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Calcium orthophosphates in medicine: from ceramics to calcium phosphate cements

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Summary[1]

Calcium phosphate (CaP) compounds are becoming of increasingly great importance in the field of biomaterials and, in particular, as bone substitutes. Recent discoveries have accelerated this process, but have simultaneously rendered the field more complicated for the everyday user. Subtle differences in composition and structure of CaP compounds may have a profound effect on their in vivo behaviour. Therefore, the main goal of this article is to provide a simple, but comprehensive presentation of CaP compounds. Reference is made to the most important commercial products.

Keywords: calcium phosphate, cement, bone, substitute, composition
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1. Introduction

Calcium orthophosphate (CaP) compounds have been studied as bone repair materials for the last 80 years. The first *in vivo* use of tricalcium phosphate (TCP) was performed by Albee and Morrison in 1920 [1]. In the following years, various CaP particles were injected in animals to test their effect on the healing of non-unions [2]. In 1951, Ray [3] implanted hydroxyapatite (HA) in rats and guinea pigs. Despite these early experiments, it was only in the 1970's that CaPs – mostly HA – were synthesized, characterized, and applied [4-9]. CaPs were prepared by sintering (thermal consolidation) as granules or blocks, porous or dense. Since then, the interest in these materials has increased. In the mid 1980's, Brown and Chow [10] discovered the first hydraulic CaP cement, i.e. a mixture of CaP powders and water that hardened with time at room temperature. This discovery opened up new perspectives for the use of CaP in the treatment of bone defects.

Despite the increasing use of CaP products in medicine, there are still very few articles in the medical literature describing CaP compounds other than the traditionally-used CaP, i.e. β-tricalcium phosphate (β-TCP) and HA. The goal of this article is to try to summarize the new CaP compounds and compare them with β-TCP and HA. In more detail, the purpose of this article is fourfold: (i) present a list of different CaPs and discuss their physical, chemical and biological differences; (ii) present calcium phosphate cements (CPC), (iii) discuss the degradability of CaP, and finally (iv) present future developments in the field.

2. Calcium orthophosphates (CaP)

With the exception of calcium pyrophosphate ($Ca_2P_2O_7$), most calcium phosphates previously used *in vivo* have been calcium orthophosphates (CaP), i.e. they contain the orthophosphate group PO_4^{3-}. Due to their importance in medicine, agriculture (fertilizer), pharmacy (tabletting, toothpaste), chromatography (columns), and the food industry (additive), for example, CaPs have been intensively studied. Van Wazer [11], Kanazawa [12], and more recently Elliot [13] have provided a comprehensive review of the topic, in particular of HA.

Two different categories of CaP should be distinguished: (i) CaP obtained by precipitation from an

[1] Abstracts in German, French, Italian, Spanish, Japanese and Russian are printed at the end of this supplement.

Table 1: Main calcium phosphate compounds. The first 6 compounds precipitate at room temperature in aqueous systems. The last 6 compounds are obtained by thermal decomposition or thermal synthesis.

Name	Formula	Ca/P	Mineral	Symbol
Monocalcium phosphate monohydrate	$Ca(H_2PO_4)_2 \cdot H_2O$	0.50	–	MCPM
Dicalcium phosphate	$CaHPO_4$	1.00	Monetite	DCP
Dicalcium phosphate dihydrate	$CaHPO_4 \cdot 2H_2O$	1.00	Brushite	DCPD
Octocalcium phosphate	$Ca_8H_2(PO_4)_6 \cdot 5H_2O$	1.33	–	OCP
Precipitated hydroxyapatite ("tricalcium phosphate")	$Ca_{10-x}(HPO_4)_x(PO_4)_{6-x}(OH)_{2-x}$	1.50–1.67	–	PHA
Amorphous calcium phosphate	$Ca_3(PO_4)_2 \cdot nH_2O$			
n = 3-4.5; 15-20% H_2O	1.50	-	ACP	
Monocalcium phosphate	$Ca(H_2PO_4)_2$	0.50	–	MCP
α-Tricalcium phosphate	α-$Ca_3(PO_4)_2$	1.50	–	α-TCP
β-Tricalcium phosphate	β-$Ca_3(PO_4)_2$	1.50	–	β-TCP
Sintered hydroxyapatite	$Ca_5(PO_4)_3OH$	1.67	Hydroxyapatite	HA
Oxyapatite	$Ca_{10}(PO_4)_6O$	1.67	–	OXA
Tetracalcium phosphate	$Ca_4(PO_4)_2O$	2.00	Hilgenstockite	TetCP

aqueous solution at or around room temperature (low-temperature CaP), and (ii) CaP obtained by a thermal reaction (high-temperature CaP). All CPCs (e.g. α-BSM, Bonesource, Norian SRS) belong to the first category, whereas most other CaP products (e.g. chronOS, Endobon, Pro Osteon, Triosite) belong to the second category (see below).

The most important property of CaP is probably its solubility in water because the *in vivo* behavior of CaPs can be predicted to a large extent by their solubility [14]. If the solubility of a CaP, e.g. HA, is less than the mineral part of bone, it degrades extremely slowly if at all. If the solubility of a CaP is greater than that of the mineral part of bone, it is degraded. Therefore, using the different solubility isotherms of CaP (Fig. 1, [15]), the *in vivo* degradation rate of CaP can be predicted to be in the order of (at pH 7.0):

MCPM > TetCP ≈ α-TCP > DCPD > DCP > OCP > β-TCP > PHA > HA

Even though all parameters except the composition were kept constant, this order was not always observed experimentally: the surface of a highly-soluble CaP is reactive and may become covered with a poorly soluble CaP, hence reducing its degradation rate [16]. A good review of the degradability of CaP was written by de Groot [17].

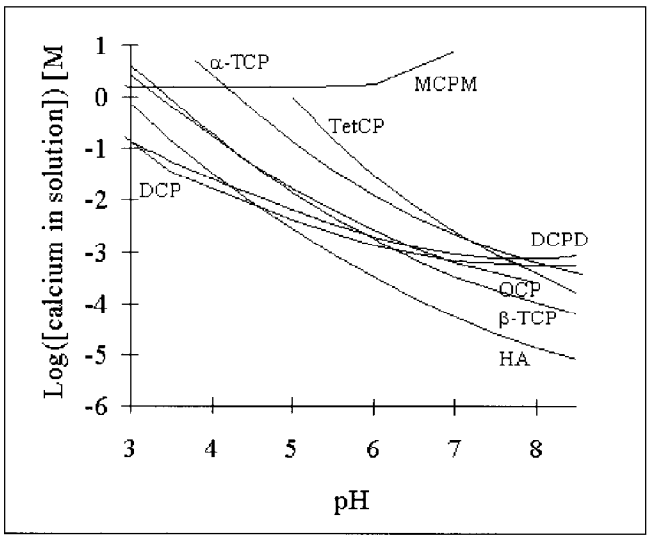

Fig. 1: Solubility isotherms of several CaP in water. The solubility is expressed in the total amount of calcium ions in solution.

In this article, we distinguish between precipitated hydroxyapatite (PHA) and hydroxyapatite (HA). We define PHA as a hydroxyapatite obtained by precipitation in an aqueous solution. PHA is normally poorly-crystalline, can have a molar ratio Ca:P between 1.50 and 1.67 and resembles the mineral part of bone. We define HA as a hydroxyapatite obtained by thermal treatment, typically above 800°C. Due to the thermal treatment, HA is crystalline, stoichiometric and less soluble than the mineral part of bone (see below).

2.1. Low-temperature CaP

Low-temperature CaPs have traditionally been used not as bone substitute, but to synthesize high-temperature CaPs. For example, β-TCP can be obtained by calcination at T>800 °C of equimolar mixtures of DCPD and PHA (Ca:P ratio = 1.67). The discovery of CPC has led to a much wider use of low-temperature CaPs in medicine. Low-temperature CaPs are included in the composition of CPC. Moreover, the end-product of the setting reaction of CPC is always a low-temperature CaP. The most common low-temperature CaPs are DCPD,

OCP and PHA. However, a few other calcium phosphates can be obtained. Most low-temperature CaPs are present in human tissues [18].

Monocalcium phosphate monohydrate (MCPM; $Ca(H_2PO_4)_2{\cdot}H_2O$) is the most acidic CaP and the most soluble CaP at almost all pH values (Fig. 1). Due to its acidity and solubility, MCPM is not biocompatible and thus cannot be used alone as a bone substitute. However, it can be used in combination with basic CaP compounds, such as α-TCP (Norian SRS) [19] or β-TCP (brushite cements) [20].

Dicalcium phosphate (DCP; $CaHPO_4$) powder has been tested *in vivo* [2,4] and has proven to be biocompatible and biodegradable. DCP has been reported to be present in fracture callus [21] and possibly in bone [22]. Even though DCP is the most stable CaP at low pH, DCP results normally from the recrystallization of DCPD [23], which precipitates faster than DCP. The conversion is faster in water and at higher temperature and acidity [24]. DCP is also a constituent of CPC, e.g. Bonesource [25-26] and Biocement D [27].

Dicalcium phosphate dihydrate (DCPD; $CaHPO_4{\cdot}2H_2O$) is the CaP that can be the most easily synthesized. DCPD has been detected in fracture callus [21], bone [22] and kidney stones [28-29]. It is also considered sometimes as a precursor of HA in bone [30-31]. DCPD is biocompatible, biodegradable and osteoconductive. DCPD is metastable and can be converted into DCP (pH < 6), OCP (pH ≈ 6-7) or PHA (pH > ~7). *In vivo* DCPD is converted into PHA [32] or biodegraded and replaced by bone [33]. Inflammatory reactions can occur when a large amount of DCPD is transformed *in vivo* in PHA. Through this reaction, a large amount of acid is released:

$$5CaHPO_4{\cdot}2H_2O \rightarrow Ca_5(PO_4)_3OH + 2H_3PO_4 + 9H_2O \quad (1)$$

Interestingly, DCPD has almost the same composition and crystallographic structure as calcium sulphate dihydrate (CSD; $CaSO_4{\cdot}2H_2O$), the hydrated form of plaster of Paris. The only difference is the replacement of HPO_4^{2-} with SO_4^{2-}. Both ions have almost the same size and the same molecular weight. However, DCPD is about 10 times less soluble than CSD at neutral pH. DCPD is the end-product of brushite CPC.

Octocalcium phosphate (OCP; $Ca_8H_2(PO_4)_6{\cdot}5H_2O$) appears to be a precursor in the formation of apatitic calcium phosphates in teeth, bones and other biominerals [13,34]. OCP is also biocompatible, biodegradable and osteoconductive. Attempts to obtain OCP by a cementious reaction have failed so far. One reason is that OCP crystallizes very slowly. Another reason is that OCP is metastable and often occurs as a transient intermediate in the precipitation of the thermodynamically more stable PHA.

Precipitated hydroxyapatite (PHA; $Ca_{10-x}(HPO_4)_x(PO_4)_{6-x}(OH)_{2-x}$) chemistry is very complex, because precipitated hydroxyapatite can have a Ca:P molar ratio from 1.50 to 1.67 [35], and sometimes even outside this range [19]. PHA with a Ca:P molar ratio of 1.50 is often called calcium-deficient hydroxyapatite (CDHA) or tricalcium phosphate (TCP). The latter name has led to confusion with β-TCP, which has almost the same chemical composition, but a different crystalline structure. PHA is obtained by precipitation in an aqueous solution above a pH of 7. PHA crystals are normally poorly crystalline and of submicron dimensions. PHA has a very large specific surface area, typically 25-100 m^2/g. PHA is thus very similar to the apatite present in bone. The main difference is the absence of impurities in the structure, mainly carbonate and magnesium ions. The solubility of stoichiometric PHA (Ca:P 1.67) has been investigated by many authors. Depending on the method of preparation, there was up to 20% difference in solubility [36]. These differences could be due to various degrees of stoichiometry, crystallinity, and size. The solubility of PHA increases with a decrease of the Ca:P molar ratio, of the crystallinity, and of the crystal size. The solubility of TCP (PHA with a Ca:P molar ratio of 1.50) is estimated to be close to that of β-TCP [36]. PHA decomposes on heating into β-TCP (Ca:P = 1.50), into a mixture of β-TCP and HA (1.67 > Ca:P > 1.50), or into pure HA (Ca:P = 1.67) [12]. The decomposition temperature lies above ~700°C [37-38]. Apart from brushite CPC, all commercial CPC (e.g. Norian SRS, Bonesource, α-BSM, Cementek) have PHA or a carbonated PHA as the main end-product of the setting reaction. The main difference between the cements after the setting reaction lies in the Ca:P molar ratio, in the cement porosity and in the crystallinity of the PHA. Small amounts of PHA are sometimes used in the initial composition of CPC to accelerate the setting reaction.

Amorphous calcium phosphate (ACP; $Ca_3(PO_4)_2 \cdot nH_2O$; n = 3-4.5; 15-20% H_2O) is normally considered to have a Ca:P molar ratio of 1.50 [12]. ACP is very close in composition to PHA, but experts seem to admit that ACP is not an amorphous PHA, but a specific compound [12-13]. The amorphous character of ACP is generally evidenced by the absence of peaks in an x-ray diffraction spectrum. ACP is reported to be more soluble than DCPD [39]. ACP is the main component of one CPC (α-BSM), and is also the end-product of one CPC [40].

2.2. High-temperature CaP

All the traditional CaPs used in medicine are high-temperature CaPs, mostly β-TCP, HA, and β-TCP-HA composites called bicalcium phosphates (BCP) [41]. High-temperature CaP, e.g. α-TCP, β-TCP and TetCP, are used as starting materials for CPC.

Monocalcium phosphate (MCP; $Ca(H_2PO_4)_2$) is obtained either by heating MCPM above 100-110°C, or by precipitation above 100-110°C [42]. MCP is very similar to MCPM. MCP is not biocompatible due to its acidity, but is very soluble (Fig. 1) and can be used in combination with basic CaP to make a CPC. In practice, MCP is hardly used, probably because it is hygroscopic [42].

β-Tricalcium phosphate (β-TCP; β-$Ca_3(PO_4)_2$) can be obtained by a thermal treatment above at least 650°C [42]. Several routes are possible, for example: (i) mixture of an equimolar amount of DCPD and PHA (Ca:P ratio = 1.67) and subsequent calcination; (ii) calcination of PHA (Ca:P ratio 1.50). β-TCP should not be confused with tricalcium phosphate (TCP) which has almost the same chemical composition, but a different crystallographic structure. TCP has an apatite structure and corresponds to a PHA with a Ca:P molar ratio of 1.50. β-TCP has been extensively used as bone substitute, either as granules or as blocks. β-TCP is degradable. Degradation occurs by osteoclastic activity [43]. There are a few products on the market. The most documented β-TCP product is probably chronOS (Mathys, Switzerland). β-TCP is the main component of a brushite CPC (Table 2).

α-Tricalcium phosphate (α-TCP; α-$Ca_3(PO_4)_2$) has exactly the same chemical composition as β-TCP but a different crystallographic structure. This difference makes α-TCP much more soluble than β-TCP (Fig. 1). α-TCP is normally obtained by heating β-TCP above 1125°C [44] or 1166°C [45], and quenching it to prevent the reverse transformation [45]. α-TCP is readily transformed into PHA (Ca:P molar ratio of 1.50) in an aqueous solution. This property is used to make apatite CPC. α-TCP has become the major component of most apatite CPC. α-TCP is biocompatible and more biodegradable than β-TCP. α-TCP bone substitutes are sold as granules, blocks and powders (BioVision, Sankin).

Biphasic calcium phosphate (BCP; β-TCP-HA composite) is a composite β-TCP-HA. It is obtained by calcining PHA (with a molar ratio Ca:P < 1.67) above ~700°C (37-38). BCP is more degradable than HA. The degradation rate increases with an increase of the β-TCP content. Most commercial products, e.g. Triosite (Zimmer, USA) and BCP (Sofamor Danek, France), contain 60% HA and 40% β-TCP.

Hydroxyapatite (HA; $Ca_5(PO_4)_3OH$) is defined here as the high-temperature form of a stoichiometric PHA (at least 700°C). HA is highly crystalline, is the most stable CaP in an aqueous solution (Fig. 1), and is the most biocompatible CaP. At temperatures higher than ~900°C, partial decomposition of HA may take place resulting eventually in oxyapatite (OXA). This reaction takes place only in the absence of water vapour [12,46]. HA, partially dehydrated HA, or OXA decompose above 1300°C into α-tricalcium phosphate (α-TCP) and tetracalcium phosphate (TetCP). The latter reaction occurs faster in the absence of water vapor [47]. Most bone substitutes present on the market are made of HA, for example, Pro Osteon (Interpore Cross, USA), Endobon (Merck, Germany), and Pyrost (Stryker Howmedica, USA). These products should be regarded as non degradable, as their degradation time is counted in decades and not in years.

Oxyapatite (OXA; $Ca_{10}(PO_4)_6O$) is obtained at temperatures higher than ~900°C. It results from the partial decomposition of HA. This reaction takes place only in the absence of water vapor [12,46]. Oxyapatite is still poorly known. One reason lies in the difficulty of detecting this phase [48]. Most HA products sold on the market probably contain some amounts of OXA. However, there is to our knowledge no commercial product consisting solely of pure OXA.

Tetracalcium phosphate (TetCP; $Ca_4(PO_4)_2O$) is obtained by a solid-state reaction at high temperatures (typically 1400°C), usually between equimolar quanti-

Table 2: Main apatite CPC

Cement name	Company	Components	End-product
α-BSM Biobone Embarc	ETEX Merck GmbH Lorenz Surgical	ACP, DCPD	PHA
Norian SRS Norian CRS	Norian (Synthes)	α-TCP, $CaCO_3$, MCPM (19)	CAP*
Bonesource	Leibinger	TetCP, DCP (10)	PHA
Cementek	Teknimed	α-TCP, TetCP, MCPM (92)	PHA
Biocement D	Merck GmbH	α-TCP, DCP, $CaCO_3$, PHA (27)	CAP*
Biopax	Mitsubishi Materials	α-TCP, TetCP, DCPD (93)	PHA
Fracture Grout	Norian (Synthes)	TetCP, $CaCO_3$, H_3PO_4 (61)	PHA

*CAP = carbonato-apatite

ties of DCP and $CaCO_3$ [49]. This reaction should be carried out in a dry atmosphere of vacuum, or with rapid cooling (to prevent uptake of water and formation of HA). TetCP is the most soluble CaP below a pH of ~5 (Fig. 1). It is also the most basic CaP. Since the discovery of CPC by Brown and Chow [10], TetCP has been more intensively studied. TetCP is the main component of several CPCs, such as BoneSource and Cementek (Table 2). TetCP is biocompatible [5] and despite its high solubility poorly biodegradable. However, there is a lack of *in vivo* studies on TetCP. There is to our knowledge no commercial product consisting solely of TetCP.

3. Calcium phosphate cements (CPC)

CPCs were discovered by Brown and Chow in the 1980's [10]. Since then, many compositions have been proposed [39,50-51]. However, despite the large number of formulations, CPC can only have three different end-products: apatite (PHA), brushite (DCPD), and amorphous calcium phosphate (ACP). The only study on ACP [40] shows that the cement is rapidly converted into PHA. Therefore, we can classify all CPC formulations into two categories: (i) apatite CPC and (ii) brushite CPC. Most research efforts have been put into apatite CPC, despite some interesting features of brushite CPC.

CPCs are made of an aqueous solution and of one or several calcium phosphates. Upon mixing, the calcium phosphate(s) dissolves and precipitates into a less soluble CaP. During the precipitation reaction, the CaP crystals grow and become entangled, thus providing a mechanical rigidity to the cement (Fig. 2).

Two types of setting reaction are possible. First, the setting reaction can occur according to an acid-base reaction, i.e. a relatively acidic CaP phase reacts with a relatively basic CaP to produce a relatively neutral CaP. A typical example is the cement of Brown and Chow [10], where TetCP (basic) reacts wit DCP (neutral) to form PHA (slightly basic):

$$Ca_4(PO_4)_2O + CaHPO_4 \rightarrow Ca_5(PO_4)_3OH \quad (2)$$

Another example is the cement of Lemaître [20] where β-TCP (slightly basic) reacts with MCPM (acidic) to form DCPD (neutral).

$$\beta\text{-}Ca_3(PO_4)_2 + Ca(H_2PO_4)_2 \cdot H_2O + 7H_2O \rightarrow 4CaHPO_4 \cdot 2H_2O \quad (3)$$

The second type of setting reaction is when the initial and final CaPs have the same Ca/P molar ratio. Typical examples are ACP and α-TCP which form PHA upon contact with an aqueous solution.

$$3\ Ca_3(PO_4)_2 \cdot nH_2O \rightarrow Ca_9(PO_4)_5(HPO_4)OH + (3n\text{-}1)H_2O \quad (4)$$

$$3\ \beta\text{-}Ca_3(PO_4)_2 + H_2O \rightarrow Ca_9(PO_4)_5(HPO_4)OH \quad (5)$$

Unlike PMMA cements, CPCs do not harden through a polymerization reaction and only a small amount of heat is released. The volume of CPC stays almost constant during the setting reaction. CPCs are fragile materials. The tensile strength is 5 to 20 times lower than the compression strength. Most CPCs have a tensile strength of 1 to 10 MPa, whereas the compression strength varies in the range of 10 to 100 MPa. Therefore, CPCs can only be used in combination with metal implants or in low or non-load bearing applications.

An important requirement for the clinician is the mixing procedure of the CPC. So far, most CPCs are mixed by hand with a mortar and either a pestle or a spatula. To be injected, the cement paste must be transferred into a syringe. Two commercial products are sold with an appropriate mixing device. Norian SRS is sold as a reactant pack containing the powder mixture and the mixing liquid and requires the use of a mixing machine and an injection gun. α-BSM is also a two-component system. The powder is in a soft pouch and the liquid is in a flask. After injecting the liquid into the powder pouch, the cement paste is mixed with the fingers. After approximately 3 minutes, the paste can be injected. This mixing system is very simple, but its simplicity has some drawbacks. As the mixing procedure depends on the user and as the setting time of the cement is temperature dependent, the setting time varies from user to user.

To be injected *in vivo*, the CPC paste must have two features: (i) injectability, and (ii) cohesion. Injectability is the ability of the cement paste to be extruded through a small and long needle (e.g. 2 mm diameter and 10 cm length) without demixing. Demixing occurs when the mixing liquid is too fluid compared to the size of the cement powders, resulting in filter-pressing: the liquid is expelled without the CaP particles. A cement paste with an appropriate cohesion sets in a fluid without disintegrating. This can be achieved by keeping a high viscosity for the CPC paste. Some CPC pastes fulfil these two criteria, e.g. Norian SRS, but other CPCs fulfil only one or even none of these requirements. For example, Bone-

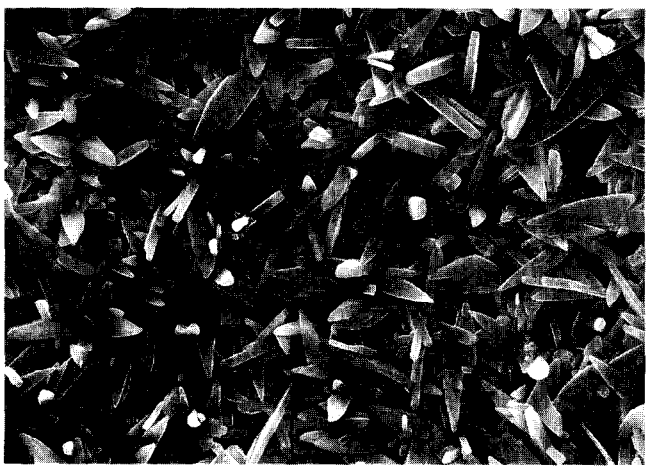

Fig. 2: Typical microstructure of a brushite CPC. Crystal entanglement providing mechanical rigidity to the cement. Micropores are formed by the intercrystalline space.

Source and Cementek are not injectable and blood must be kept away from the implanting site until setting. The decohesion of the cement during mixing may lead to inflammatory reactions [52]. The injectability and cohesion of a cement can be markedly improved by replacing the mixing solution by viscous polymer solutions [53]. Polysaccharides are particularly interesting due to their compatibility and good rheological properties. Only small amounts (a few weight%) are needed to dramatically increase the viscosity of the cement paste. Certain polysaccharides, such as sodium alginate, gel in contact with calcium ions. This property can be used to make putty-like cement pastes [54].

After setting, CPCs can reach mechanical properties comparable to those of CaP blocks with the same porosity. In theory, CPCs can be made with almost any porosity, but most commercial products have a porosity of around 50 vol%. The pore size is close to 1 micrometer. Thus, the pores are too small to allow fast bone ingrowth and the CPC degrades layer-by-layer. This feature is the main drawback of CPC when compared to open-macroporous CaP blocks.

CPCs have been used mostly in maxillofacial surgery [26,55-56] and for the treatment of the distal radius fracture [19]. However, attempts have been made to use CPC for (i) calcaneal fractures [57], (ii) hip fractures [58-59], (iii) the augmentation of osteoporotic vertebral bodies [60], (iv) tibial plateau fractures [61], (v) the restoration of pedicle screw fixation [62], (vi) the reinforcement of thoracolumbar burst fractures [63], and (vii) the reinforcement of cancellous bone screws [64].

3.1. Apatite CPC

Since the invention of CPC [10], numerous formulations have been proposed. Some commercial formulations of apatite CPC are given in Table 2. All apatite CPC formulations have PHA as the end-product of the reaction, except Norian SRS and Biocement D which contain small amounts of carbonates to form a carbonato-apatite (CAP; $Ca_{8.8}(HPO_4)_{0.7}(PO_4)_{4.5}(CO_3)_{0.7}(OH)_{1.3}$ (19)). All apatite CPC have a long intrinsic setting time. To remedy this, the amount of mixing liquid is reduced to a minimum. Therefore, all apatite CPC are viscous, easily moldable, but tend to be difficult to inject. The setting time can also be reduced by means of additives, such as phosphoric acid, MCPM, orthophosphate ions, and PHA particles. With these additives, a setting time in the range of 10-15 minutes can normally be obtained.

The setting reaction of most CPCs occurs according to one reaction, but Norian SRS and Cementek set according to two reactions: (i) precipitation of DCPD, and (ii) precipitation of PHA (65). The initial reaction is very fast and provokes the hardening of the cement paste within seconds. To obtain a viscous paste again, the hardened cement must be ground, either with a pestle and mortar, or with an adequate mixer. After a while, the paste re-hardens due to the precipitation of PHA.

The mechanical properties of the apatite CPC can vary widely depending on the composition. The main determining factor is the ratio between the amount of cement powder (P) and mixing liquid (L). When this P/L ratio is high, the porosity of the CPC is low. The mechanical properties decrease exponentially with an increase in porosity. As a rule of thumb, the tensile strength increases twofold with a 10 vol% decrease of the porosity, i.e. 5, 10, 20, 40 and 80 MPa for 80, 70, 60, 50 and 40% porosity, respectively. The mechanical properties reported by CPC producers are never documented so it is difficult to compare different apatite CPCs. Several authors have attempted to compare CPC cements. For example, Driessens [66] has obtained the following compression strength and setting time for (i) Norian SRS: 33±5 MPa and 8.5±0.5 min. (≈ 50% porosity), (ii) Cementek: 8±2 MPa and 17±1 min., (iii) Biocement D: 83±4 MPa and 6.5±0.5 min. (≈ 40% porosity), and (iv) α-BSM: 4±1 MPa and 19±1 min. (≈ 80% porosity). Biocement D has by far the largest compressive strength, but also the lowest porosity. A high compressive strength does not necessarily mean that Biocement D is the least breakable implant. *In vivo*, shear and tensile forces indeed play a very important role. Therefore, the tensile strength of the CPC should also be considered, for example using the Mohr circle approach [67]. Finally, it should be kept in mind that the initial mechanical properties of the apatite CPC may vary with implantation time. Animal studies indicate that the mechanical properties of apatite CPC tend to increase continually [68], in contrast to those of brushite CPC which decrease initially and increase when bone grows [69].

The biocompatibility of apatite CPC is normally excellent. Some inflammatory reactions may apparently occur when the CPC does not set [52]. The biodegradability of apatite CPC is larger than that of HA, but still very slow. For example, Young et al. [70] report on a 30% decrease of the Norian SRS amount after 24 months in a rabbit femur. Moreover, some differences can be expected depending on the cement type. As the end-product of BoneSource and Teknimed is a very crystalline PHA, BoneSource and Teknimed are expected to resorb more slowly than other apatite CPCs. Eppley [55] has indeed observed no resorption of BoneSource after several years implantation, but has observed some resorption of Biobone. However, this could stem from the cement porosity, as Biobone is much more porous than BoneSource. The CPC porosity is indeed a very important factor for the CPC degradability.

3.2. Brushite CPC

As indicated by its name, DCPD is the product of the setting reaction of so-called brushite cements. Several compositions have been proposed, e.g. β-TCP + MCPM

[20], β-TCP + H_3PO_4 [71-72], and TetCP + MCPM + CaO [32]. All brushite CPCs are obtained by an acid-base reaction. The paste of brushite CPC is acidic during setting because brushite can only precipitate at a pH value lower than ~6 [13]). For example, β-TCP + MCPM mixtures have a pH value close to 4 during setting [73]. After setting, the pH of the cement paste slowly changes towards the equilibrium pH [73]. If the cement paste contains an excess of basic phase, the equilibrium pH is given by the intersection of the solubility isotherm of the basic phase with that of DCPD. For example, the equilibrium pH of β-TCP + MCPM, HA + MCPM, and TetCP + MCPM are 5.9, 4.2 and 7.6, respectively (Fig. 1).

The setting time of brushite CPC depends very much on the solubility of the basic phase: the higher the solubility of the basic phase, the faster the setting time. Therefore, the setting time of a CPC made of MCPM + basic CaP is in the order: HA > β-TCP > α-TCP. For example, HA + MCPM mixtures have a setting time of several minutes. β-TCP + MCPM mixtures have a setting time of 30 to 60 seconds [20,74]. α-TCP + MCPM mixtures have a setting time of a few seconds [74]. Additives that inhibit the crystal growth of DCPD have been succesfully used to increase the setting time of β-TCP + MCPM mixtures [75]. In contrast to apatite CPC, brushite CPC can be initially very liquid and still set within a short period of time.

Brushite CPC is slightly weaker than apatite CPC. Tensile strengths of 10 MPa [76] and compressive strengths of 60 MPa have been obtained with brushite CPC. In comparison, apatite cements can reach a tensile strength of 16 MPa [77] and a compressive strength of 83 MPa [66]. *In vivo*, the difference between apatite CPC and brushite CPC increases: the mechanical properties of apatite CPC increase [68], whereas those of brushite CPC decrease [69]. The latter phenomenon is attributed to the higher solubility of DCPD compared with that of PHA. After a few weeks of implantation, the mechanical properties of brushite CPC increase due to bone growth [69].

Brushite CPC is biocompatible. However, inflammatory reactions have been reported when large CPC volumes were used [78]. New results indicate that these reactions are due to the transformation of DCPD into PHA [79]. This reaction releases large amounts of acid (reaction (1)). The transformation of DCPD into PHA can be prevented by adding magnesium ions to the cement paste [80]. Brushite CPC cannot only be resorbed by osteoclastic activity, like apatite CPC, but also by simple dissolution. Therefore, brushite CPCs degrade faster than apatite CPC. A linear degradation rate of 0.25 mm/week has been measured [81]. This rapid degradation rate may lead to the formation of immature bone. This problem can be solved by adding β-TCP granules to the cement paste. The granules act as bone anchor and encourage the formation of mature bone [81]. Despite their high degradation rate, brushite CPCs degrade much more slowly than gypsum [82], probably because the solubility of DPCD at neutral pH is 10 times larger than that of gypsum [74].

4. Future developments

Only a few commercial apatite CPCs are currently available [19,25-26]. New apatite and brushite CPC are expected to come onto the market soon, hence offering more choice regarding biodegradability, ease of mixing, and viscosity. However, the appearance of several CPCs is only the first step in the use of CPC. New commercial products will need to be improved from the first CPC generation in order to take advantage of the large range of possibilities offered by CPC. These products could be (i) injectable and open-macroporous CPC to optimize their osteoconduction, (ii) drug-loaded CPC for the treatment of bone diseases, or (iii) open-macroporous CaP blocks for tissue engineering.

The main disadvantage of CPC is its lack of macropores. As a result, biodegradation takes place layer-by-layer, from the outside to the inside. To solve this problem, soluble particles, such as sugar [83] and calcite [32], may be incorporated into the cement. As soon as the cement is implanted, the particles are dissolved, leaving pores in the cement matrix, but the pores are not connected. An alternative could be to use a hydrophobic liquid instead of soluble particles. Exploratory results [84] have shown that an open macroporous structure could be obtained using a mixture of an oil and a CPC paste. The macropore size produced by the oil droplets can be modified with the emulsifier concentration (Fig. 3). However, the incorporation of macropores into the cement matrix decreases its mechanical properties.

CPC can be used as a delivery system for therapeutic peptides [85], antibiotics [86-87], anticancer drugs [88], antiinflammatory drugs [89], and bone morphogenetic protein [90]. The drug is incorporated into the mixing

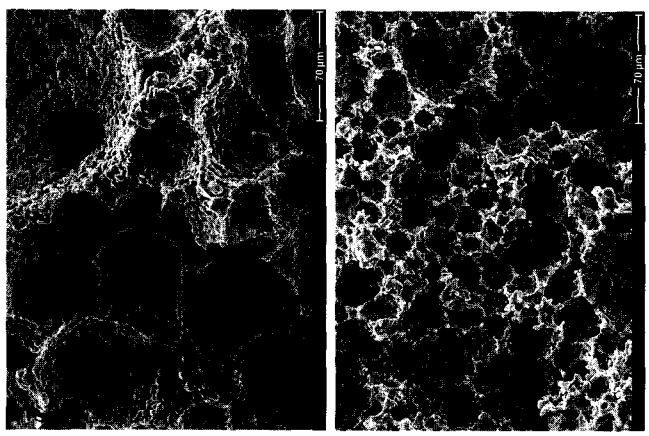

Fig. 3: Effect of the emulsifier concentration on the microstructure of CPC – oil mixtures after washing off the oil and sintering. After sintering, the blocks consisted of β-TCP.

liquid or the CaP powders. After setting, the drug is slowly released through the cement pores. The possibility of using a bone substitute as a drug delivery system offers an attractive and efficient solution for the treatment of bone diseases such as tumours, osteoporosis, or osteomyelitis.

The discovery of CPC has also opened up new alternatives in the synthesis of CaP blocks [91]. In the past, CaP blocks could only be obtained by sintering. Now, using appropriate techniques, open macroporous blocks containing low-temperature phases such as DCP, DCPD, OCP and PHA can be made. This type of material could prove to be very useful for tissue engineering applications. PHA is particularly interesting due to its excellent biocompatibility and its large specific surface area.

5. Conclusion

In this article, the use of calcium phosphate compounds as bone substitutes (granules, blocks, cements) has been reviewed. In particular, calcium phosphate compounds have been presented and their physical, chemical and biological differences have been discussed. Furthermore, a comprehensive review of the field of calcium phosphate cements has been provided. Finally, new perspectives in the field of calcium phosphates have been commented on, in particular the possibilities offered by low temperature calcium phosphates as biodegradable bone substitutes and drug carriers.

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