JOURNAL OF MATERIALS SCIENCE: MATERIALS IN MEDICINE **10** (1999) 177–183

Calcium phosphate bone cements for clinical applications

Part II: *Precipitate formation during setting reactions*

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Calcium phosphate bone cements (CPBC) have been of great interest in medicine and dentistry due to their excellent biocompatibility and bone-repair properties. In this article, a review is presented of the scientific literature concerning precipitate formation during setting reactions of CPBCs. Firstly, the available information has been classified according to the intended final product or calcium phosphate formed during setting reactions. Taking the final product into account, a second classification has been made according to the calcium phosphates present in the original powder mixture. This is the most natural classification procedure because it is based on thermodynamic reasons supported by solubility diagrams for the calcium phosphate salts. By understanding the thermodynamics of calcium phosphate salts in an aqueous solution at room or body temperature it is possible to optimize the manufacturing technology involved in the production of CPBCs. Knowledge of the limitations of this thermodynamic approach opens up new possibilities in the search for CPBCs with better *in vitro* and *in vivo* properties for clinical applications.

1. Introduction

1.1. Stability of calcium phosphates in an aqueous solution

Solution chemistry and thermodynamics, both controlling dissolution and precipitation processes of calcium phosphates systems, have been reviewed in another article [1]. However, before classifying calcium phosphates cements (CPC) according to the final crystalline phase formed during setting, it is necessary to understand the stability of calcium phosphates in a solution.

The stability or instability of a calcium phosphate in a solution is directly correlated with its mechanism of formation. Some calcium phosphates can be obtained by precipitation from a supersaturated solution at a certain temperature while others can only be obtained by solid state reactions at high temperature. Therefore, the stability of these calcium phosphates in an aqueous solution depends not only on the relative position of their solubility isotherms [1] but also on the thermal stability during preparation.

1.1.1. Calcium phosphates obtained by precipitation

In the system $Ca(OH)_2 - H_3PO_4 - H_2O$ only a limited number of calcium phosphates can be obtained by precipitation in the form of crystalline solids with well defined stoichiometry, physical and thermodynamic properties [2]. In fact, attention in the biomedical field is generally focused on monocalcium phosphate (MCPM), dicalcium phosphate dihydrate (DCPD), octacalcium phosphate (OCP) and precipitated hydroxyapatite (PHA) because their respective solubility products are well established [1].

It should be noted that dicalcium phosphate (DCP) is rarely obtained by precipitation from an aqueous solution [2] at room temperature. It is usually obtained by heating DCPD at temperatures between 120 and 170 °C. Likewise, the hydration processes of DCP are usually effective at temperatures higher than 50 °C [3, 4]. Therefore, when analysing singular points [1] between any calcium phosphate and DCP at ambient or body temperature, care should be taken in drawing any conclusions.

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Although less well documented than the abovementioned phosphates, there are other calcium phosphates obtained by precipitation playing an important role in the solution behaviour of the $Ca(OH)_2 - H_3PO_4 - H_2O$ system. Precipitation studies from weak acid or neutral supersaturated calcium phosphate solutions have shown that, in fact, the first crystalline solid to precipitate has the stoichiometry $Ca_9(HPO_4)(PO_4)_5(OH)$. This compound has well defined physical and thermodynamic properties and it is called calcium deficient hydroxyapatite (CDHA). Although, the solubility constant of this compound is not known accurately, some estimations give the value as $\log(K_{sp}) = -85.1$ [2]. Therefore, accurate conclusions concerning the thermodynamic behaviour between any other calcium phosphate and CDHA cannot be obtained until the position of the solubility isotherm is known. It has also been observed that before this CDHA precipitate is obtained another precipitate, amorphous to X-ray diffraction (XRD), is formed and it is known as amorphous calcium phosphate (ACP) [2, 5].

Table I summarizes the crystalline solids that can be obtained by precipitation at ambient or body temperature [6] and their pH stability ranges [7, 8]. These are the setting reaction products on which biomedical applications are based, because CPCs are developed to be used as implant materials at body temperature ($T = 37\,^{\circ}C$).

1.1.2. Calcium phosphates obtained by solid state reactions

The calcium phosphates from Table I can only be obtained by precipitation from an aqueous solution, but there are other calcium phosphates that can only be obtained by solid state reactions at high temperature ($T > 1000\,^{\circ}C$) [6, 9]. Table II summarizes the calcium phosphates that belong to the ternary system $CaO - P_2O_5 - H_2O$ and whose solubility isotherms are known [10]. Hence, interest is focused on using these calcium phosphates alone or in combination with other calcium phosphates that can result in cement materials [1].

Details concerning the manufacture of these phases and their respective stable temperature ranges are well documented in the literature [2, 3, 9, 11].

TABLE I Crystalline compounds obtained by precipitation at ambient or body temperature and pH stability ranges in the system $Ca(OH)_2 - H_3PO_4 - H_2O$

Ca/P	Formula	Name	pH
0.5	$Ca(H_2PO_4)_2 \cdot H_2O$	MCPM	0.0–2.0
1	$CaHPO_4 \cdot 2H_2O$	DCPD	2.0–6.0
1.33	$Ca_8(HPO_4)_2(PO_4)_4 \cdot 5H_2O$	OCP	5.5–7.0
1.5	$Ca_9(HPO_4)(PO_4)_5OH$	CDHA	6.5–9.5
1.67	$Ca_{10}(PO_4)_6(OH)_2$	PHA	9.5–12

TABLE II Calcium phosphates prepared by solid state reactions at high temperature

Ca/P	Compound	Formula	Name
1.5	α-tricalcium phosphate	$\alpha - Ca_3(PO_4)_2$	α-TCP
1.5	β-tricalcium phosphate	$\beta - Ca_3(PO_4)_2$	β-TCP
1.67	Sintered hydroxyapatite	$Ca_{10}(PO_4)_6(OH)_2$	SHA
2.0	Tetracalcium phosphate	$Ca_4(PO_4)_2O$	TTCP

1.1.3. Relative position of two isotherms (singular points)

The intersection point of the isotherms of two mineral compounds in the system $A(OH)_n - H_nX - H_2O$, where $A(OH)_n$ is a base and H_nX is a weak acid, is called a singular point. Singular points predict the thermodynamic behaviour of several compounds in a solution [1] due to their attraction effect [1, 12]. However, conclusions about this attraction effect and about the dissolution-precipitation process involved until the pH of the singular point is reached should be taken carefully [1, 13, 14]. The problem arises when the isotherms of both mineral compounds obtained by precipitation and by solid state reaction at high temperatures are represented on the same solubility diagram [1]. To avoid mistakes it has to be clear that the only crystalline phases that can be formed at ambient or body temperature as a result of a setting reaction between a mixture of two calcium phosphates and an aqueous solution are PHA, CDHA, OCP and DCPD [1]. It is not possible to obtain TTCP, α-TCP, β-TCP nor DCP as an intermediate product of any setting reaction.

2. Discussion

2.1. Setting reactions forming PHA or CDHA

The setting reactions leading to the formation of PHA or CDHA are usually classified in three groups taking into account the number and type of calcium phosphates used in the powder mixture. A first group includes those calcium phosphates that hydrolyze to form PHA or CDHA. A second group includes those systems formed by two calcium phosphates, one of which is TTCP. Finally, a third group includes those systems formed by two calcium phosphates whose Ca/P ratio is lower than the stoichiometric ratio for hydroxyapatite.

2.1.1. Hydrolysis of a simple calcium phosphate compound

It is known [1] that PHA is the least soluble phase at $pH > 4.2$. This means that any other calcium phosphate present in an aqueous solution at that pH range will tend to dissolve, so PHA will precipitate. If this process is

rapid and spreads over to a considerable extent, cement formation will be derived from this hydrolysis reaction.

The thermodynamics of the ternary system $Ca(OH)_2 - H_3PO_4 - H_2O$ [1], without any other acids or bases, shows that the formation of PHA from the hydrolysis of one calcium phosphate is kinetically very slow. This is due to a decrease of the supersaturation level, as the reaction proceeds, between both the isotherms of the calcium phosphate under consideration and PHA [1].

The calcium phosphates normally considered in clinical applications [1], except TTCP, have a Ca/P ratio lower than PHA ($Ca/P < 1.67$). This means, thermodynamically, that the hydrolysis reaction will proceed with a release of phosphoric acid (H_3PO_4) into the solution

$$5Ca(H_2PO_4)_2 \cdot H_2O \rightarrow Ca_5(PO_4)_3OH + 7H_3PO_4 + 4H_2O \quad (1)$$

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

$$5Ca_8H_2(PO_4)_6 \cdot 5H_2O \rightarrow 8Ca_5(PO_4)_3OH + 6H_3PO_4 + 17H_2O \quad (3)$$

$$5Ca_3(PO_4)_2 + 3H_2O \rightarrow 3Ca_5(PO_4)_3OH + H_3PO_4 \quad (4)$$

The supersaturation level decrease can be understood, for example, through the analysis of Equation 2 for DCPD. While DCPD is present in excess in the solution, the composition of the solution will remain on the solubility isotherm if the DCPD reaction proceeds. However, the increasing amount of H_3PO_4 will drive the pH of the solution to lower values and the supersaturation level with respect to PHA will diminish, due to the approach of the isotherms [1]. Finally, the reaction will stop when the composition of the solution reaches the intersection of the isotherms, because at that point the solution will be saturated with respect to both mineral phases.

When TTCP is considered, hydrolysis produces $Ca(OH)_2$ as a by-product, as indicated in Equation 5.

$$3Ca_4(PO_4)_2O + 3H_2O \rightarrow 2Ca_5(PO_4)_3OH + 2Ca(OH)_2 \quad (5)$$

The $Ca(OH)_2$ formation results in a pH increase, which means that the solution will become less supersaturated with respect to PHA. According to Xie and Monroe [15], from the standpoint of biocompatibility of CPCs, the high pH resulting from the presence of $Ca(OH)_2$ does not lead to cytotoxicity.

According to the above results, it seems that of all of the possible cement reactions, Equations 1–5, are not suitable for clinical application because the reaction kinetics decrease as the setting reaction proceeds. In order that the hydrolysis reaction proceeds to completion it would be necessary that the reaction mechanism would remove the by-products [H_3PO_4 or $Ca(OH)_2$]. However, the use of $Ca(OH)_2$ or NaOH in Equations 1–4 to neutralize H_3PO_4 causes additional problems due to the initial high pH where setting reactions occur. Generally, in clinical applications, high pH values are avoided due to cellular death and cytotoxicity [16].

The only system formed by one calcium phosphate compound that results in a cement was reported by Monma and coworkers [17, 18]. These authors showed that the conversion of α-TCP into CDHA takes place in solutions with a pH of 7.5 or higher. However, according to these authors the speed of the conversion reaction was very slow, of the order of 5% at 37 °C. Recently [19–26], important advances have been made in improving the setting properties and the reaction speed of an α-TCP based cement that forms CDHA as a setting reaction product at room or body temperature. The setting reaction is represented by Equation 6.

$$3\alpha - Ca_3(PO_4)_2 + H_2O \rightarrow Ca_9(HPO_4)(PO_4)_5OH \quad (6)$$

2.1.2. Mixtures between TTCP and any other calcium phosphate

TTCP is the only calcium phosphate having a Ca/P ratio higher than PHA. Therefore, TTCP can be combined with one or more calcium phosphates (with lower Ca/P ratio) to obtain mixtures with a PHA or CDHA stoichiometry without the formation of acids or bases as by-products. From a theoretical point of view, any calcium phosphate more acid than PHA can react directly with TTCP to form PHA or CDHA according to the following chemical reactions

$$7Ca_4(PO_4)_2O + 2Ca(H_2PO_4)_2 \cdot H_2O \rightarrow 6Ca_5(PO_4)_3OH + 3H_2O \quad (7)$$

$$2Ca_4(PO_4)_2O + Ca(H_2PO_4)_2 \cdot H_2O \rightarrow Ca_9(HPO_4)(PO_4)_5OH + 2H_2O \quad (8)$$

$$Ca_4(PO_4)_2O + CaHPO_4 \cdot 2H_2O \rightarrow Ca_5(PO_4)_3OH + 2H_2O \quad (9)$$

$$3Ca_4(PO_4)_2O + 6CaHPO_4 \cdot 2H_2O \rightarrow 2Ca_9(HPO_4)(PO_4)_5OH + 13H_2O \quad (10)$$

$$Ca_4(PO_4)_2O + CaHPO_4 \rightarrow Ca_5(PO_4)_3OH \quad (11)$$

$$3Ca_4(PO_4)_2O + 6CaHPO_4 \rightarrow 2Ca_9(HPO_4)(PO_4)_5OH + H_2O \quad (12)$$

$$3Ca_4(PO_4)_2O + Ca_8H_2(PO_4)_6 \cdot 5H_2O \rightarrow 4Ca_5(PO_4)_3OH + 4H_2O \quad (13)$$

$$3Ca_4(PO_4)_2O + 3Ca_8H_2(PO_4)_6 \cdot 5H_2O \rightarrow 4Ca_9(HPO_4)(PO_4)_5OH + 14H_2O \quad (14)$$

$$Ca_4(PO_4)_2O + 2Ca_3(PO_4)_2 + H_2O \rightarrow Ca_5(PO_4)_3OH \quad (15)$$

The TTCP + OCP, TTCP + α-TCP and TTCP + β-TCP combinations shown in Equations 13–15 have singular points located very near to the solubility isotherm of PHA. Therefore, these combinations have a very low supersaturation level and setting reactions are so slow that these systems are not suitable for the manufacture of cement materials [10].

Only TTCP + MCPM, TTCP + DCPD and TTCP + DCP mixtures offer suitable combinations in terms of the setting and hardening properties of the resulting cement.

The TTCP + MCPM mixture does not often produce the one step reactions indicated by Equations 7 and 8. It is well documented that during setting reactions, the formation of DCPD, as an intermediate reaction product, is kinetically favoured [27, 28]. However, the final product of the setting reaction will be PHA or CDHA according to the initial system stoichiometry.

The most widely studied combinations are in fact the TTCP + DCPD and TTCP + DCP mixtures [13–15, 27–38]. These mixtures offer the possibility of producing cement materials that set and harden with time at ambient or body temperature in a pH range around neutral.

The most important results obtained from investigation of the TTCP + DCPD or TTCP + DCP systems show that, in addition to thermodynamic factors [1], kinetic factors that control both phase dissolution and the precipitation of PHA phase are also very important [27, 28, 33–43] especially in a cement type system where time factor is limited [33]. These conclusions can be extended to any other calcium phosphate system resulting in cement type materials.

For this reason, while kinetic mechanisms controlling setting and hardening processes of any possible cement system are not known, the thermodynamic conclusions that can be derived from an analysis of the solubility and relative stability diagrams [1] of the different calcium phosphates must be taken as a first approximation but never as an exhaustive explanation of what is actually happening during the setting reaction.

2.1.3. Mixtures between calcium phosphates with a Ca/P < 1.67

It is also possible to form PHA as the final setting product using mixtures of calcium phosphates with a Ca/P ratio lower than PHA and using an additional source of calcium ions such as, for example, $CaCO_3$ or $Ca(OH)_2$, instead of TTCP.

One of these systems is formed by $\beta - TCP + DCPD + CaCO_3$ mixtures [44–46]. According to these studies, the crystals of PHA formed from the initial reaction between DCPD and $CaCO_3$ work as binders between β-TCP particles. When DCPD is finally consumed in the mixture, the formation of PHA is controlled by the reaction between the remaining β-TCP and $CaCO_3$ particles. However, it seems that this last reaction has a detrimental effect on the mechanical properties of the setting cement.

Another system that caused a great interest due to its reported setting and hardening properties was the product developed by Norian Corporation [47]. This system is formed by a mixture of $\alpha - TCP + MCPM + CaCO_3$ (Norian SRS™, Skeletal Repair System). It is reported that the initial setting process involves the formation of DCPD while the final setting product is *dahllite,* a carbonated hydroxyapatite with a Ca/P ratio between 1.67 and 1.69 with a carbonate ion content similar to bone mineral [48, 49].

2.2. Setting reactions forming OCP

The solubility diagram of calcium phosphates [1] shows that the OCP isotherm lies below the solubility isotherms of DCP, DCPD, α-TCP and TTCP in a broad range of pH values. Therefore, the composition of these phases on their isotherms are super-saturated in relation to OCP; and so from a thermodynamic point of view, this phase can precipitate. However, OCP is more soluble than PHA. Therefore, although OCP can be formed faster than PHA, the favoured final setting product will be PHA [50–52].

The advantage of OCP, as a crystalline phase in a calcium phosphate cement, is that it is the precursor in the initial formation processes of bone mineral [2, 51]. This is the reason why interest has been focused on finding CPCs for clinical applications where the crystalline phase of the setting reaction process would be OCP.

OCP formation through the hydrolysis of a single reactant has been favoured, in some systems [18, 53, 54], by careful control of both temperature and the pH of the solution.

For one system, involving DCPD [53] it has been reported that OCP formation was favoured at pH = 6 when the hydrolysis process was kept at 40 °C. This result could be disputed, because according to the isotherm position of DCPD and OCP at 37 °C [1] it can be shown that at pH = 6 both isotherms cross at a singular point and, therefore at that point, DCPD and OCP are in equilibrium with the solution and neither of them can precipitate.

In a system formed only by α-TCP [18, 54] the effect of both temperature and pH on OCP precipitation was studied and it was observed that this process was favoured for the following pairs of temperature and pH range values: ($T = 40\,^{\circ}C$, $5.5 < pH < 7.5$) [18]. ($T = 60\,^{\circ}C$, $pH = 5$) [54], ($T = 70\,^{\circ}C$, $4.5 < pH < 5.5$) [54]. Thus, a temperature increase is related to a decrease of the optimum pH range in the acid pH direction. It is known [1] that when temperature increases, for a fixed pH value, the solubility of calcium phosphates decreases. Therefore, to increase α-TCP solubility it is necessary to drive the solution pH towards lower values [1]. According to the above results it is difficult to explain why a fixed pH range exists where OCP formation is favoured. A possible answer could be that temperature has a different influence on the solubility isotherms of OCP and α-TCP and, therefore, on the kinetics of both the α-TCP dissolution and OCP precipitation processes.

The relative proportions of solid reactants in a mixture of calcium phosphates is another factor extensively studied to predict the possible formation of OCP as the main product of hydrolysis processes. Systems formed by mixtures of α-TCP + DCPD [55], MCPM + CaO [56], α-TCP + MCPM [57], α-TCP + DCP [58–60], TTCP + DCPD [59], TTCP + DCP [32] TTCP + MCPM [59] and MCPM + $CaKPO_4$ [59] have also been studied.

The results of setting times and/or compressive strength versus Ca/P ratio, where Ca/P ratio is indicative of the relative proportions of compounds in the mixture, show the existence of a minimum in the setting times [55, 56, 58, 59] and a maximum in the compressive strength [55, 56, 58] that occurs when the Ca/P ratio of the range studied tends to the Ca/P ratio of OCP. Most authors [55–59] justify the presence of OCP as the reaction product for those mixtures with a stoichiometric ratio between reactants of Ca/P = 1.33. Some authors

[57] extend this result and state that it is possible to obtain OCP cements if both:

1. the main reactive proportions in the mixture match the Ca/P ratio of OCP (in which case OCP would be favoured as the final product of setting reaction), and
2. the reaction is thermodynamically possible.

However, some authors justify their results solely on the basis of thermodynamics. In the system α-TCP + DCPD [55], authors have used thermodynamic justification for OCP formation for all Ca/P ratio ranges studied ($1.20 < \text{Ca/P} < 1.47$). All authors [55–59] used XRD and/or Fourier transform infrared spectroscopy (FTIR) techniques to prove experimentally the presence of OCP as the actual setting phase. However, these techniques cannot confirm the presence of OCP and, therefore, they are inconclusive.

These results seem to indicate that it is not possible to obtain OCP calcium phosphate cements simply taking into account stoichiometric and/or thermodynamic considerations. Moreover, according to the enormous quantity of experimental conditions that must be fulfilled to obtain OCP as a precursor phase [51] and the low efficiency that these reactions have at 37 °C, it seems still more difficult to obtain OCP cements for clinical applications where this phase should be present in large quantities [54].

Some authors [32, 60] have been interested in kinetic aspects of setting reactions and have studied the TTCP + DCP [32] and α-TCP + DCP [60] systems. In both studies, the setting reaction was stopped at different time intervals and the reactants and products in the cement were analysed. The TTCP + DCP system was initially adjusted to a Ca/P ratio of $\text{Ca/P} = 1.67$ and although the favoured phase as final product of the setting reaction was PHA, there were some thermodynamic reasons why the detection of OCP as an intermediate setting reaction product might be expected. The α-TCP + DCP system was initially adjusted to a Ca/P ratio of $\text{Ca/P} = 1.33$ and in addition to the thermodynamic reasons also there were stoichiometric reasons to suppose that the final setting reaction product would be OCP. However, in neither study was it possible to detect OCP either by XRD [32, 60] or by FTIR [60] as neither the precursor phase nor as the final phase of setting reaction, for the interval times studied. In spite of all these results, opposed to the OCP formation, some authors [32] justify the possible presence of the phase by taking crystal morphology [15] into consideration. However, it has also been observed that in the α-TCP + DCP [60] system (where it was clearly demonstrated that the kinetic mechanisms of setting reactions do not involve the presence of OCP) some types of crystal formation are very similar to those observed in the TTCP + DCP [32] system. Therefore, microstructure observations cannot be assumed to demonstrate the presence of this crystalline phase.

2.3. Setting reactions forming DCPD

The most stable phases in the pH range 2–4.5 are DCPD and DCP. Therefore, when a calcium phosphate more basic than DCPD and DCP is placed in an acid solution at ambient or body temperature, DCPD will be the precipitating phase.

The solubility diagram [1] shows that DCPD is more stable than α-TCP at a pH lower than approximately pH 7. These thermodynamic conclusions agree with the results of Monma *et al*. [18] who showed that during an α-TCP hydrolysis process at 37 °C at pH values lower than 5.5 the main phase obtained by precipitation was DCPD.

In very acid conditions ($\text{pH} < 2$) the most stable phase is MCPM. In the pH range 2–4.5 the dissolution of MCPM in an aqueous solution involves DCPD precipitation as a more stable phase. In that case the results of Mirtchi *et al*. [61, 62] agree also with thermodynamic conclusions. According to these authors, in a cement formed by a mixture of β-TCP + MCPM the final product of the setting reactions was DCPD.

This kind of cement, where the setting reaction product is DCPD, has a series of disadvantages for clinical applications, as have been described [59]:

1. a high acidity during setting, that probably would involve inflammatory processes in the tissues after implantation; or
2. a loss of mechanical strength due to the gradual transformation of DCPD into PHA after implantation.

3. Conclusions

The thermodynamics of calcium phosphate salts in an aqueous solution, at room or body temperature, enable the prediction of the calcium phosphate precipitates that might be expected to result from a supersaturated solution during the setting reaction of a CPC [1]. During precipitation, the pH of the solution changes and this is a major factor influencing the basicity or acidity of the cement, i.e. the suitability of the cement for clinical applications, and conclusions concerning the possible *in vivo* stability of the cement can be drawn. Those cements for which the precipitation process occurs at around neutral pH will be the most suitable for clinical application.

However, the kinetics of cement reactions can be affected by a large number of technological factors during manufacture and processing of these cement materials. These factors affect considerably the properties of CPCs, such as the solubility, the setting times, the porosity, the compressive strength and the rate of *in vivo* resorption.

Therefore, it is expected that the use of factorial design of experiments [63] will open-up new possibilities in the search for CPCs with better *in vitro* and *in vivo* properties, for clinical applications.

Acknowledgements

This work was supported by a post-doctoral Spanish Grant No. PF96 0036982735 and by a European Grant TMR No. ERB4001GT961668. Further, the authors thank the CICYT (Dirección Científica y Técnica of

Spain) for funding this work through project MAT96-0981. The EPSRC are gratefully acknowledged for their support of the IRC in biomedical materials.

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Received 2 September 1997
and accepted 26 January 1998