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Calcium phosphate bone cements for clinical applications

Part I: *Solution chemistry*

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Calcium phosphate cements have been the subject of many studies in the last decade because of their biocompatibility, their capacity to fill bone cavities and their hardening properties; properties which are desirable in a broad range of surgical applications. The setting and hardening of these materials are controlled by dissolution–precipitation chemical reactions at room or body temperature and involve crystalline phase transformations.

In this paper, the solution chemistry of calcium phosphates is reviewed to highlight the way in which the thermodynamics of these systems has influenced the development of the various calcium phosphate cement formulations under investigation today. With this approach, a bibliographic review is given of the information available concerning calcium phosphate bone cements which focuses on the necessity of studying the kinetics of different calcium phosphate systems in real setting and hardening situations. Improved understanding of system kinetics together with a statistical approach will allow the optimization of cement properties.

1. Introduction

A surgical implant may be defined [1] as an object comprising non-living materials introduced into the human body and designed to fulfil a specific function over a specified time span. According to their required function, implants are used to: (a) substitute a diseased part of the anatomy; (b) replace an absent part of the anatomy; (c) help with the healing process of a tissue; (d) correct any congenital, traumatic or pathological deformity; and/or (e) rectify the operational mode of a vital organ.

A more accurate classification can be made according to both the material characteristics of the implant and its application. Basically, the important properties of a material can be classified into four categories: mechanical, physical, chemical and biological properties. Physical and mechanical properties control the active functional characteristics of most implants; chemical and biological properties control the ability of the implant to maintain its functionality throughout implantation time. The material selection, based on the properties required for the application and by the characteristics of the material, determines the functional suitability of the implant.

Calcium phosphates, specifically hydroxyapatite ceramics, have generated a great deal of interest [2] in relation to hard tissue applications due to their bioactivity (i.e. their capacity to form a chemical bond with the surrounding tissues). Traumatology, plastic surgery and orthodontics require solutions to problems related with bone tissue. However, diseases such as osteoarthritis, arthrosis, osteosarcoma or caries, result in bone tissue problems which are more difficult to solve and require tissue replacement, filling, fixation and osteointegration. There is now a substantial amount of information available about the physicochemical and biological properties of calcium phosphate materials [3, 4].

Calcium phosphate ceramics, such as hydroxyapatite (HA) or β-tricalcium phosphate (β-TCP), are used for cavity filling applications and work via the colonization of the implant by new bone tissue such that, and where porous implants are used, the interconnected porous structure allows new bone tissue apposition within the structure by osteoblasts. From a crystallographic point of view, HA is more similar to natural bone tissue apatite than β-TCP and so it represents a better structural material for bone growth. However, the resorption rate of HA is extremely slow as compared with β-TCP [3, 4]. The solubility of other calcium phosphate ceramics is higher than the rate of bone tissue regeneration and they are therefore not useful for cavity filling and the gradual

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process of new bone tissue replacement. Other problems relating to these bone type substitutes include the inability to shape them *in situ* in the operating theatre, so that they must be used in the form of granules or blocks with the possible associated problems of lack of mechanical integrity due to their migration away from the implant site [3].

In the 1980s, the idea of a new bone substitute material was introduced and the materials were referred to as calcium phosphate bone cement (CPBC), biomaterials which have the advantages of calcium phosphates, but which could be used as a cement. There are significant advantages in using these cements since they offer the surgeon moldability, injectability and complete filling of a cavity, *in situ*, within the operating theatre. Implanted bone tissue also takes benefits from initial setting characteristics of the material which gives, in an acceptable clinic time, suitable mechanical strength for a shorter tissue functional recovery. Further advantages relate to the ability of CPBCs to activate the osteoclastic and osteoblastic functions of bone regeneration with the additional advantage that now these functions work on the cement material changing it with time to an organized structure characteristic of a newly formed bone. The excellent biocompatibility of CPBCs means that these materials can be used in a wide range of surgical applications.

This paper will concentrate on dissolution and precipitation processes in calcium phosphate cements (CPC) as these mechanisms control their chemistry of setting properties. The chemistry of CPCs has been considered to highlight the origin of the different calcium phosphate cement formulations that have been investigated up to now and also to understand the endeavors of different research groups to improve the setting and hardening properties of their cements.

2. Basic concepts of solution chemistry

This section deals with those concepts of solution chemistry used to explain thermodynamic and kinetic effects taking place in calcium phosphate solutions [3–6]. In heavily supersaturated systems or far away from equilibrium conditions, as is the case for CPC, the application of these general concepts, which were, in fact developed for dilute or weakly supersaturated solutions, allows the explanation of the thermodynamics and kinetics of setting and hardening.

2.1. Solubility product for mineral compounds

Precipitation of a mineral compound from an aqueous solution tends to occur when the aqueous solution becomes supersaturated with that mineral compound. Dissolution of a mineral compound takes place when the surrounding aqueous solution is undersaturated with that mineral compound. Driving forces controlling dissolution and precipitation reactions are related to respective super or undersaturation levels defined with regard to the thermodynamic solubility product.

The thermodynamic solubility product describes the equilibrium state between a mineral compound and an aqueous phase. The reaction that controls this equilibrium for a single compound AX can be represented by

$$\mathrm{AX(s)} \leftrightarrow \mathrm{A}^{n+}\mathrm{(aq)} + \mathrm{X}^{n-}\mathrm{(aq)} \tag{1}$$

where (s) indicates solid and (aq) aqueous states, respectively. A rise in Gibbs free energy (ΔG) in Equation 1 is represented by

$$\frac{\Delta G}{RT} = \frac{\mu^0_{\mathrm{A,ac}} + \mu^0_{\mathrm{X,ac}} - \mu_{\mathrm{AX,s}}}{RT} + \ln I_{\mathrm{p}}^{\mathrm{AX}} \tag{2}$$

where μ^0 is the molar Gibbs free energy under normal conditions of ionic species in solution and $\mu_{\mathrm{AX,s}}$ is the Gibbs free energy of the solid compound. R is the gas constant, T is the absolute temperature and $I_{\mathrm{p}}^{\mathrm{AX}}$ is the ionic activity product of compound AX. The ionic activity product of compound AX in solution is defined as

$$I_{\mathrm{p}}^{\mathrm{AX}} = (\mathrm{A}^{n+})(\mathrm{X}^{n-}) \tag{3}$$

where (A^{n+}) and (X^{n-}) are the molar activity of cation and anion, respectively. In a state of equilibrium $\Delta G = 0$ so that Equation 2 reduces to

$$\frac{\mu^0_{\mathrm{A,ac}} + \mu^0_{\mathrm{X,ac}} - \mu_{\mathrm{AX,s}}}{RT} = -\ln I_{\mathrm{p}}^{\mathrm{AX}} \equiv -\ln K_{\mathrm{sp}}^{\mathrm{AX}} \tag{4}$$

$\mu_{\mathrm{AX,s}}$ is a constant for a pure solid of fixed composition and μ_{i}^0 are fixed, by definition, at a determined temperature and pressure and therefore the term on the left of Equation 4 is also constant. So, Equation 4 shows that the ionic activity product for compound AX in a saturated aqueous solution must also be constant. This constant is called the thermodynamic solubility product or solubility product, $K_{\mathrm{sp}}^{\mathrm{AX}}$, of the compound AX. Combining Equations 2 and 4 we obtain the next general expression

$$\frac{\Delta G}{RT} = \ln \frac{I_{\mathrm{p}}^{\mathrm{AX}}}{K_{\mathrm{sp}}^{\mathrm{AX}}} = \ln S \tag{5}$$

where S is defined as the thermodynamic saturation level. When $S = 1$ the aqueous solution is saturated in relation to the compound AX. When $S < 1$ the aqueous solution is undersaturated and $\Delta G < 0$. In that case, the reaction in Equation 1 will tend to move to the right and the solid will dissolve. When $S > 1$ the aqueous solution will be supersaturated and $\Delta G > 0$. In that case the reaction in Equation 1 will tend to move to the left and precipitation or growth of compound AX will occur. For a compound of general composition $\mathrm{A}_a\mathrm{B}_b\mathrm{C}_c\mathrm{X}_k\mathrm{Y}_l\mathrm{Z}_m$ the ionic activity product is expressed as

$$I_{\mathrm{p}} = (\mathrm{A})^a(\mathrm{B})^b(\mathrm{C})^c(\mathrm{X})^k(\mathrm{Y})^l(\mathrm{Z})^m \tag{6}$$

and the same principles can be applied. For more detailed information the bibliography should be reviewed [3–7].

2.2. Solubility diagrams for a mineral compound

The solubility of a mineral compound, whose chemical formula is AX, in an aqueous solution from the $\mathrm{A(OH)}_n$–$\mathrm{H}_n\mathrm{X}$–$\mathrm{H_2O}$ system can be adequately described on the

basis of analytical concentrations of A^{n+} and X^{n-} ions. However, in the case of a base $A(OH)_n$ and a weak acid H_nX it is necessary to use pH as a third variable for a complete description of solubility and solubility behavior of compound AX. A graph describing the relationship between those variables is called a solubility diagram. A hypothetical case has been represented in Fig. 1 for a mineral compound AX, where H_nX is a weak polyprotic acid. In Fig. 1 the logarithm of the ion concentration of A (log [A]) versus solution pH is shown.

When equilibrium occurs between a solution and a solute excess, the solution becomes saturated. Far from equilibrium (i.e. away from the saturation line or solubility isotherm) the solution can be either under- or supersaturated. In the first case, the solid tends to dissolve (undersaturation zone). In the second case, the solid tends to precipitate until equilibrium is reached (supersaturation zone).

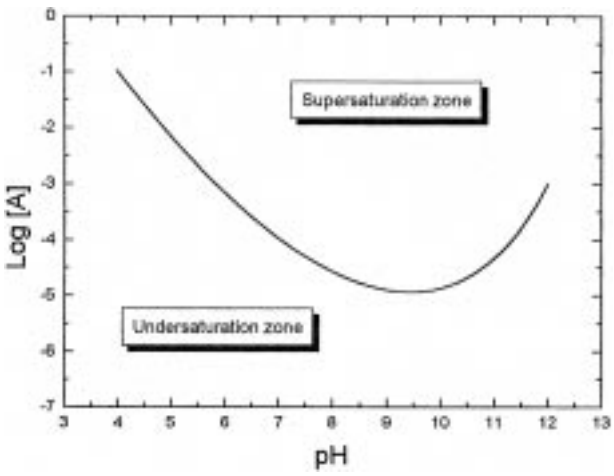

Figure 1 Solubility diagram of a general mineral compound AX, for a certain A/X molar ratio, in the system $A(OH)_n$–H_nX–H_2O, where H_nX is a weak acid.

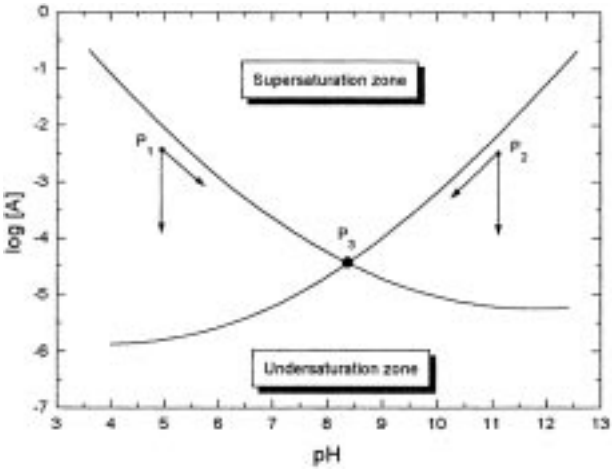

Figure 2 Relative position of isotherms of two hypothetical compounds in the system $A(OH)_n$–H_nX–H_2O for a given A/X molar ratio in the solution.

2.3. Relative position of two isotherms. Singular points

Fig. 2 shows the relative position of the isotherms of two hypothetical mineral compounds in the system $A(OH)_n$–H_nX–H_2O. Singular points predict the thermodynamic behavior of several compounds in a solution. For example, if two compounds are in excess in a more acid solution (P_1) than the singular point (P_3), the more basic compound will dissolve and the most acid will precipitate since, at that pH, the solution is supersaturated in relation to the most acid compound. This dissolution–precipitation process continues until pH and composition reach the singular point, where both compounds will be in equilibrium with the solution and neither will precipitate. The conclusion would be similar if the initial mixture composition is located in a more basic solution (P_2) than the singular point. In that case, the more acid compound will dissolve and the more basic will precipitate since, at that pH, the solution is supersaturated in relation to the most basic compound. Finally, the singular point pH will be reached as has been explained above. That property of singular points on solubility diagrams is called the attraction effect of singular points [8, 9].

However, conclusions about this attraction effect of singular points and about dissolution–precipitation processes involved until the singular point pH is reached must be taken carefully [10–12] when isotherms of mineral compounds obtained by precipitation and isotherms of compounds obtained by solid-state reaction at high temperatures are presented on the same solubility diagram. It is also important to consider that isotherms like those of Fig. 2 are valid only for certain values of the A/X molar ratios so that the pH of the singular point shifts slightly with changes in the A/X ratio in the solution. In that sense, singular points are also called quasi-singular points.

3. Solution chemistry in the case of calcium phosphates

According to Gibbs' phase rule, a ternary system with two phases, a solution and a solid salt, in equilibrium at a known temperature and pressure, has one degree of freedom. The geometric figure defined is a line called the solubility isotherm when it is represented in a phase diagram. The solubility isotherm fixes compositions of all saturated solutions in relation to that salt. The solubility isotherm of a calcium phosphate can be calculated taking into account the solubility product constant, dissociation constants of phosphoric acid (H_3PO_4) and calcium hydroxide $(Ca(OH)_2)$, stability constants of the different formed complexes and an appropriate model to calculate the activity coefficients of the different chemical species involved [4]. In many cases it is necessary to use computer calculations taking into account all possible interactions to obtain results and conclusions [13–16].

This section deals with some solubility diagrams obtained for the ternary system $Ca(OH)_2$–H_3PO_4–H_2O and with some important thermodynamic conclusions relating to the production of calcium phosphate mixture phases which hydrolyze, resulting in cement type materials through a setting reaction.

3.1. Solubility product constant for calcium phosphate salts

Orthophosphate salts are distinguished from meta- and pyrophosphates in that they contain PO_4^{3-} groups rather than PO_3^- or $P_2O_7^{4-}$, respectively. We are only interested in orthophosphate salts because pyro- and metaphosphates hydrolyze in body fluids and because high concentrations of these ions can result in extraosseous calcification [8]. That is the reason why only orthophosphate salts are considered. So, from now on the prefix ortho will be eliminated.

Table I summarizes the solubility product constant of the main calcium phosphates at 25 and 37 ℃. Increasing the calcium to phosphorus ratio (Ca/P) is associated with an increase in the basicity of these salts [7, 9, 10].

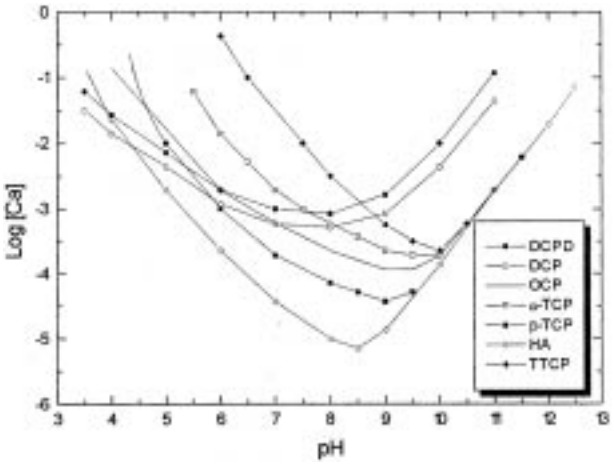

Figure 3 Solubility isotherms of different calcium phosphate salts in equilibrium with their solutions for the ternary system $Ca(OH)_2$–H_3PO_4–H_2O at 37 ℃ in a representation of log [Ca] versus pH.

3.2. Solubility diagrams of calcium phosphates

Figs 3 and 4 show the solubility diagrams for the ternary system $Ca(OH)_2$–H_3PO_4–H_2O at 37 ℃ [7, 9]. Fig. 3 shows the solubility isotherms of different calcium phosphate salts in equilibrium with their saturated solution, in a representation of the logarithm of calcium concentration (log [Ca]) of the saturated solution versus pH. Fig. 4 is equivalent and shows the logarithm of phosphorus ion concentration (log [P]) versus pH for the same saturated solutions. These figures show solubility isotherms of seven calcium phosphate salts: tetracalcium phosphate (TTCP), dicalcium phosphate dihydrate (DCPD), dicalcium phosphate anhydrous (DCP), octacalcium phosphate (OCP), α-tricalcium phosphate (α-TCP), β-tricalcium phosphate (β-TCP) and hydroxyapatite (HA).

A common characteristic of the isotherms in Figs 3 and 4 is that they have a negative slope in the neutral and acid regions (pH < 7) of the solubility diagrams. This means that these compounds became more soluble as the pH decreases. The gradient of the slope gives an idea of the solubility increase of the salt as the pH decreases. In that sense, the isotherm slope is taken as a measure of the salt basicity because the solubility of a basic salt will be greater than the one of an acid salt for an equal decrease in pH. According to this criterion, DCPD and DCP are acid salts in comparison to OCP, α-TCP, β-TCP, HA and TTCP because they have lower negative slopes.

In the alkaline regions of the solubility diagrams the calcium concentration, [Ca], increases as the pH increases (see Fig. 3) but, except for DCPD and DCP, the phosphorus concentration, [P], diminishes as the pH increases (see Fig. 4). The reasons that explain the behavior of isotherms in a representation of log [P] versus pH have been correlated also with the compound basicity [7].

Figs 3 and 4 are important because they give information about the relative stability of the different salts for different pH values. In general, for a given pH value, any salt whose isotherm lies below another, will be relatively more stable and so less soluble.

According to the solubility diagram shown in Fig. 3 it can be observed that, at 37 ℃, HA is the least soluble salt down to a pH of 4.2 (pH ≈ 4.2); for pH values lower than this, DCP is the least soluble salt. Also, it can be observed that for pH values lower than 8.5 (pH < 8.5) the most soluble salt is TTCP; for pH values higher than 8.5 (pH > 8.5) the most soluble salt is DCPD.

According to the thermodynamics of these systems it is thought that the driving force controlling possible chemical reactions taking place in calcium phosphate cement type materials must be related to the relative stability between different calcium phosphate salts.

The diagrams shown in Figs 3 and 4 are only valid for the ternary system $Ca(OH)_2$–H_3PO_4–H_2O at 37 ℃. This means that calcium and phosphorus concentration have

TABLE I Solubility product constants for some calcium phosphate compounds at 25 and 37 ℃

Ca/P ratio	Compound	Formula	$-\log(K_{sp})$ at 25 ℃	$-\log(K_{sp})$ at 37 ℃
0.5	Monocalcium phosphate monohydrate (MCPM)	$Ca(H_2PO_4)_2.H_2O$	1.14	–
0.5	Monocalcium phosphate anhydrous (MCPA)	$Ca(H_2PO_4)_2$	1.14	–
1	Dicalcium phosphate dihydrate (DCPD)	$CaHPO_4.2H_2O$	6.59	6.63
1	Dicalcium phosphate (DCP)	$CaHPO_4$	6.90	7.02
1.33	Octacalcium phosphate (OCP)	$Ca_8H_2(PO_4)_6.5H_2O$	96.6	95.9
1.5	α-Tricalcium phosphate (α-TCP)	α-$Ca_3(PO_4)_2$	25.5	25.5
1.5	β-Tricalcium phosphate (β-TCP)	β-$Ca_3(PO_4)_2$	28.9	29.5
1.67	Hydroxyapatite (HA)	$Ca_5(PO_4)_3(OH)$	58.4	58.6
2.0	Tetracalcium phosphate (TTCP)	$Ca_4(PO_4)_2O$	38–44	42.4

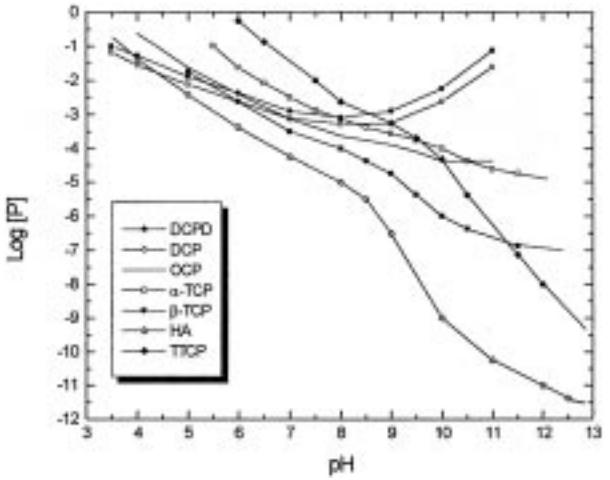

Figure 4 Solubility isotherms of different calcium phosphate salts in equilibrium with their solutions for the ternary system $Ca(OH)_2$–H_3PO_4–H_2O at 37 ℃ in a representation of log [P] versus pH.

been measured when a selected salt in an aqueous solution of only phosphoric acid (H_3PO_4) or calcium hydroxide ($Ca(OH)_2$) has attained equilibrium. Hence, the solution does not contain any additional compound such as hydrochloric acid (HCl) or sodium hydroxide (NaOH) [7], or potassium hydroxide (KOH), nitric acid (HNO_3) or carbon dioxide (CO_2) [13].

In the next subsections some factors are considered which have an effect on the solubility diagrams and so influence the reactivity and relative stability of different salts (as for example Ca/P ratio, temperature (T) or the effect of carbonate ion formation (CO_3^{2-})). The effects of these factors on the solubility isotherms are important in making conclusions about the setting behavior of CPC.

3.2.1. Effect of Ca/P ratio

According to Figs 3 and 4 it can be observed that the Ca/P ratio of the solution changes through the solubility isotherm of each compound due to the fact that the solution pH in the ternary system $Ca(OH)_2$–H_3PO_4–H_2O is adjusted by addition of $Ca(OH)_2$ or H_3PO_4.

Fig. 5 shows the variation of log [Ca]/[P] (right y-axis) versus pH (x-axis) for the isotherms (in a representation of log [Ca] versus pH) of HA and DCP [13]. It can be observed that for pH < 8 the Ca/P ratios for HA and DCP are the same and are not particularly sensitive to pH variation. This behavior is generally observed in systems with low pH values and high electrolyte concentrations [11]. In the interval 3 < pH < 6 the Ca/P ratio approaches a value of 0.5 (Ca/P ≈ 0.5).

Some computer calculations [13] show that this behavior is the result of satisfying the electroneutrality condition of the solution where calcium and phosphate ions are found as Ca^{2+}, $CaH_2PO_4^+$ and $H_2PO_4^-$. It can be shown that at pH = 8 the Ca/P ratio approaches 1 (Ca/P ≈ 1) for HA and DCP, changing both phases at higher pH values. The Ca/P ratio of the solution in contact with DCP increases slowly above 1; for HA, the Ca/P ratio of the solution attains higher values (Ca/P ≈ 220 for pH = 9.5 and Ca/P ≈ 13 500 for pH = 10). These results are as a consequence of the large amounts

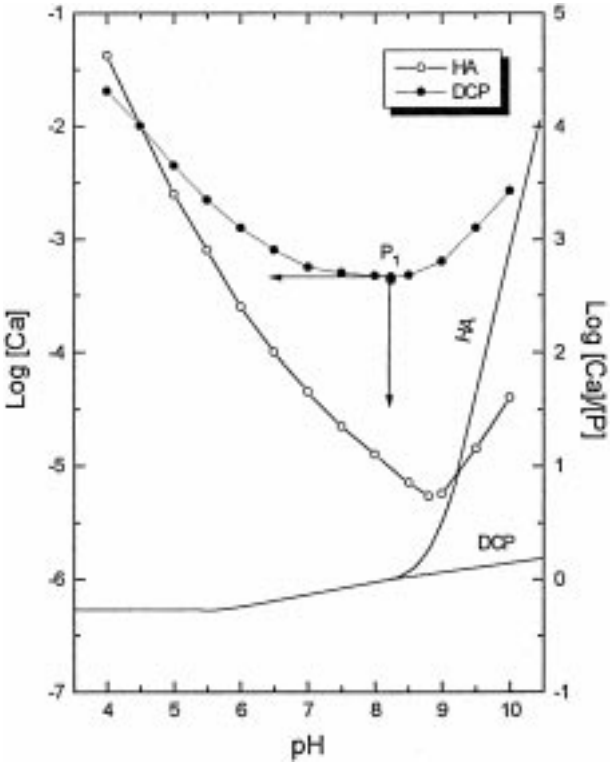

Figure 5 Evolution of Ca/P ratio of solution through solubility isotherms of HA and DCP in the ternary system $Ca(OH)_2$–H_3PO_4–H_2O at 25 ℃. P_1 represents a metastable equilibrium state of DCP in water (pH = 8.2; [Ca]/[P] = 1).

of $Ca(OH)_2$ needed to adjust the pH and of the low phosphorus concentration values found in solution due to the low solubility of HA under those conditions. Fig. 5 shows that HA and DCP will only coexist in equilibrium in that system at pH = 4.5 where the solution will attain a Ca/P ratio of approximately 0.5 (Ca/P ≈ 0.5).

The differences found between the Ca/P ratio of the solution and the corresponding Ca/P ratio of HA (Ca/P = 1.67) and DCP (Ca/P = 1) can be understood by taking into account HA precipitation in a metastable aqueous solution saturated with respect to DCP. This situation is reflected in Fig. 5 for a pH value of 8.2 and a Ca/P = 1. This precipitation process can be summarized by the following chemical reaction

$$5CaHPO_4 + H_2O \rightarrow Ca_5(PO_4)_3OH + 2HPO_4^{2-} + 4H^+ \quad (7)$$

According to this reaction, protons liberated during HA precipitation will reduce the solution pH and, at the same time, the excess of hydrogen phosphate ions will diminish the Ca/P ratio of the solution to below 1. As has been indicated, this spontaneous evolution of one metastable state in solution to the intersection of two solubility isotherms, is called the attraction effect of the singular points [4, 7, 11, 13].

To indicate the influence of the Ca/P ratio of the solution on the solubility isotherms the behavior of isotherms in more complex systems than the ternary system $Ca(OH)_2$–H_3PO_4–H_2O have to be analyzed as for example in the case of $Ca(OH)_2$–H_3PO_4–MX–H_2O, where MX is an electrolyte added to the system for electroneutrality and where M^+ and X^- ions do not

affect the solid phases and do not form complexes with different calcium and phosphate species [4].

Fig. 6 shows the effect of the Ca/P ratio of the solution, in a representation of log [Ca] versus pH, on the solubility isotherms for HA and DCP (at a CO_2 partial pressure of $p(CO_2) = 1.013 \times 10^{-25}$ Pa) and calcite ($CaCO_3$; at a CO_2 partial pressure of $p(CO_2) = 1.013 \times 10^{1.48}$ Pa) in the system $Ca(OH)_2$–H_3PO_4–KOH–HNO_3–CO_2–H_2O at 25 ℃ [13].

Fig. 6 shows that an increase in the Ca/P ratio of the solution is related to an increase in the calcium ion concentration [Ca] in the solution at a fixed pH for different calcium phosphates. The reverse effect on the phosphorus concentration [P] in a representation of log [P] versus pH also applies [13]. The calcium concentration increase is related to a balance mechanism of negative charges coming from NO_3^- ions to satisfy the solution electroneutrality. So, an increase of calcium concentration is related to a decrease in phosphorus concentration in the solution so that the solubility product K_{sp} of the salt is maintained [7]. Similarly, an increase in phosphorus concentration is related to a charge balance mechanism between $H_2PO_4^-$ and K^+ ions. In that case an increase of the phosphorus concentration implies a decrease in the calcium concentration to satisfy the K_{sp} of the calcium phosphate salt. When plotted on a log [Ca]–pH solubility diagram, the points mentioned above indicate that the amount of calcium phosphate salt required to saturate a unit volume of solution is smaller when the difference between the Ca/P ratio of the solution and the Ca/P ratio of the salt is low. This property is called the common ion effect [12]. This effect has to be taken into account when calcium phosphate type cement materials are developed because some additives in the liquid phase can work as accelerators or retarders in the setting reaction acting as common ions [17]. Fig. 6 also shows the tendency of singular points to move to lower pH values when the Ca/P ratio of the solution increases. Moreover, the solubility of $CaCO_3$ increases when the Ca/P decreases as a result of a high proportion of calcium ions forming calcium–phosphate complexes in solution [4, 7, 13].

3.2.2. Effect of temperature

Fig. 7 shows the effect of temperature on solubility isotherms of HA, DCP and $CaCO_3$ in the $Ca(OH)_2$–H_3PO_4–KOH–HNO_3–CO_2–H_2O system [13] for a Ca/P = 1 and a partial CO_2 pressure for HA and DCP of $p(CO_2) = 1.013 \times 10^{-25}$ Pa and for $CaCO_3$ of $p(CO_2) = 1.013 \times 10^{1.48}$ Pa. Temperature influences markedly the HA and DCP solubility isotherms but not that of $CaCO_3$. In general, the solubility of calcium phosphates decreases as temperature increases and this effect is more important at lower pH values. Also, singular points are affected by temperature; the singular point between HA and DCP moves to lower pH values when temperature increases due to the higher sensitivity of HA versus temperature changes as compared with DCP. Given the clinical application of CPBC, body temperature is of great interest. However, as the influence of temperature on isotherms, and so, on singular points, in the interval $25 < T < 37$ ℃ is not important, solubility isotherms at 25 ℃ can be used to predict the thermodynamic behavior of a mixture of calcium phosphates in a cement when solubility isotherms at 37 ℃ are not available.

3.2.3. Effect of CO_3^{2-} ion formation

Fig. 8 shows the influence of partial CO_2 pressure ($p(CO_2)$) on HA, DCPD and $CaCO_3$ isotherms in the $Ca(OH)_2$–H_3PO_4–CO_2–H_2O system [13] and how CO_3^{2-} ion formation in solution can modify the solubility behavior of calcium phosphates. It can be observed that the solubility of HA and DCPD in equilibrium with a saturated pure water solution (see highlighted points in Fig. 8) increases significantly above a certain pH value which is lower for higher $p(CO_2)$. The solubility increase is related to the formation of calcium–carbonate

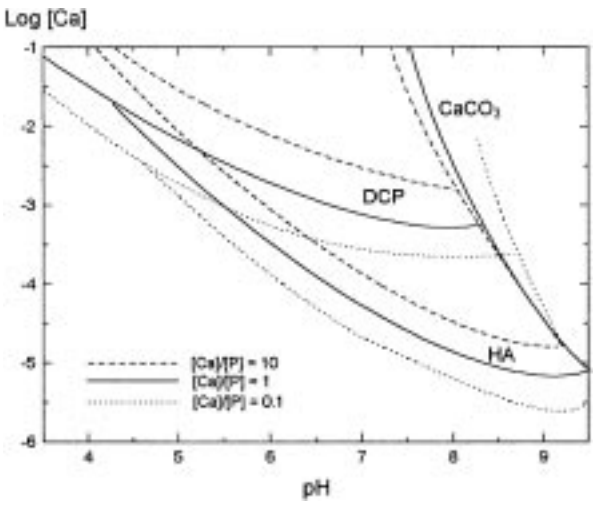

Figure 6 Solubility isotherms of HA and DCP ($p(CO_2) = 1.013 \times 10^{-25}$ Pa) and $CaCO_3$ ($p(CO_2) = 1.013 \times 10^{1.48}$ Pa) at different Ca/P ratios, in the system $Ca(OH)_2$–H_3PO_4–KOH–HNO_3–CO_2–H_2O ($T = 25$ ℃).

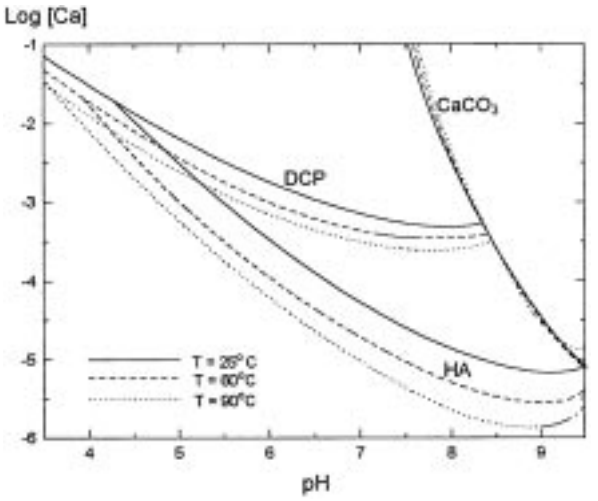

Figure 7 Effect of temperature on the isotherms of HA and DCP ($p(CO_2) = 1.013 \times 10^{-25}$ Pa) and on the isotherm of $CaCO_3$ ($p(CO_2) = 1.013 \times 10^{1.48}$ Pa) in the system $Ca(OH)_2$–H_3PO_4–KOH–HNO_3–CO_2–H_2O (Ca/P = 1).

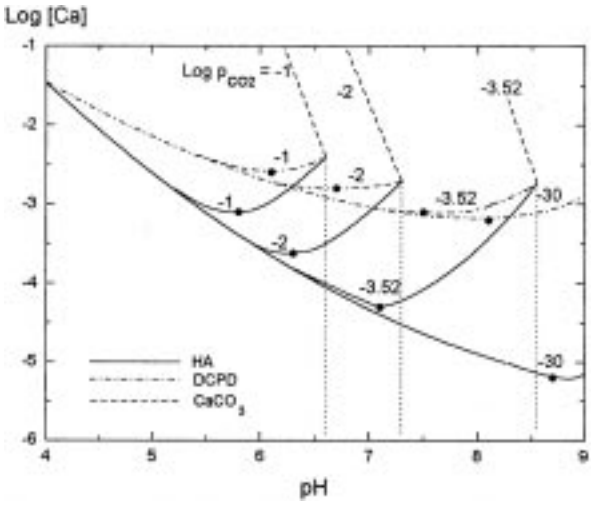

Figure 8 CO_2 partial pressure effect on HA, DCPD and $CaCO_3$ solubility isotherms in the system $Ca(OH)_2$–H_3PO_4–CO_2–H_2O at 25 ℃. Equilibrium conditions in pure water are highlighted for each $p(CO_2)$ by (•) for HA and DCPD and by vertical dotted lines for $CaCO_3$.

complexes that result in a significant increase in the Ca/P ratio of the solution [4, 13]. One of the effects of increasing $p(CO_2)$ is to reduce differences between solubility of different calcium phosphates. For a fixed $p(CO_2)$ value, the solubility of calcium phosphates increases at high pH values up to a point (see dotted vertical lines on Fig. 8) where $CaCO_3$ will be the least soluble phase, so reducing the stability range of calcium phosphates. These effects are known as apatite stability field reduction [3, 4].

According to Fig. 8, the CO_2 partial pressure of the solution must be taken into account when the thermodynamic behavior of a calcium phosphate cement type material is being analyzed. The thermodynamic behavior that results in a dissolution–precipitation process of an aqueous calcium phosphate solution free of CO_2($p(CO_2) = 1.013 \times 10^{-25}$ Pa) is markedly affected when the process develops at a CO_2 partial pressure similar to that of body fluid ($1.67 < p(CO_2) < 6.58$ mPa) [4, 13, 18]. However, the effect of $p(CO_2)$ on the position of singular points is at a minimum [16] and in that sense can be ignored.

3.3. Singular points between calcium phosphates

Table II summarizes all possible singular points occurring in the $Ca(OH)_2$–H_3PO_4–H_2O system at 37 ℃ and at a CO_2 partial pressure of $p(CO_2) = 1.013 \times 10^{-25}$ Pa [7] (see Figs 3 and 4) and $p(CO_2) = 1.66$ mPa [18] with equilibrium pH values. According to the effect of CO_2 partial pressure on position of solubility isotherm and on apatite stability field reduction, the pH of singular points will be the same where pH < 7 [18], for a CO_2 partial pressure of $p(CO_2) = 1.66$ MPa. As can be seen in Table II differences are small except for TTCP. This can be explained according to the large variation in the solubility product constant found for TTCP, as was shown in Table I.

In vitro thermodynamic studies of the above systems under simulated physiological conditions ($T = 37$ ℃ and $p(CO_2) = 1.66$ MPa) give data on the expected *in vivo* behavior of a calcium phosphate system, at least during first setting reaction stages. However, the *in vivo* behavior of a cement in contact with body fluids can not be predicted over long periods of time during hardening and/or resorption processes [19]. Still, some studies show that the bioresorption rate for different systems are related to the relative solubility of calcium phosphates in the cement [20–23]. So, Table II reveals many possibilities of developing CPC for clinical applications and this is the reason why an increasing number of patents [24–34] have evolved in the last decade.

4. Conclusions and future perspectives

The thermodynamics of calcium phosphate salts in an aqueous solution at room or body temperature are the basis for understanding the manufacturing technology involved in CPBCs for clinical applications. Knowledge of the limitations of this thermodynamic approach and understanding the necessity of performing kinetic studies for different calcium phosphate systems in real setting and hardening situations opens-up the possibilities for new CPBCs with better *in vitro* and *in vivo* properties for clinical applications.

CPBCs are formed by the combination of a solid powder phase of calcium phosphates and an aqueous solution. Although the principle of the idea is simple, the properties of CPCs such as setting times, compressive strength, porosity, solubility, *in vivo* resorption velocity, etc., are affected by a large number of technological factors during manufacture and processing.

Better control of cement powder microstructure and chemistry may lead to improvements in initial setting properties and the final mechanical strength. The incorporation of biodegradable polymers in cement formulations can improve the rheology and workability of cement pastes, helping to improve surgical technique through less invasive procedures. By the optimization of calcium phosphate cement resorption and osteoconduction through microstructural modifications and by the incorporation of bone growth factors, it is thought that the bone healing process will be accelerated. In that sense, future research is being directed towards systems with amorphous characteristics and which have a faster *in vivo* resorption than systems currently under investigation.

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TABLE II Singular points between calcium phosphates in the system $Ca(OH)_2$–H_3PO_4–H_2O at 37 ℃

Pairs	Chemistry description	pH ($p = 1.013 \times 10^{-25}$ Pa)	pH ($p = 1.66$ MPa)
TTCP-MCPM	$Ca_4(PO_4)_2O$–$Ca(H_2PO_4)_2.H_2O$	6.5	5.3
TTCP-DCPD	$Ca_4(PO_4)_2O$–$CaHPO_4.2H_2O$	8.5	6.5
TTCP-DCP	$Ca_4(PO_4)_2O$–$CaHPO_4$	8.8	6.8
TTCP-α-TCP	$Ca_4(PO_4)_2O$–α-$Ca_3(PO_4)_2$	9.5	*
TTCP-OCP	$Ca_4(PO_4)_2O$–$Ca_8(HPO_4)_2(PO_4)_4.5H_2O$	10.0	*
TTCP-β-TCP	$Ca_4(PO_4)_2O$–β-$Ca_3(PO_4)_2$	11.3	*
α-TCP-MCPM	α-$Ca_3(PO_4)_2$–$Ca(H_2PO_4)_2.H_2O$	5.5	5.5
α-TCP-DCPD	α-$Ca_3(PO_4)_2$–$CaHPO_4.2H_2O$	7.8	*
α-TCP-DCP	α-$Ca_3(PO_4)_2$–$CaHPO_4$	8.2	*
β-TCP-MCPM	β-$Ca_3(PO_4)_2$–$Ca(H_2PO_4)_2.H_2O$	4.4	4.4
β-TCP-DCPD	β-$Ca_3(PO_4)_2$–$CaHPO_4.2H_2O$	5.4	5.7
β-TCP-DCP	β-$Ca_3(PO_4)_2$–$CaHPO_4$	6.0	6.0
OCP-β-TCP	$Ca_8(HPO_4)_2(PO_4)_4.5H_2O$–β-$Ca_3(PO_4)_2$	4.7	4.7
OCP-DCPD	$Ca_8(HPO_4)_2(PO_4)_4.5H_2O$–$CaHPO_4.2H_2O$	6.2	6.2
OCP-DCP	$Ca_9(HPO_4)(PO_4)_5OH$–$CaHPO_4$	6.9	*
HA-MCPM	$Ca_{10}(PO_4)_6(OH)_2$–$Ca(H_2PO_4)_2.H_2O$	3.5	3.3
HA-DCPD	$Ca_{10}(PO_4)_6(OH)_2$–$CaHPO_4.2H_2O$	3.8	3.1
HA-DCP	$Ca_{10}(PO_4)_6(OH)_2$–$CaHPO_4$	4.3	4.3
MCPM-DCP	$Ca(H_2PO_4)_2.H_2O$–$CaHPO_4$	2.7	2.7
MCPM-DCPD	$Ca(H_2PO_4)_2.H_2O$–$CaHPO_4.2H_2O$	3.2	3.5

*Not found in the reviewed literature

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