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Bioceramics of Calcium Phosphate

Edited by
Klaas de Groot

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Editor

Klaas de Groot, Ph.D.
Professor of Materials Science
Department of Biomaterials
Schools of Dentistry and Medicine
Free University
Amsterdam, The Netherlands

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INTRODUCTION

The discovery, by medical researchers, that the mineral phase of bones and teeth consisted of calcium phosphate salts, has been the start of interest in these salts as a material to enhance healing of bony fractures. This means that calcium phosphate has been in the picture for almost a century. Nevertheless, ceramics of calcium phosphate salts are considered to be "new" materials. The word "new" obviously refers neither to the calcium phosphate salts themselves, nor to their potential importance for bone repair, but to the fact that only at the end of the 1960s the preparation of solids from calcium phosphate powders was achieved. The technique used most often is sintering.

Less than 15 years after the first publication appeared on preparing solid materials of calcium phosphate, this new class of bioceramics is on the verge of being widely applied in the clinic. Several producers have already put their products on the market.

Still, the material has several biomechanical limitations, while some other aspects, like rate of biodegradation, cannot be quantitatively predicted yet. In this book, a number of authors have tried to put together the current knowledge related to calcium phosphate bioceramics.

The first chapters are fundamental, in that the physical chemistry of calcium phosphate salts is discussed, along with mineralization (with emphasis on teeth) and remodelling of mineralized tissues. Thereafter follows a treatment of the influence of implants on surrounding hard tissues. This topic is followed by a chapter on preparation methods and biomechanical and biological aspects of calcium phosphate implants. In conclusion, two chapters are devoted to (possible) dental and medical applications. It is hoped that basic researchers can use the book in their efforts to improve this promising class of materials further, and that clinicians are inspired to define further possibilities and — at least as important — limitations.

THE EDITOR

Klaas de Groot, Ph.D., is Professor of Biomaterials in the Schools of Dentistry and Medicine at the Free University of Amsterdam, The Netherlands. He is head of the Department of Biomaterials. He received his Ph.D. in Physical Chemistry in 1968 from the University of Groningen, The Netherlands. His thesis was based on research carried out at the University of North Carolina, Department of Chemistry. During the years 1968 to 1971, he worked as research associate at various Dutch universities. Since 1971, he has been on the faculty of the Free University, first as Associate Professor of Biomaterials and, since 1980, as full professor. In 1972, he spent a sabbatical half-year at the UCLA Bone Research Laboratory, and in 1977, a summer course as visiting associate professor at the University of Utah. Professor de Groot is a member of several professional societies, among which include the IADR, the Society of Biomaterials, and the European Society of Biomaterials. During the years 1976 to 1980, he was council member of the latter society.

He has been recipient of many research grants and contracts from Dutch funding agencies and collaborated closely with several indutries. He has been Dean of the Dental School of the Free University, and Chairman of its Research Committee. Currently, he is Vice-Dean.

Professor de Groot has authored or co-authored more than 100 scientific communications in the field of biomaterials. His major research interests include bioceramics of calcium phosphate.

CONTRIBUTORS

Klaas de Groot, Ph.D.
Professor of Materials Science
Department of Biomaterials
Schools of Dentistry and Medicine
Free University
Amsterdam, The Netherlands

F. C. M. Driessens, Ph.D.
Professor of Dental Materials and Technology
Dental School
Catholic University of Nijmegen
Nijmegen, The Netherlands

Louw Feenstra, M.D.
Professor of ENT
Department of ENT
Academic Hospital
Free University
Amsterdam, The Netherlands

Peter Griss, M.D., P.D.
Lindenhof Orthopaedic Hospital
Faculty for Clinical Medicine at Mannheim
University of Heidelberg
Mannheim, West Germany

Gunther Heimke, Ph.D.
Friedrichsfeld GmbH
Steinzeug- und Kunststoffwerke
Mannheim, West Germany

J. C. Maltha, Ph.D.
Department of Oral Histology
University of Nijmegen
Nijmegen, The Netherlands

P. J. van Mullem, Ph.D.
Department of Oral Histology
University of Nijmegen
Nijmegen, The Netherlands

J. H. M. Woltgens, Ph.D., D.M.D.
Department of Biomaterials
Schools of Dentistry and Medicine
Free University
Amsterdam, The Netherlands

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Chapter 1

FORMATION AND STABILITY OF CALCIUM PHOSPHATES IN RELATION TO THE PHASE COMPOSITION OF THE MINERAL IN CALCIFIED TISSUES

F. C. M. Driessens

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I. INTRODUCTION

Choices must be made on several levels of magnification for the design of materials for implantation. On the molecular level, it is important to choose either a material that is indifferent under physiological conditions or a material that resembles the tissue for which it is substituted. Calcium phosphates belong to the second category. They are used mainly as substitutes for or improvement of calcified tissues such as bone and dental hard tissues. The main components of the mineral particles in these tissues are calcium and phosphate.

For the preparation of calcium phosphates for the purpose of implantation, knowledge about the formation and stability of calcium phosphates in general is a prerequisite. This chapter is partly intended to convey knowledge about these aspects of calcium phosphates. In this context it is also important to pay attention to the degree of resemblance that can be obtained between synthetic calcium phosphates and the biominerals of the calcified tissues. Therefore, it is necessary to include in this chapter the different concepts published about the nature of these biominerals, either in bone, dentin, or tooth enamel.

In the following chapter, attention will focus on the biological factors that determine the stability of the above-mentioned biominerals under physiological and eventually pathological conditions. This will be done for tooth enamel in Chapter 2 and for bone and bone mineral in Chapter 3. In order to relate the biological stability of the biominerals with these concepts published concerning their nature, an estimate about the physicochemical factors that determine the stability of these biominerals is also presented here.

II. FORMATION OF CALCIUM PHOSPHATES

Polycrystalline calcium phosphates can be obtained in the form of a loose powder by precipitation from aqueous solution. These precipitates can contain different amounts of H^+ and OH^- ions as well as water molecules, depending on the experimental conditions. Through hydrothermal techniques, the temperature can be raised above 100°C and in practice up to about 1000°C. The preparations can also contain "foreign ions" when the precipitations are carried out in their presence in the aqueous solution.

A way to obtain polycrystalline calcium phosphates in the form of more or less dense bodies is by applying ceramic techniques. In this way, the porosity can be lowered either by "hotpressing" or by liquid sintering. Also, the calcium phosphates can be doped with "foreign ions" in these techniques. Both ways of synthesis are relevant to the production of calcium phosphates for the purpose of implantation and, therefore, will be dealt with in this section.

A. Formation of Calcium Phosphates by Precipitation From Aqueous Solutions

Early studies used the addition of Ca^{2+}-containing aqueous solutions to phosphate-containing aqueous solutions or the reverse to obtain precipitates of calcium phosphates. Cameron and Hurst[22] have mentioned the existence of dicalcium phosphate (DCP), dicalcium phosphate dihydrate (DCPD), tricalcium phosphate (TCP), and apatite, of which all but the latter were characterized by their chemical composition at that time, whereas apatite was known as a mineral. Bassett[10] specified the apatite being in equilibrium with aqueous solutions erroneously as oxyapatite, but found firm evidence for metastable equilibria, in which $CaHPO_4$ (DCP) and $CaHPO_4 \cdot 2\ H_2O$ (DCPD) could exist as solid phases, the latter forming preferentially under 36°C.[11] The first author to present the right formula for hydroxyapatite $Ca_{10}(PO_4)_6(OH)_2$ probably was Forster.[58] Schleede, Schmidt, and Kindt[148] were able to prepare chemically pure hydroxyapatite OHA by precipitation. For this purpose, they subjected either an unstable precipitate of defective hydroxyapatite $Ca_9(PO_4)_5(HPO_4)(OH)$ or a high-temperature product of tetracalcium phosphate $Ca_4(PO_4)_2O$ to hydrolysis at temperatures up to 90°C.

The preparation of pure octocalcium phosphate (OCP) was first carried out by Newesely.[123] The exact number of water molecules in its formula $Ca_8(HPO_4)_2(PO_4)_4 \cdot 5H_2O$ was elucidated by the determination of its crystal structure.[19] According to Newesely,[123] OCP is formed in a pure form, when $CaHPO_4$ is hydrolyzed in a solution buffered somewhere between pH 5.8 and 7.1. The temperature must be kept below 65°C at pH 5.8 and below 38°C at pH 7.1. Direct precipitation is also possible at pH 6.5 from acetate-phosphate buffers by the addition of calcium nitrate solutions.

Sanfourche[142] found that under certain conditions, the first precipitate was neither one of the above-mentioned crystalline compounds. It was "gelatinous" and it could take days before it was transformed into one of these crystalline compounds. Amorphous calcium phosphate (ACP) has been characterized by several methods.[161] It contains HPO_4^{2-} ions and its Ca/P ratio was found to be 1.36 ± 0.02, initially. Upon washing it changed to 1.47 ± 0.03.[163] However, unwashed samples had a constant Ca/P ratio of 1.42 ± 0.02 during suspension over several hours (see Table 2).[163] This indicates that ACP is primarily a very finely dispersed whitlockite which can absorb either HPO_4^{2-} or Ca^{2+} ions. The structure of the mineral whitlockite was studied by Frondel.[60] It can also exist without foreign ions and then has the composition $Ca_{10}(HPO_4)(PO_4)_6$.[147] The conclusion that ACP is a very finely dispersed whitlockite is enforced by the fact that Meyer and Eanes[110] found that the ionic product of whitlockite is constant over ACP suspensions.

A compilation of the calcium phosphates pertinent to aqueous systems is given in Table 1, together with the space group of their crystal structure and the most reliable value of their solubility product.

The occurrence of metastable states during the precipitation and formation of calcium phosphates has already been mentioned. Even among more recent studies there is not much agreement about the nature of the first precipitate and the consecutive transitions into other calcium phosphates, although physical methods like monitoring of pH[188] and X-ray diffraction analysis[168] have been applied in this field since their development. The latter authors postulate the formation of defective hydroxyapatites which can vary in composition from $Ca_9(PO_4)_6(H_20)_2$ to $Ca_{10}(PO_4)_6(OH)_2$. Sanfourche[142] observed that it could take days before such compounds were formed from the original "gelatinous" precipitate which apparently was ACP. Fouretier[59] found that the first precipitate was a mixture of DCPD and ACP, which hydrolyzed to a "hydrated" apatite. Arnold[4] proposed that OCP and OHA form a continuous series of solid solutions so that no two preparations with composition lying between them

Table 1
PERTINENT CALCIUM PHOSPHATES RELEVANT TO AQUEOUS SYSTEMS, THEIR FORMULA, STRUCTURE AND NEGATIVE LOGARITHM OF THE SOLUBILITY PRODUCT pK_{sp}

Ca/P	Notation	Formula	Space group	pK_{sp}	Mineral same
1	DCP	$CaHPO_4$	$P\bar{1}$	6.90	Monetite
1	DCPD	$CaHPO_4 \cdot 2H_2O$	C2/c	6.59	Brushite
1.33	OCP	$Ca_8(HPO_4)_2(PO_4)_4 \cdot 5H_2O$	$P\bar{1}$	68.6[a]	—
1.43	WH	$Ca_{10}(HPO_4)(PO_4)_6$	R3c	81.7[a]	Whitlockite
1.67	OHA	$Ca_{10}(PO_4)_6(OH)_2$	$P6_3/m$	117.2	Hydroxyapatite
1.50	DOHA	$Ca_9(HPO_4)(PO_4)_5(OH)$	$P6_3/m$	85.1[a]	Defective hydroxy-apatite

[a] Estimate.

would be likely to be identical. Strates, Neuman, and Levinkes[158] found that DCPD is the first precipitate and that this hydrolyzes into a defective hydroxyapatite. Brown, Smith, Lehr, and Frazier[20] postulated that OCP and OHA do not form solid solutions, but form instead epitactical and topotactical mixtures with a sandwich structure. Eanes, Gillesen, and Posner[46] first found an amorphous calcium phosphate which hydrolyzes in about 5 hr into a defective apatite. Newesely[126] proved that the type of first precipitate depends largely on the degree of supersaturation. At low supersaturation, DCPD was formed which, above pH 6.3, hydrolyzed into OCP. At high supersaturation an amorphous product was formed directly from aqueous solution. Combining this information, one comes to the scheme of reactions given in Figure 1. Most experiments mentioned here were carried out in the range $5<pH<8$. It must be kept in mind that the transformations are pH-sensitive[126] which may explain, together with the varying degrees of supersaturation, the apparent differences found between the various authors.

Meyer and Eanes[111] found that the aqueous solutions in equilibrium with the crystalline phase first formed from OCP show up the constant solubility product of OCP. However, at the end of the amorphous-to-crystalline transformation, not the solubility product of OCP, but that of TCP appeared to be constant. In agreement with this Heughebaert and Montel[76] found that the composition of the crystalline phase right after completion of its formation from ACP agrees with the formula $Ca_9(HPO_4)_x(PO_4)_{6-x}(OH)_x$. This compound at $x=1$ will be called defective hydroxyapatite (DOHA). It is not clear yet whether preparations having a composition between that of DOHA and OHA are solid solutions or mixtures of these two apatites.

From the reaction scheme of Figure 1, it is seen that OHA is the end product. This appears to be so in the range $pH > 4$. Elevation of the temperature increases the rate with which the end product is formed. Therefore, the most common method of preparation of OHA is by precipitation from a boiling aqueous solution.[178] Hydrothermal syntheses at higher temperatures and pressures have also been carried out.[3,140,154] The main effect is the increase of the average particle size.

1. Incorporation of "Foreign" Ions: Fluoride

Preparation of calcium phosphates in the presence of certain "foreign" ions results in the partial incorporation of these ions in the crystals of the precipitate. In this way, Moreno, Kresak, and Zahradnik[116] were able to prepare solid solutions of OHA and fluorapatite FA of the formula

$$Ca_5(PO_4)_3 OH_{1-X} F_X \qquad (1)$$

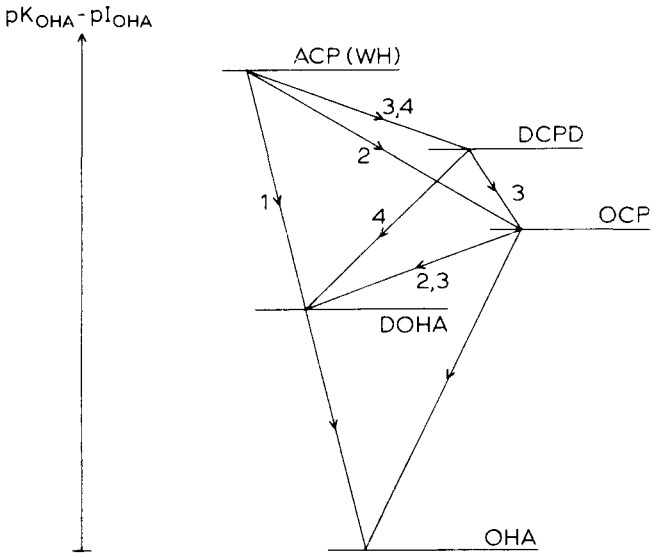

FIGURE 1. Pathways of maturing of calcium phosphate precipitates. (From Driessens, F. C. M., *Bull. Soc. Chim. Belg.*, 89, 663, 1980. With permission.)

by mixing an ammonium phosphate and ammonium fluoride-containing solution with a calcium nitrate solution at a certain rate at boiling temperatures. CO_2 was excluded from the reaction vessel. Care must be taken in this technique to avoid the formation of CaF_2 as an impurity phase due to its limited solubility.

It appears that the presence of F^- ions in the aqueous solution promotes the formation of the apatite phase.[7,8,47,124] It curtails the metastable states. Hydrolysis of acidic calcium phosphates such as DCPD and OCP into OHA is also accelerated by the presence of some F^- ions in the aqueous solutions.[43,44,123]

2. Incorporation of "Foreign" Ions: Carbonate

The CO_3^{2-} ions also interfere with calcium phosphates. Labarthe, Bonel, and Montel[97] succeeded in obtaining carbonated apatites by co-precipitation of calcium carbonate and phosphate. X-ray analysis of the products revealed their apatitic nature, whereas chemical analysis showed that their structure formula is probably

$$Ca_{10-x+u}(PO_4)_{6-x}(CO_3)_x(OH)_{2-x+2u} \quad (2)$$

with $0 \leqslant x \leqslant 2$ and $0 \leqslant u \leqslant \frac{1}{2}x$.[98] An alternative formula for the same compounds was proposed by Bonel, Labarthe, and Vignoles:[15]

$$Ca_{10-x+u}(PO_4)_{6-x}(CO_3)_x(H_2O)_z(OH)_{2-x+2u} \quad (3)$$

Through the equilibrium

$$H_2O + PO_4^{3-} \rightleftharpoons OH^- + HPO_4^{2-} \quad (4)$$

which was proven to play a role in defective apatites by infrared spectroscopy.[62] Equation 3 might account for HPO_4^{2-} ions and for additional OH^- groups within these apatites. The lattice parameters of such preparations are not yet well established and apparently depend on the way of precipitation.[99]

A probably less crystalline product was obtained by Hayek, Konetschny, and Schnell.[75] They made a slurry of DCPD and $CaCO_3$, heated it to 37°C for several days while air bubbled through the mixture. Analysis of the solid particles revealed the composition

$$Ca_8\ (HPO_4)_{0.8}\ (CO_3)_{1.2}\ (PO_4)_4 \cdot 5\ H_2O \qquad (5)$$

whereas the vague X-ray diffraction pattern and the infrared spectrum were similar to that of OCP preparations. This suggests a partial substitution of HPO^{2-} by CO_3^{2-} ions leading to the extreme composition

$$Ca_8\ (CO_3)_2\ (PO_4)_4 \cdot 5\ H_2O \qquad (6)$$

which, apart from the water molecules, is identical to the extreme composition of Equation 3 at x=2 and z=u=0. The composition of these compounds indicates that CO_3^{2-} ions replaces PO_4^{3-} ions in their structure, which is confirmed by their infrared spectrum.[15]

LeGeros, Shirra, Miravite, and LeGeros[103] studied the stability of ACP in CO_3^{2-} containing aqueous solutions and found that the crystallization was retarded. Although it is not clear in which parts of the pathways of Figure 1 this happens, it might well be in the first crystallization to OCP, as Newesely[124] had suggested that carbonate reacts with OCP.

Eysel and Roy[51] carried out a reaction between phosphate-containing aqueous solutions and $CaCO_3$ in the form of aragonite under hydrothermal conditions in the range of 260° to 400°C. They found an intergrowth and overgrowth of the aragonite crystals with an apatite-like calcium phosphate. They[141] also claimed that in this way porous, but coherent apatite bodies could be made from coral which might be suitable for implantation.

3. Incorporation of "Foreign" Ions: Sodium and Carbonate

Particular attention must be paid to the combined effect of Na^+ and CO_3^{2-} incorporation into calcium phosphates. Early reports on the preparation of such compounds do not mention their alkali content.[94,136] Newesely[125] prepared a number of apatites containing sodium and carbonate by hydrothermal synthesis at 400°C. Newesely mentioned that the samples contained between 0.5 and 1.1% sodium without giving the exact composition of each individual product.

Simpson[151] prepared carbonated apatites containing up to 2.2% sodium by reaction of $CaCO_3$ with Na^+ and phosphate-containing aqueous solutions. The CO_3 content was about 7.5%. Their X-ray diffraction pattern was that of well crystalline apatites, when prepared at pH 7. Later Simpson[152] showed that there was an inverse relation between the carbonate content of the precipitate and the PO_4^{3-} content of the aqueous solution during precipitation.

Zapanta-LeGeros[193] prepared well crystalline, sodium- and carbonate-containing apatites by dropwise addition of a calcium acetate solution to a boiling aqueous solution of Na_2HPO_4 and $NaHCO_3$. Carbonate probably substitutes for phosphate in their structure because there was an inverse relation between the carbonate and the phosphate content.[101] The sodium content was proportional to the carbonate content.[100]

Vignoles, Bonel, and Montel[184] have repeated the preparations of these apatites according to LeGeros and reported that their composition agrees with the formula

$$Ca_{10-x}\ Na_{2/3\,x}\ (PO_4)_{6-x}\ (CO_3)_x\ (H_2O)_y\ (OH)_{2-1/3\,x} \qquad (7)$$

whereby $0 \leqslant x \leqslant 3$ and $0 \leqslant y \leqslant x$. According to this formula the Ca/P ratio can vary from 1.67 to 2.33

4. Incorporation of "Foreign" Ions: Potassium and Carbonate

The combination of potassium with carbonate has similar effects on calcium phosphates. Simpson[151] reacted potassium phosphate-containing aqueous solutions with calcite. Below pH 6.1 only DCPD formed. Above pH 6.1 a poorly crystalline apatite formed which contained about 3% CO_3 and 0.5% potassium. Above pH 8 better crystalline apatites were formed. Later, Simpson[153] reported on the formation of potassium- and carbonate-containing apatites by evaporation of water from a solution containing Ca-EDTA and potassium phosphate 100°C between pH 6 and 14. These products contained up to 1% CO_3 and 1% potassium.

LeGeros[100] prepared potassium- and carbonate-containing apatites from a boiling solution of potassium phosphate and potassium carbonate by adding dropwise a solution of calcium acetate. From the reported chemical composition, the following approximate formula can be calculated:

$$Ca_{10-\frac{1}{2}x}\, K_{\frac{1}{2}x}\, (PO_4)_{6-\frac{1}{2}x}\, (CO_3)_x (OH)_{2-\frac{1}{2}x} \qquad (8)$$

The products were contained in the range of $1 \leqslant x \leqslant 3$.

5. Incorporation of "Foreign" Ions: Magnesium

The presence of Mg^{2+} ions in the aqueous solution stabilizes the structure of whitlockite and causes its formation in preference of other calcium phosphates under conditions of precipitation.[74] Boulet, Marier, and Rose[17] produced evidence from precipitation studies that Mg^{2+} ions are incorporated in the "gelatinous" precipitate of ACP. Bachra, Trautz, and Simon[7] determined a so-called precipitation diagram for the system "calcium-carbonate-phosphate" and found that in the presence of Mg^{2+} ions, the ACP phase field expanded at the expense of the DOHA field. In another paper they reported that the Mg^{2+} ion stabilized the ACP precipitate and disturbed the crystallization of the apatite phase. Termine and Posner[161] reported that at a given degree of supersaturation the presence of Mg^{2+} ions enhanced ACP formation. Rowles[139] prepared Mg-containing whitlockite by precipitation and found that its formula was

$$Ca_9\, (Ca_{1-x}\, Mg_x)(HPO_4)\, (PO_4)_6 \qquad (9)$$

for preparations below 100°C. Gopal, Calvo, Ito, and Sabine[63] made such preparations under hydrothermal conditions and found the same formula for their products prepared in the range of 700 to 1000°C.

The presence of Mg^{2+} ions can retard the transformation of ACP (finely dispersed whitlockite) into other calcium phosphates. Termine, Peckauskas, and Posner[162] determined the time that elapsed during the solution-mediated transformation of ACP into DOHA. They found that addition of small amounts of Mg^{2+} ions increased this period considerably. Brown, Smith, Lehr, and Frazier[20] reported that Mg^{2+} ions in a concentration as low as 0.001 mol l^{-1} completely blocked the hydrolysis of OCP into DOHA. Boulet, Marier, and Rose[17] found that Mg^{2+} ions had no effect on the formation of DCPD in precipitation studies from slightly acidic solutions. Neuman and Mulryan[122] carried out exchange studies on DOHA slurries with Mg^{2+}-containing aqueous solutions and found that the Mg^{2+} ions were not incorporated in the solid apatite.

6. Incorporation of Other "Foreign" Ions

Because of their biological importance the effect of the "foreign ions" mentioned

here has been investigated thoroughly. Other "foreign ions" may have similar effects like Sr^{2+},[174] Pb^{2+}, Zn^{2+}, Mn^{2+}, Fe^{3+}, and Cd^{2+}.[23-25,56,120,192] They mainly affect the apatite structure, but are not likely to be biologically advantageous for making calcium phosphates for implantation purposes.

B. Formation of Calcium Phosphates By Solid-State Reaction

Solid state reactions at temperatures beyond about 700°C ultimately result in one calcium phosphate or a mixture of more calcium phosphates, of which the composition depends only on the proportioning of nonvolatile components, the partial pressure of the volatile components, the temperature, and the total pressure. For this reason it is not necessary to name the exact ingredients from which the different authors obtained the several calcium phosphates. As calcium phosphates with a ratio $Ca/P < 1$ are easily soluble and hydrolyze very quickly, they are not suitable for implantation purposes and therefore will not be considered here.

In the range $Ca/P \geqslant 1$ the phases CPP or calcium pyrophosphate $Ca_2P_2O_7$, TCP or tricalcium phosphate $Ca_3(PO_4)_2$ and tetracalcium phosphate $Ca_4(PO_4)_2O$ are known to be formed from the melt. The first two phases occur in different crystallographic forms as a function of temperature, as will be shown in Section III. Tetracalcium phosphate is not stable in air below about 1420°C, but reacts with water vapor according to:[167]

$$3\,Ca_4(PO_4)_2O + H_2O \rightarrow Ca_{10}(PO_4)_6(OH)_2 + 2\,CaO \qquad (10)$$

Although Tromel[167] rightly claimed that pure oxyapatite $Ca_{10}(PO_4)_6O$ does not exist, Riboud,[131] Seuter,[150] and Verbeeck, Heyligers, Driessens, and Schaeken[179] produced evidence that "hydroxyapatites" obtained by solid-state reaction at high temperatures are in fact oxyhydroxyapatites of the formula

$$Ca_{10}(PO_4)_6(OH)_{2-2x}O_x\,V(OH)_x \qquad (11)$$

in which V(OH) means a vacancy in the OH sublattice. The value of x depends on the temperature and the partial water vapor pressure.

Welch and Gutt[187] have shown that α-TCP as well as β-TCP, being the high and low temperature form of TCP, both show another type of deviation from stoichiometry. They both seem to be stable in a certain range $Ca/P < 3/2$. These authors made their investigations at temperatures beyond 1000°C. Recently, Schaeken, Driessens, and Verbeeck[147] found that "β-TCP" prepared at about 900°C under moist CO_2 has the stoichiometry of whitlockite and is stable only in a narrow range: $Ca/P = 1.48 \pm 0.01$. Whether these preparations contain water is still under investigation. In this context it is important to note that the transformation α-TCP$\leftrightarrow\beta$-TCP depends strongly on the partial water vapor pressure.[18] It is also noteworthy that these authors[18] observed that extra CaO was necessary to form α-TCP out of β-TCP. Although these data show that one might doubt whether the nature of "β-TCP" in fact is that of whitlockite, the designation β-TCP will be maintained in this paper to preparations of this phase at high temperature.

1. Incorporation of Halides

Wallaeys[186] demonstrated that fluorapatite $Ca_{10}(PO_4)_6F_2$ and chlorapatite $Ca_{10}(PO_4)_6Cl_2$ were formed when calcium phosphates were heated with CaF_2 and $CaCl_2$, respectively. This was confirmed by Montel[113] for fluorapatite. Montel also showed that in the absence of water vapor, the excess of phosphorus and fluoride volatilizes as POF_3. Later, Prener[132] showed that these apatites had deviations from stoichiometry according to the formula

$$Ca_{10-x}(PO_4)_6F_{2-2x} \quad (12)$$

due to the fact that they tend to be in equilibrium with CaF_2 vapor.

Schaeken, Verbeeck, Driessens, and Thun[145] intended to prepare solid solutions of hydroxyapatite and fluorapatite of the formula

$$Ca_{10}(PO_4)_6(OH)_{2-2x}F_{2x} \quad (13)$$

by heating mixtures of $CaHPO_4$, $CaCO_3$, and CaF_2 under moist air. Their samples lost some fluoride during this heating and they propose a formula

$$Ca_{10}(PO_4)_6(OH)_{2-2x-2y}F_{2x}O_yV(OH)_y \quad (14)$$

which involves deviations from stoichiometry of the type in Equation 11.[176]

Wallaeys and Chaudron[185] prepared solid solutions of fluorapatite and chlorapatite of the formula

$$Ca_{10}(PO_4)_6Cl_{2-2x}F_{2x} \quad (15)$$

by heating mixtures of chlorapatite and CaF_2. Heating results in the formation of $CaCl_2$ as a byproduct which shows that fluorapatite is more stable than chlorapatite.

From the work of McConnell,[108] Hägele and Machatschki,[70] and Klement,[90] it follows that the phosphorus atoms in fluorapatite can be replaced partially or totally by other atoms. Charge compensation can be achieved in various ways:

$2\,P^{5+}$ replaced by Si^{4+} and S^{6+}

Ca^{2+} and P^{5+} replaced by Me^{3+} and Si^{4+}, in which Me^{3+} = rare earth

Ca^{2+} and P^{5+} replaced by Me^{+} and S^{6+}, in which $Me^{+} = Na^{+}$

Klement and Haselbeck[91] described mixed apatites of the formula

$$Ca_{10-x}Me_x(PO_4)_6Cl_2 \quad (16)$$

where Me stands for Zn and Cu (x up to 4) and for Co (x up to 3). A compound of the formula $Ca_8Na_2(PO_4)_6$ has been reported by Harth.[73] Kreidler and Hummel[93] showed that fluorapatites similar to Equation 16 can be formed for nickel and magnesium (up to x=0.8).

2. Incorporation of Silicate

Nurse, Welch, and Gutt[127] investigated the system Ca_2SiO_4–$Ca_3(PO_4)_2$. They found that the incorporation of small amounts of Ca_2SiO_4 in TCP stabilized the α-TCP structure down to lower temperatures. In this system, silicocarnotite is found as a separate phase. Its composition varies somewhat around the formula $Ca_5(PO_4)_2(SiO_4)$ and it is stable up to 1450°C. Its structure is somewhat related to that of hydroxyapatite.[31] Nurse, Welch, and Gutt[127] also formed a new compound having the formula $Ca_7(PO_4)_2(SiO_4)_2$ which is stable up to 1125°C. They confirmed the existence of a very high temperature form of TCP, the so-called $\bar{\alpha}$-TCP form which is isostructural with Ca_2SiO_4 and which forms a continuous series of solid solutions at temperatures greater than 1440°C.[9] Such solid solution at the composition $Ca_9(PO_4)_2(SiO_4)_3$ seems to be stable down to 500°C and may be lower. Their results have been confirmed largely by Fix, Heymann, and Heinke.[55]