5 according to the Mohs' scale of mineral hardness), most stable and least soluble compound among all calcium orthophosphates Table 1. Perhaps, such "extreme" properties of FA are related to the specific position of F^- ions in the center of $\text{Ca}(2)$ triangles of the crystal structure [5,88]. Due to its properties, FA is the only calcium orthophosphate that naturally forms large deposits suitable for the commercial use [12-14] (see also Figure 2. Preparation techniques of the chemically pure FA are similar to the aforementioned ones for HA but the synthesis must be performed in presence of the necessary amount of F^- ions (usually, NaF or NH_4F is added). Under some special crystallization conditions (e.g., in presence of gelatin or citric acid), FA might form unusual dumbbell-like fractal morphology that finally are closed to spheres Figure 8 [298,299]. In addition, FA is the only calcium orthophosphate, which melts without decomposition (the melting point is $\sim 1650^\circ\text{C}$); therefore, big (up to 30 cm long and, for shorter lengths, up to 1.9 cm wide) single FA crystals might be grown from FA melts [300,301]. Similar to that for HA (see CDHA), an existence of CaF_2 -deficient FA was also detected but for the crystals grown from the FA melt only [300,302]. In addition, FA with an excess of CaF_2 was prepared [303]. A hierarchical structure for FA was proposed [304]. The crystal structure of FA for the first time was studied in 1930 [305,306] and is well described elsewhere [5,88,89]. The detailed analysis of the electronic structure, bonding, charge transfer and optical properties is available as well [246]. In addition, there are reviews on FA solubility [268] and the dissolution mechanism [269].

FA easily forms solid solutions with HA with any desired F/OH molar ratio. Such compounds are called fluorhydroxyapatites (FHA) [307-309] or hydroxyfluorapatites (HFA) [310,311] and described with a chemical formula $\text{Ca}_{10}(\text{PO}_4)_6(\text{OH})_{2-x}\text{F}_x$, where $0 < x < 2$. If the F/OH ratio is either uncertain or not important, the chemical formula of FHA and HFA is often written as $\text{Ca}_{10}(\text{PO}_4)_6(\text{F},\text{OH})_2$. The lattice parameters, crystal structure, solubility and other properties of FHA and HFA lay in between of those for the chemically pure FA and HA. Namely, the substitution of F for OH results in a contraction in the a -axis with no significant change in the c -axis dimensions and greater resolution of the IR absorption spectra.

Similar to pure HA, pure FA never occurs in biological systems. Obviously, a lack of the necessary amount of toxic fluorides (the acute toxic dose of fluoride is ~ 5 mg/kg of body weight) in living organisms

is the main reason of this fact (pure FA contains 3.7 % mass. F). Enameloid of shark teeth [11,81,312-316] and some exoskeletons of mollusks [317] seem to be the only exclusions because they contain substantial amounts of fluoride, with is presented there as ion-substituted, non-stoichiometric FHA or HFA. Among all normal calcified tissues of humans, the highest concentration of fluorides is found in dentine and cementum, while the lowest – in dental enamel Table 2. Nevertheless, one should stress that the amount of fluorides on the very surface of dental enamel might be substantially increased by using fluoride-containing toothpastes and mouthwashes [318,319]. However, in no case, the total amount of fluorides is enough to form FA.

Contrary to the initial expectations [320], chemically pure FA is not used for grafting purposes. Presumably, this is due to the lowest solubility, good chemical stability of FA and toxicity of high amounts of fluorides. However, attempts to test FA-containing formulations [321-325], ion-substituted FA [326,327], FHA [328,329] and porous FA bioceramics [330] are kept performing. The effect of fluoride contents in FHA on both osteoblast behavior [331,332] and leukemia cells proliferation [333] has been described. Non-biomedical applications of FA include fluorescent light tubes [334], laser materials [335,336] (in both cases dopants are necessary), as well as catalysts [337].

OA (or OAp, or OXA)

Oxyapatite ($\text{Ca}_{10}(\text{PO}_4)_6\text{O}$; the IUPAC name is decacalcium oxide hexakis(phosphate), mineral voelckerite) is the least stable and, therefore, the least known calcium orthophosphate, which, probably, does not exist at all. Nevertheless, a name "voelckerite" was introduced in 1912 by A.F. Rogers (1887 – 1957) for a hypothetical mineral with the chemical composition of $3\text{Ca}_3(\text{PO}_4)_2 + \text{CaO}$ [338,339], to honor an English agricultural chemist John Christopher Augustus Voelcker (1822 – 1884), who, in 1883, first showed an apparent halogen deficiency in some natural apatites [340]. Therefore, 1883 might be accepted as the earliest hearing of OA.

To the best of my findings, pure OA has never been prepared; therefore, its properties are not well established. Furthermore, still there are serious doubts that pure OA can exist. However, a mixture (or a solid solution?) of OA and HA (oxy-HA) might be prepared by a partial dehydroxylation of HA at temperatures exceeding $\sim 900^\circ\text{C}$ (e.g., during plasma-spray of HA) only in the absence of water vapor [341-345]. It also might be crystallized in glass-ceramics [346]. OA is

Figure 8: A biomimetically grown aggregate of FA that was crystallized in a gelatin matrix. Its shape can be explained and simulated by a fractal growth mechanism. Scale bar: 10 μm . Reprinted from Ref. [298] with permission.

very unstable and has no stability field in aqueous conditions [347]. Namely, data are available, that oxy-HA containing less than 25% HA (*i.e.*, almost OA) during further dehydration decomposes to a mixture of α -TCP and TTCP. In addition, OA is very reactive and transforms to HA in contact with water vapor [341]. Computer modeling techniques have been employed to qualitatively and quantitatively investigate the dehydration of HA to OA [348]. OA has the hexagonal space group symmetry $P6$ (174) of cesanite type [88], while the space group symmetry for partially dehydrated HA was found to change from hexagonal $P63/m$ to triclinic $P1$ when more than *ca.* 35% of the structurally bound water had been removed [343]. On the *c*-axis, pure OA should have a divalent ion O^{2-} coupled with a vacancy instead of two neighboring monovalent OH^- ions.

Due to the aforementioned problems with OA preparation, it cannot be found in biological systems. In addition, no information on the biomedical applications of OA is available either. Plasma-sprayed coatings of calcium orthophosphates, in which OA might be present as an admixture phase, seem to be the only exception [274].

TTCP (or TetCP)

Tetracalcium phosphate or tetracalcium diorthophosphate monoxide ($Ca_4(PO_4)_2O$; the IUPAC name is tetracalcium oxide bis(orthophosphate); the mineral hilgenstockite) is the most basic calcium orthophosphate, however, its solubility in water is higher than that of HA Table 1. TTCP has been known since 1883 [349], while the mineral hilgenstockite was named to honor a German metallurgist Gustav Hilgenstock (1844 – 1913), who first discovered it in Thomas slag from blast furnaces [349,350]. Its major industrial importance stems from the fact that it is formed by the reactions between orthophosphates and lime in the manufacture of iron, and through these reactions, TTCP has a significant role in controlling the properties of the metal.

TTCP cannot be precipitated from aqueous solutions. It can be prepared only under the anhydrous conditions by solid-state reactions at temperatures above $\sim 1300^\circ\text{C}$, *e.g.*, by heating homogenized equimolar quantities of DCPA and $CaCO_3$ in dry air, or in a flow of dry nitrogen [5,205,351]. These reactions should be carried out in a dry atmosphere, in vacuum or with rapid cooling (to prevent uptake of water and formation of HA). Easily DCPA might be replaced by ammonium orthophosphates [352,353], while calcium carbonate might be replaced by calcium acetate [353]; however, in all cases, Ca/P ratio must be equal to 2.00. Furthermore, TTCP often appears as an unwanted by-product in plasma-sprayed HA coatings, where it is formed as a result of the thermal decomposition of HA to a mixture of high-temperature phases of α -TCP, TTCP and CaO [354]. TTCP is metastable: in both wet environment and aqueous solutions it slowly hydrolyses to HA and calcium hydroxide [5,205,355]. Consequently, TTCP is never found in biological calcifications. In medicine, TTCP is widely used for preparation of various self-setting calcium orthophosphate formulations [104,354]; however, to the best of my knowledge, there is no commercial bone-substituting product consisting solely of TTCP. For the comprehensive information on TTCP, the readers are referred to a special review [354], while the spectra [356] and solubility [173] of TTCP are well described elsewhere.

To conclude the description of the individual calcium orthophosphates, one should mention on an interesting opinion [89,142], that all calcium orthophosphates listed in Table 1 might be classified into three major structural types. They comprise: (i) the apatite type, $Ca_{10}(PO_4)_6X_2$, which includes HA, FA, OA, CDHA, OCP

and TTCP; (ii) the glaserite type, named after the mineral glaserite, $K_3Na(SO_4)_2$, which includes all polymorphs of TCP and, perhaps, ACP; (iii) the $Ca-PO_4$ sheet-containing compounds, which include DCPD, DCPA, MCPM and MCPA. According to the authors, a closer examination of the structures revealed that all available calcium orthophosphates could be included into distorted glaserite type structures, but with varying degrees of distortion [89,142].

Biphasic, triphasic and multiphasic calcium orthophosphate formulations

Calcium orthophosphates might form biphasic, triphasic and multiphasic (polyphasic) formulations, in which the individual components cannot be separated from each other. Presumably, the individual phases of such compositions are homogeneously “mixed” at a far submicron level ($< 0.1 \mu\text{m}$) and strongly integrated with each other. Nevertheless, the presence of all individual phases is easily seen by X-ray diffraction technique [230].

The usual way to prepare multiphasic formulations consists of sintering non-stoichiometric compounds, such as ACP and CDHA, at temperatures above $\sim 700^\circ\text{C}$. Furthermore, a thermal decomposition of the stoichiometric calcium orthophosphates at temperatures above $\sim 1300^\circ\text{C}$ might be used as well; however, this approach often results in formation of complicated mixtures of various products including admixtures of CaO, calcium pyrophosphates, *etc.* [230]. Namely, transformation of HA into polyphasic calcium orthophosphates by annealing in a vacuum occurs as this: the outer part of HA is transformed into α -TCP and TTCP, while the α -TCP phase of the surface further transforms into CaO. Besides, in the boundary phase, HA is transformed into TTCP [357].

Historically, Nery and Lynch with co-workers first used the term biphasic calcium phosphate (BCP) in 1986 to describe a bioceramic, that consisted of a mixture of HA and β -TCP [358]. Based on the results of X-ray diffraction analysis, these authors found that the “tricalcium phosphate” preparation material used in their early publication [359] was in fact a mixture of $\sim 20\%$ HA and $\sim 80\%$ β -TCP. Currently, only biphasic and triphasic calcium orthophosphate formulations are known; perhaps, more complicated formulations will be manufactured in future. Furthermore, nowadays, multiphasic and/or polyphasic compositions consisting of high-temperature phases of calcium orthophosphates, such as α -TCP, β -TCP, HA and, perhaps, high-temperature ACP, OA and TTCP, are known only. No precise information on multiphasic compositions, containing MCPM, MCPA, DCPD, DCPA, low-temperature ACP, OCP and CDHA has been found in literature [230]. Perhaps, such formulations will be produced in future.

All BCP formulations might be subdivided into two major groups: those consisting of calcium orthophosphates having either the same (*e.g.*, α -TCP and β -TCP) or different (*e.g.*, β -TCP and HA) molar Ca/P ratios. Among all known BCP formulations, BCP consisting of HA and β -TCP is both the most known and the best investigated [230]. In 1986, LeGeros in USA and Daculsi in France initiated the basic studies on preparation of this type of BCP and its *in vitro* properties. This material is soluble and gradually dissolves in the body, seeding new bone formation as it releases calcium and orthophosphate ions into the biological medium. Presently, commercial BCP products of different or similar HA/ β -TCP ratios are manufactured in many parts of the world as bone-graft or bone substitute materials for orthopaedic and dental applications under various trademarks and several manufacturers [230]. A similar combination of α -TCP with HA forms BCP as well

[191,360-362].

Recently the concept of BCP has been extended by preparation and characterization of biphasic TCP (BTCP), consisting of α -TCP and β -TCP phases [363-365]. It is usually prepared by heating ACP precursors [363-365], in which the α -TCP/ β -TCP ratio can be controlled by aging time and pH value during synthesis of the amorphous precursor [364]. Furthermore, triphasic formulations, consisting of HA, α -TCP and β -TCP [366] or HA, α -TCP and TTCP [357] have been prepared [230].

It is important to recognize, that the major biomedical properties (such as bioactivity, bioresorbability, osteoconductivity and osteoinductivity) of the multiphasic formulations might be adjusted by changing the ratios among the phases. When compared to both α - and β -TCP, HA is a more stable phase under the physiological conditions, as it has a lower solubility (Table 1) and, thus, slower resorption kinetics. Therefore, due to a higher biodegradability of the α - or β -TCP component, the reactivity of BCP increases with the TCP/HA ratio increasing. Thus, *in vivo* bioresorbability of BCP can be adjusted through the phase composition. Similar conclusions are also valid for both the biphasic TCP (in which α -TCP is a more soluble phase) and the triphasic (HA, α -TCP and β -TCP) formulations. Further details on this subject might be found in a topical review [230].

Ion-substituted calcium orthophosphates

Finally, one should very briefly mention on existence of carbonateapatite [367-369], chlorapatite [370-372], as well as on a great number of calcium orthophosphates with various ionic substitutions [23,63,373,374]. In principle, any ion in calcium orthophosphates might be substituted by other ion(s). Usually, the ion-substituted calcium orthophosphates are of a non-stoichiometric nature with just a partial ionic substitution and there are too many of them to be described here. Currently, this is a hot investigation topic; therefore, the readers are referred to the special literature [23,63,373,374]. In addition, there is a very good review, in which the structures of more than 75 chemically different apatites have been discussed [88].

To conclude this topic, it is interesting to note, that chemical elements not found in natural bones can be intentionally incorporated into calcium orthophosphate biomaterials to get special properties. For example, addition of Ag^+ [375-377], Zn^{2+} [377,378] and Cu^{2+} [377-379] has been used for imparting antimicrobial effect, while radioactive isotopes of ^{90}Y [380], ^{153}Sm [381-383] and ^{186}Re [381] have been incorporated into HA bioceramics and injected into knee joints to treat rheumatoid joint synovitis [380,381,383]. More to the point, apatites were found to incorporate individual molecules, such as water, oxygen and carbon dioxide [63].

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