CHAPTER 2
THEORY

2.1 Chemistry and physics of calcium phosphate ceramics

Calcium phosphate (Ca-P) of biological significance are:
(LeGeros, 1991)

- Amorphous calcium phosphate (ACP)

- Brushite or dicalcium phosphate dihydrate (DCPD) ,$CaHPO_4. 2H_2O$

- Monetite or dicalcium phosphate anhydrous (DCPA) , $CaHPO_4$

- Tetracalcium phosphate (TTCP), $Ca_4P_2O_9$

- Octacalcium phosphate (OCP) , $Ca_8H_2(PO_4)_6. 5H_2O$

-Whitlockite or tricalcium phosphate (β-TCP) , $Ca_3(PO_4)_2$

- Calcium pyrophosphate dihydrate (CPPD) , $Ca_2P_2O_7$

- Apatite (Ap) calcium-OH-apatite , $Ca_{10}(PO_4)_6(OH)_2$,HA

The current knowledge of calcium phosphate bioceramics is best summarized in Figs. 2.1 – 2.4
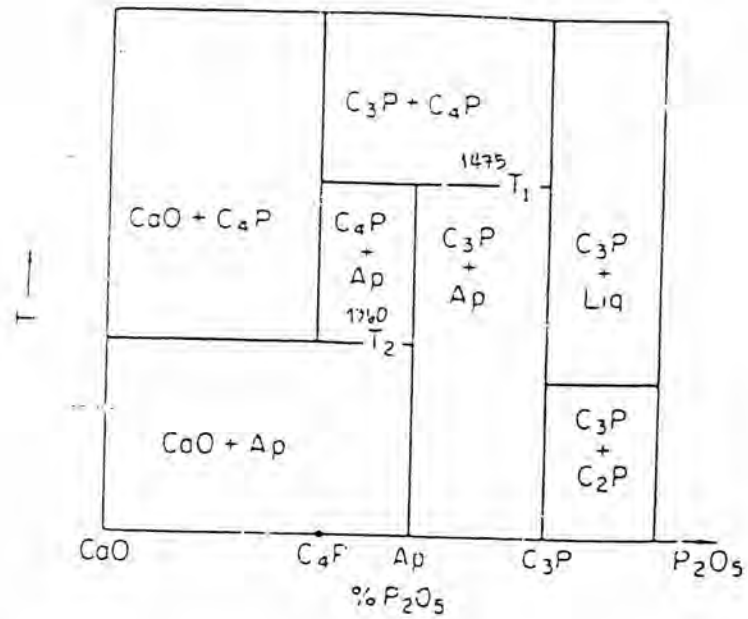
Fig. 2.1 Phase diagram of CaO/P_2O_5 mixtures AP: apatite(HA), C_nP :
component with the formula $(CaO)_n(P_2O_5)$ with Ca/P = n/2
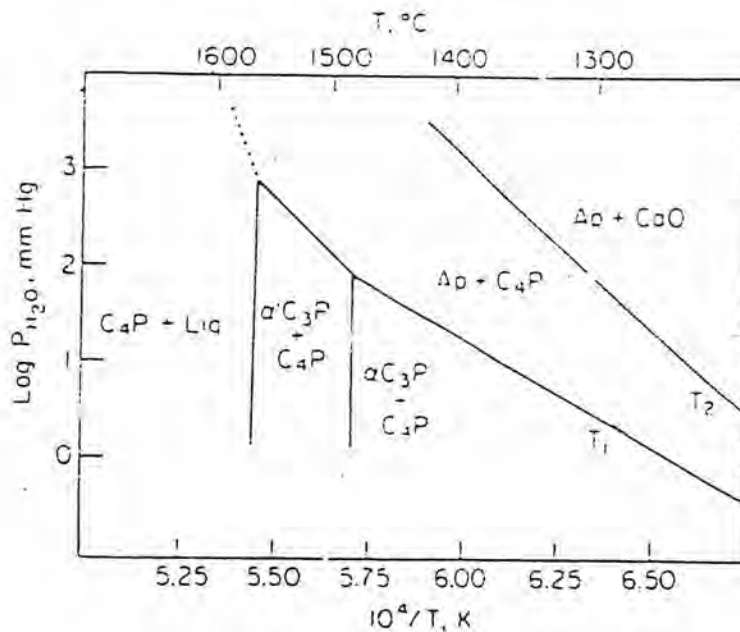(Riboud, 1973)

Fig. 2.2 Phase diagram of CaO/P_2O_5 mixtures showing influence of ambient
water vapor pressure. Vertical axis: log pH_2O (mmHg); horizontal
axis: $10^4/T$ (T in K) (Riboud, 1973)

Fig. 2.1 shows the possible phases of CaO/P_2O_5 mixtures. At temperature T_1 there exists the equilibrium for hydroxylapatite (HA) : Ap => $2C_3P + C_4P + XH_2O$. Temperature T_2 separates the phase HA +CaO from the phase HA + C_4P. Temperature T_1 and T_2 depend on partial water pressure, as Fig.2.2 shows.

Fig. 2.2 shows the influence of partial vapor pressure (pH_2O) on the stability of various calcium phosphates as a function of temperture. The temperture T_2 (see also Fig. 2.1) shows that at a given temperature, for example, 1250 $^\circ$C a variety of coexisting phase may exist : if log pH_2O (mmHg) < 0 , the phases $\alpha C_3P + C_4P$ are stable ; if log pH_2O (mmHg) < 1, the phases HA + C_4P are stable.
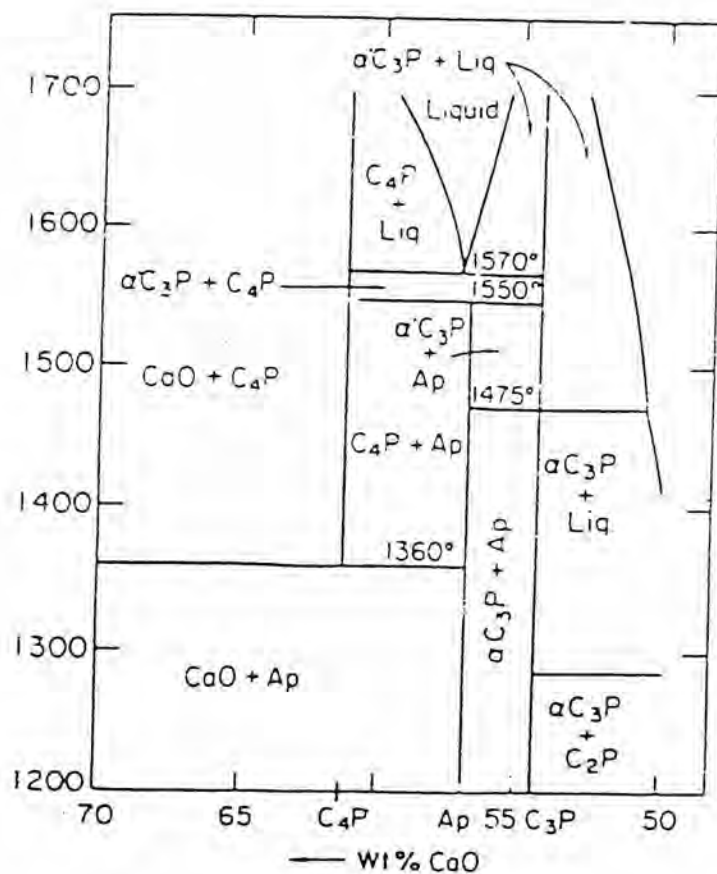

Fig. 2.3 Phase diagram of CaO/P_2O_5 mixtures at high temperature (vertical axis: temperature($^\circ$C). Water vapor :pH_2O = 500 mmHg (Riboud, 1973)
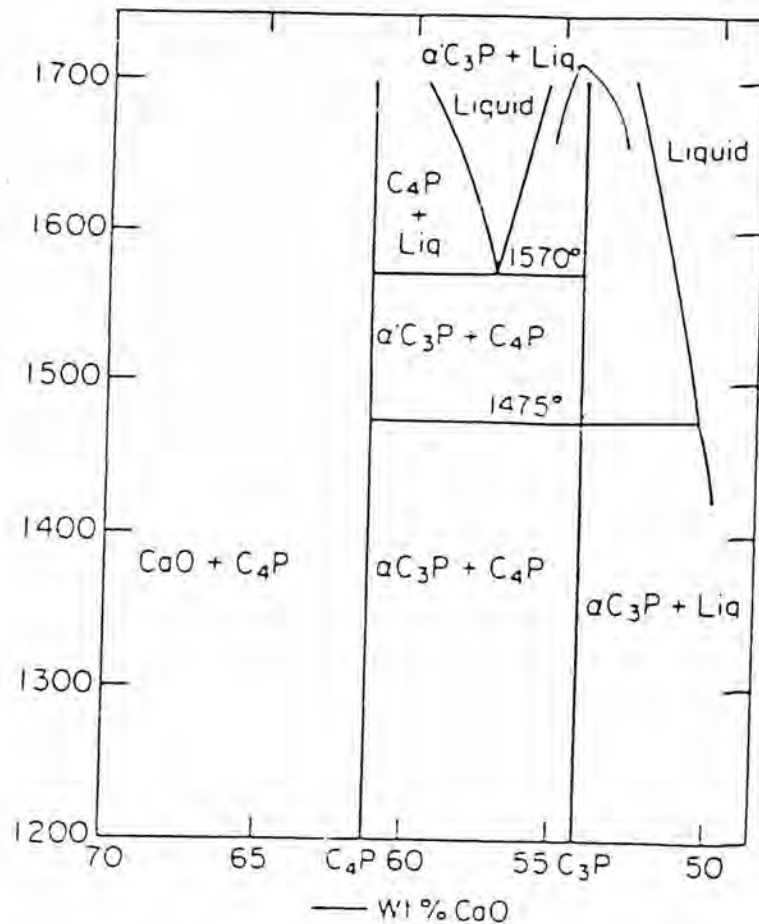
Fig. 2.4 phase diagram of the system CaO-P$_2$O$_5$ at high temperatures .No water present (Riboud, 1973)

Fig. 2.3 and 2.4 only differ in that the phases without water vapor (Fig. 2.4) are quite different from those with a vapor pressure (Fig. 2.3). It is obvious that control over temperture, Ca/P ratio and vapor pressure during sintering gives one the ability to produce a wide range of well-defined calcium phosphate products.

2.2 Phase at room temperature

2.2.1 Phases of calcium and phosphate only , in Aqueous Equilibrium

Since any practical, i.e., clinical, use of calcium phosphate

bioceramics involves contact with water (and other components present in body fluids), it is important to know the stability of materials composed of calcium and phosphate in the presence of water.

As Driessens (1983) showed, there are only two calcium phosphate materials that are stable at room temperature in aqueous solution. At a pH lower than 4.2, the component $CaHPO_4 \cdot 2H_2O$ (dicalcium phosphate dihydrate) is the most stable, while at pH higher than 4.2, hydroxyapatite $[Ca_{10}(PO_4)_6(OH)_2]$ is the stable phase.

This means that at thermodynamic equilibrium the situation is uncomplicated : only dicalcium phosphate (at pH lower than 4.2) or hydroxylapatite (at pH higher than 4.2) can be found in contact with aqueous solution (Fig. 2.5).
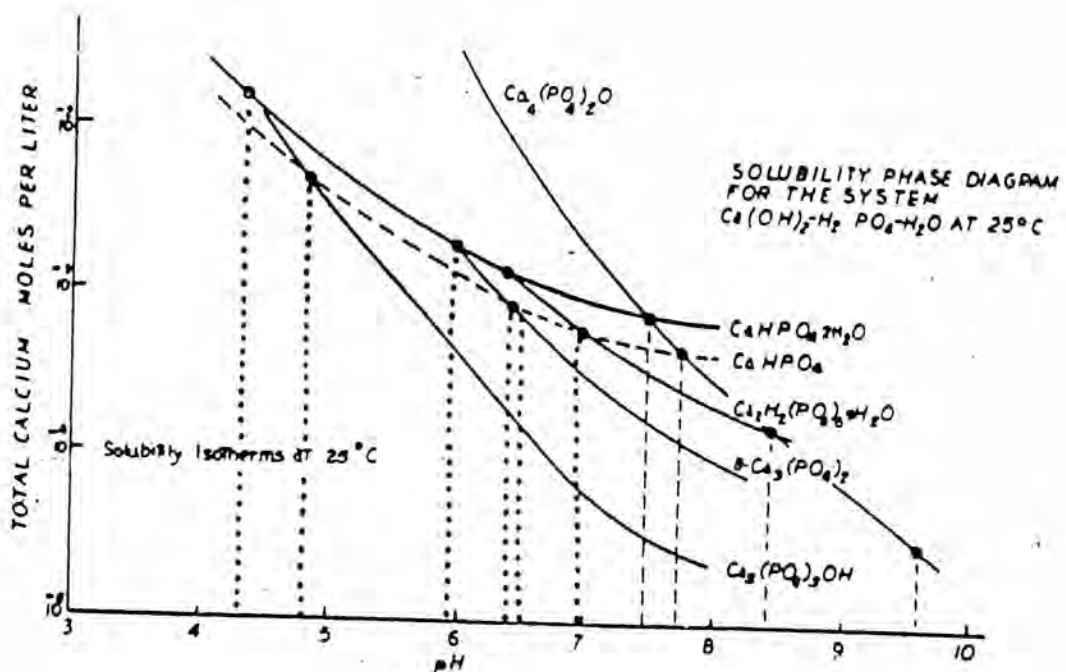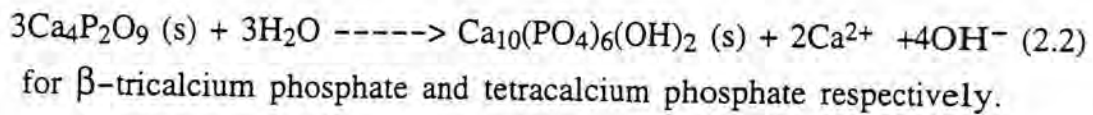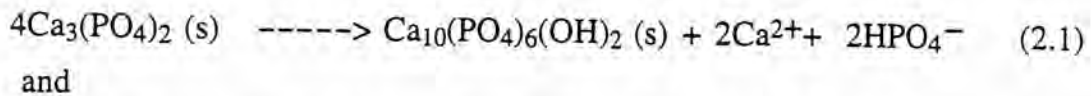

Fig.2.5 Solubility curves for DCPA, HA and TTCP. Solubility curves those obtained by plotting the negative logarithm of the calcium ion concentration for each compound over the range of pH from the perspective of Gibb's phase rule. (after Brown, 1973)

However, at higher temperatures, many other phases can be formed that, when cooled, keep their thermodynamically unstable composition due to the absence of solid-state reactions. The most relevant ones are β-tricalcium phosphate ($Ca_3(PO_4)_2$) and tetracalcium phosphate ($Ca_4P_2O_9$).

Adam et al. (1988) discussed in their publication on solubilities of calcium phosphate bioceramics that phases other than hydroxyapatite will have a surface gradually covered with hydroxyapatite. Newesely (1977) described these reactions for β-tricalcium phosphate and tetracalcium phosphate as :

$$4Ca_3(PO_4)_2 \text{ (s)} \quad \text{-----}> \quad Ca_{10}(PO_4)_6(OH)_2 \text{ (s)} + 2Ca^{2+} + 2HPO_4^- \quad (2.1)$$
and

$$3Ca_4P_2O_9 \text{ (s)} + 3H_2O \text{ -----}> Ca_{10}(PO_4)_6(OH)_2 \text{ (s)} + 2Ca^{2+} + 4OH^- \quad (2.2)$$
for β-tricalcium phosphate and tetracalcium phosphate respectively.

From the above reactions it also follows that β-tricalcium phosphate decreases the pH while being covered with a thin apatite layer (pK value of $CaHPO_4$ is 2.4), while tetracalcium phosphate does the opposite ($Ca(OH)_2$ is a strong base). Since for both β-tricalcium phosphate and tetracalcium phosphate the solubility decreases with increasing pH, one may reason that, if no buffering takes place, not only the gradual phase change into hydroxylapatite influences the solubility, but also the associated change in pH. The solubility of β-tricalcium phosphate should then increase , and that of tetracalcium phosphate should decrease.

2.2.2 Phases of calcium and phosphate and other ions , in Aqueous Equilibrium (de Groot. et al., 1990)

Both Ca^{2+} and PO_4^{3-} ions, as well as OH^- group in hydroxyapatite, can be replaced by other ions, several of them present in physiological surroundings. A well-known ion is fluorine, leading to fluor-containing apatites.

$$Ca_{10}(PO_4)_6(OH)_{2-x}F$$
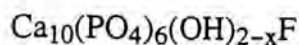
$$0 < x < 2$$

Another wellknown ion is carbonate (CO_3^{2-}) while, when incorporated into hydroxyapatite yields that so-called carbonated apatites with various chemical formulas.

$$Ca_{10}(PO_4)_6(OH)_{2-2x}(CO_3)_x$$

and $\qquad Ca_{10-x+y}(PO_4)_{6-x}(OH)_{2-x+2y}(CO_3)_x$
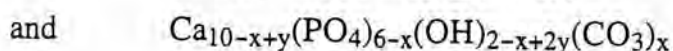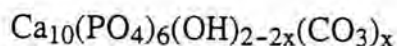
$$0 < x < 2$$

$$0 < y < 1/2x$$

The first formula suggests a partial replacement of the OH group only, while the second one corresponds with a partial replacement of both PO_4 and OH group.

However, by variations in the methods of synthesis, compounds having Ca/P mole ratio from 1.41-1.75 are obtained and which all have nearly the same x-ray patterns. (Kanazawa, 1989)

$$Ca_5(PO_4)_3OH \quad : \quad uniaxial$$

$$a \quad = \quad 9.422 \quad A^o$$

$$c \quad = \quad 6.883 \quad A^o$$

Infrared spectra 1000-1100 cm $^{-1}$

Specific gravity 3.21

Decomposed temperature 1400 ^{o}C

2.3. Crystallographical and mechanical properties

2.3.1 Crystallography (de Groot. et al., 1990)

Since hydroxyapatite (HA) is the only stable phase of calcium phosphate in an aqueous environment at neutral pH. HA is a specific solid of a large class with the general formula $M_{10}(XO_4)_6Z_2$, where M is a biovalent metal ion. XO_4 is a trivalent negative ion, and Z is a monovalent negative ion. The metal ion can be Ca^2, but also Pb^{2+} and Cd^{2+}, while

examples of XO_4 are $PO_4{}^{3-}$ and $MnO_4{}^{3-}$. The monovalent Z ion may be OH^-, F^-, and others.

A typical x-ray diffraction pattern of powdered and sintered HA is shown in Fig. 2.6. Crystal structure of related calcium phosphates are also well defined.
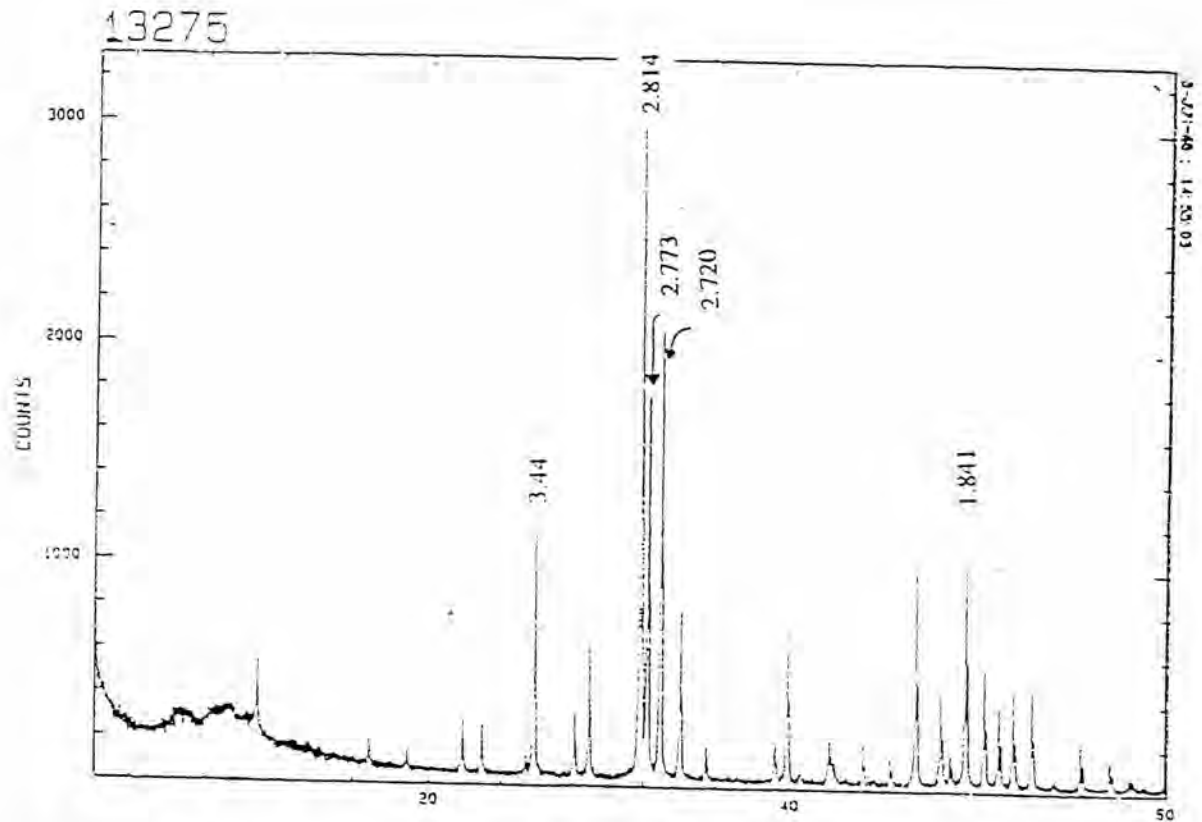
Fig.2.6 X-ray diffraction pattern of well-crystallized hydroxyapatite
    (horizontal axis: 2θ)

β-tricalcium phosphate shows an x-ray pattern (Fig. 2.7) consistent with a pure hexagonal crystal structure, although the related α-tricalcium phosphate is monoclinic.
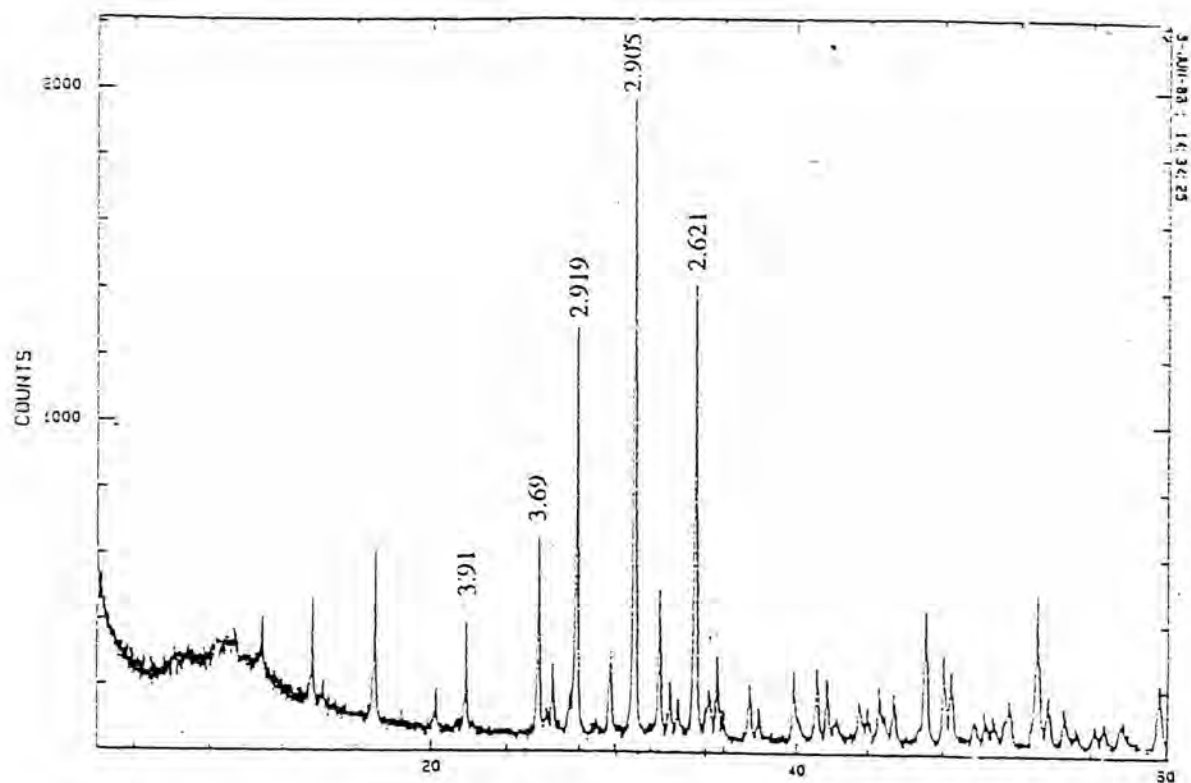
Fig.2.7 X-ray diffracton pattern of well-crystallized α-tricalcium phosphate

Tetracalcium phosphate is also a monoclinic substance. A name would be tetracalcium monoxide diphosphate. An x-ray diffraction pattern (see Fig. 2.8) shows distinct differences from the other patterns.
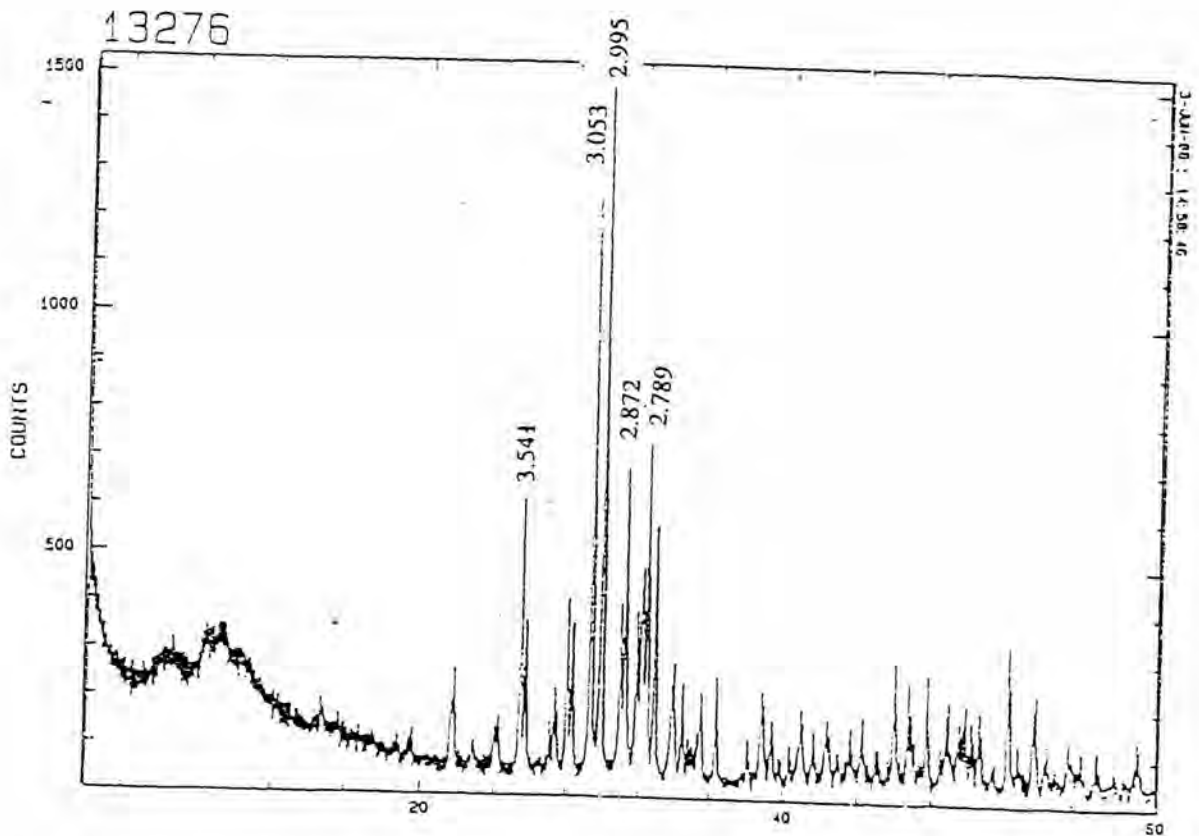
Fig. 2.8 X-ray diffraction pattern of well-crystallized tetracalcium phosphate

2.3.2 Mechanical properties

Both tensile and compressive strength of calcium phosphate ceramics depend on the portion of the total volume of the material occupied by interstices. These interstices, or pores, are classified as either micropores (with diameters of about 1 μm) or macropores (having diameters of several hundred microns); allowing bone growth.

De Putter. et al. (1983) studied the relative between compressive strength (σc) and the portion of the total volume occupied by pores (Vp) ($0 < Vp < 0.5$) may be described with the following equation:

$$\sigma c(Vp) = 700 \exp(-5\ Vp) \qquad \text{(in MPa)} \qquad (2.3)$$

A similar relation holds for tensile strength, σt, and microporosity (Vm) (Vm < 0.05)

$$\sigma t \ (Vm) \quad = \quad 220 \ \exp \ (- \ 20 \ Vm) \quad (in \ MPa) \qquad (2.4)$$

Hydroxyapatite can only withstand compressive forces. Tensile or bending forces as are always encountered when physiologically loaded,lead to fatigue failure. Therefore, only small implants, in nonload-bearing situations such as replacements for middle ear ossicles can be used. For filling defects, both (macroporous blocks, while after several weeks are strengthened by bony ingrowth, and granular material have been successful.

The weak point of all calcium phosphate ceramics is their susceptibility to fatigue failure. Besides reinforcement by strong filler materials. such as zirconium oxide, other techniques are currently in use, such as plasma sprayed coatings onto strong metallic surfaces and use as fillers with appropriate polymers.

2.4. Biocompatibility and degradation

Biocompatibility of calcium phosphates will be discussed two aspects of a physiochemical nature. Those being the importance of degradation and porosity. Degradation of calcium phosphate can be explained by two processes : (de Groot. et al.,1990)

1) Physiochemical dissolution

2) Disintegration of the bulk implant into small particles.

Physiochemical dissolution rate is governed by a number of factors :

1) pH and chemical composition of incubation fluid (including composition of buffers)

2) surface per unit weight of material

3) crystallinity of the material

4) solubility product

As mentioned earlier, at the same material (HA) and the same pH, dissolution rates vary considerably in different buffers. For example, the dissolution rate of hydroxyapatite at pH 7.2 varies from 97.4(ppm), when buffered in citrate, to 44.3 in Gomori's buffer, as shown in Table 2.1

Table 2.1 Concentration of Ca and P after 1 week of incubation : in various buffers. (de Groot. et al., 1990)

Material	Citrate (pH 7.2)		Gomoris (pH 7.2)		Deionized water	
	Ca	P	Ca	P	Ca	P
TCP[a]	85.0	45.9	48.9	19.6	4.6	1.7
HA[a]	97.4	43.8	44.3	17.5	5.1	2.2
TetraCP[a]	70.3	47.9	77.6	13.6	9.7	2.2
TCP[b] coating	153.0	82.5	17.1	8.8	3.3	1.5
HA[b] coating	44.0	19.8	10.8	4.25	4.4	2.3
Tetra CP[b] coating	351.0	127.5	94.4	9.0	8.8	0.20

[a] 30 mg of powder incubated in 30 ml of buffer.
[b] A coated cylinder with about 15 mg of coating incubated in 30 ml of buffer.

When the same buffer is used, hydroxyapatite has a lower solubility rate than both tricalcium phosphate and tetracalcium phosphate; however, it is not certain that this is relevant for the *in vivo* situations, when the fluids are probably saturated with calcium and phosphate. (de Groot. et al., 1990)

According to Bauer et al.(1985), there is direct contact between implant and surrounding bone for samples with a Ca/P ratio of 1/6 or higher (70 to 90% covered with bone), while TTCP implants show hardly any direct bony contact (less than 25%). Below a ratio of 1/4, only scantly contact is found , but instead a thick soft tissue layer has been found.

Animal studies by Klein (1983) showed that of eight samples tested (HA and TCP, in dense, microporous, macroporous, and microporous various), only macroporous and microporous TCP samples degraded. Of these degraded samples, particles were found in neighboring lymph nodes, thus indicating that the biological degradation process is mainly a disintegration of the implant into smaller particles, which, while being transported to neighboring tissues by phagocytes, are dissolved in part or in whole.

2.5. Tetracalcium phosphate (Kanazawa., 1989)

2.5.1 Structure

Crystal data are as follow :

monoclinic system.

$a = 7.023$, $b = 11.986$, $c = 9.473$ A°

$\beta = 90.90$ ° , $Z = 4$

The structure is shown in Fig 2.9
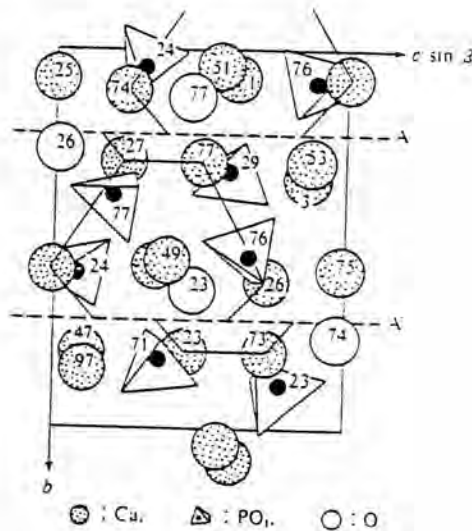
Fig. 2.9 Structure of $Ca_4(PO_4)_2O$

There are eight Ca atoms , four PO_4 groups and two O atoms.

Each of seven Ca atoms is coordinated to seven oxygens and the remaining one to eight oxygens. The structure contains the glaserite type cell , and four sheets perpendicular to [010]. Each sheet contains two [Ca-PO$_4$] columns and one [Ca-Ca] column. Two adjacent sheets are related crystallographically to the other two by the 2_1 symmetry. A Ca. 2A°-shift of the layer AA' along the c axis forms apatite Ca hexagons.

2.5.2 Preparation

When the stoichiometric mixture of $Ca_2P_2O_7$ and $CaCO_3$ is heated in

air, the following reactions occur. (Kanazawa., 1989)

$$\underset{\text{I}}{Ca_2P_2O_7 + 2CaCO_3} \xrightarrow[650-840^\circ C]{} \underset{\text{II}}{Ca_2P_2O_7 + 2\,CaO + 2CO_2} \xrightarrow{700^\circ C} Ca_3(PO_4)_2O +$$

$$\underset{\text{III}}{CaO} \xrightarrow{800^\circ C} \underset{\text{IV}}{1/3\ HA + 2/3\ CaO} \xrightarrow{1200^\circ C} Ca_4(PO_4)_2O + H_2O \qquad (2.5)$$
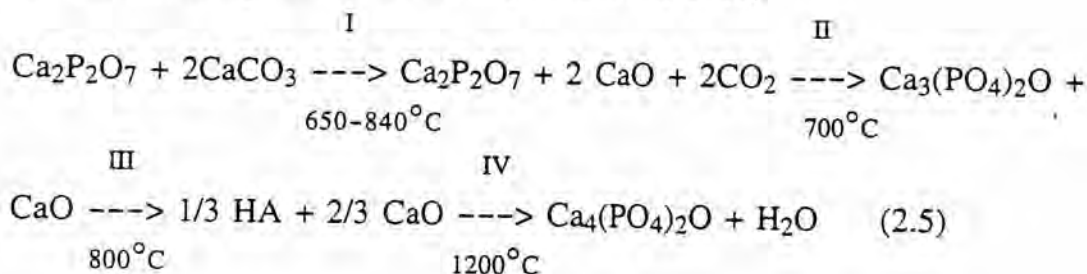
When the atmosphere is H_2O-free, $Ca_4(PO_4)_2O$ forms through the process I ->II -> IV. Namely, the preparation of $Ca_4(PO_4)_2O$ can be carried out by rapid cooling in air to prevent the inverse reaction of IV, and by normal cooling in H_2O-free atmosphere , from above $1200^\circ C$. In fact, it is prepared by heating the mixture at $1300^\circ C$ for 6 hours in air and subsequent rapid cooling.

Ciesla K. and Rudnicki R.(1987) showed that tetracalcium phosphate was obtained by annealing a mixture composed to $CaHPO_4 + CaCO_3$ at $1500^\circ C$ under vacuum. It was also obtained at $1300^\circ C$ but the diffractogram of the product obtained in this way displayed a relatively high content of calcium hydroxyapatite. The reaction of calcium hydroxyapatite formation from $Ca_3(PO_4)_2$, CaO and H_2O, or a reaction between tetracalcium phosphate and water vapor from the atmosphere (these reactions are known from literature) might be the reason for this.

The direct reactions, as result of which tetracalcium phosphate was formed, occur either (i) between calcium hydroxyapatite formed in the air at a lower ($1200^\circ C$) temperature and calcium oxide; or (ii) between calcium oxide and α-tricalcium phosphate(under nitrogen).

Ciesla and Rudnicki (1987) reported that the preparation of tetracalcium phosphate is obtained by means of a reaction in solid phase, as a result of heating an equimolar mixture of $CaHPO_4$ and $CaCO_3$ in the air or in purified nitrogen within the temperature range from 1200 to 1400° C. It is shown that pure tetracalcium phosphate may be obtained in the air at $1400^\circ C$, while in purified nitrogen at $1300^\circ C$.

During heating of the mixture $CaHPO_4$ + $CaCO_3$ thermal dissociation of $CaHPO_4$ and $CaCO_3$ occured at first, according to the following stoichiometric equations :

$$2\ CaHPO_4 \quad = \quad Ca_2P_2O_7 + H_2O \quad (2.6)$$
$$CaCO_3 \quad = \quad CaO + CO_2 \quad (2.7)$$
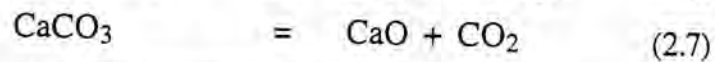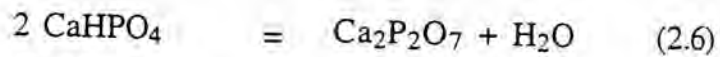
Further reactions occurred within the temperature range from 1200 to 1400°C. They may be discribed by the following stoichiometric equations :

$$\alpha\text{-}Ca_2P_2O_7 + CaO = \alpha\text{-}Ca_3(PO_4)_2 \quad (2.8)$$
$$\alpha\text{-}Ca_3(PO_4)_2 + CaO = Ca_4P_2O_9 \quad (2.9)$$
$$\alpha\text{-}Ca_2P_2O_7 + 2CaO = Ca_4P_2O_9 \quad (2.10)$$
$$3\alpha\text{-}Ca_3(PO_4)_2 + CaO + H_2O = Ca_{10}(PO_4)_6(OH)_2 \quad (2.11)$$
$$Ca_{10}(PO_4)_6(OH)_2 = 2\alpha\text{-}Ca_3(PO_4)_2 + Ca_4P_2O_9 + H_2O \quad (2.12)$$
$$Ca_{10}(PO_4)_6(OH)_2 + 2CaO = 3\ Ca_4P_2O_9 + H_2O \quad (2.13)$$
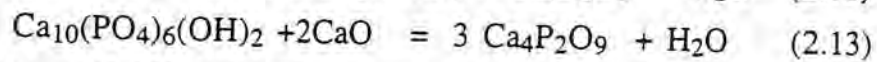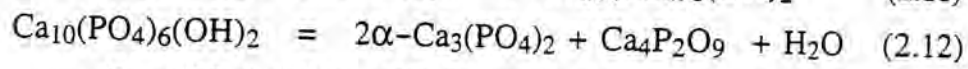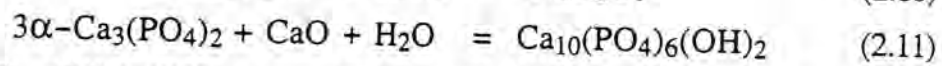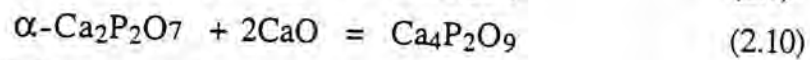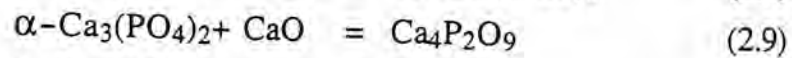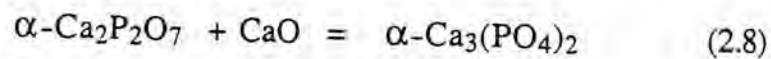
Reaction (2.11) occurred at temperatures slightly above 1200°C, while reaction (2.12) at higher temperatures.

Since, in the case of annealing the reaction mixture, in the air calcium hydroxyapatite was formed in the half product, but during annealing under purified nitrogen $\alpha\text{-}Ca_3(PO_4)_2$ was formed in the half product. It was evident that the proper reaction of tetracalcium phosphate formation occurred between $Ca_{10}(PO_4)_6(OH)_2$ and CaO, as well as between $\alpha\text{-}Ca_3(PO_4)_2$ and CaO.

During heating in air at temperatures from 400 to 1100°C, tetracalcium phosphate could react with water vapor and carbon dioxide.

$$3Ca_4P_2O_9\ (s) + H_2O\ (g) \dashrightarrow Ca_{10}(PO_4)_6(OH)_2\ (s) + 2CaO\ (s) \quad (2.14)$$
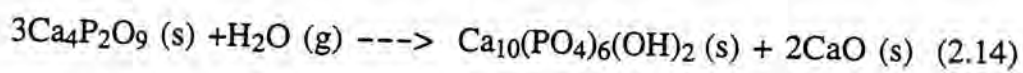
This reaction was known from the literature of Wallaeys (1952) and Barak (1956), but it had not found the precise temperature range within

while it occurred. Neither had it found in the literature any detailed data concerning the action of CO_2 on $Ca_4P_2O_9$.
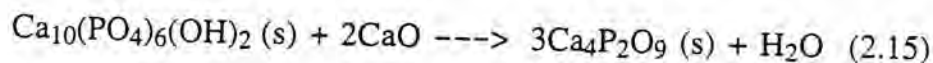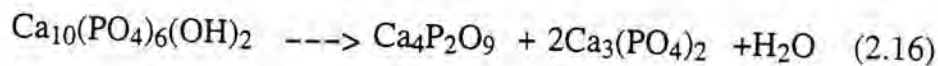
Riboud (1973) found that , e.g., at $pH_2O = 73.6$ mmHg, the reaction

$$Ca_{10}(PO_4)_6(OH)_2 \text{ (s)} + 2CaO \text{ ---> } 3Ca_4P_2O_9 \text{ (s)} + H_2O \quad (2.15)$$

occurred already at $1302^\circ C$ as compared with the initial temperature of $1477^\circ C$ needed for the reaction :

$$Ca_{10}(PO_4)_6(OH)_2 \text{ ---> } Ca_4P_2O_9 + 2Ca_3(PO_4)_2 + H_2O \quad (2.16)$$

On the other hand, Ciesla and Rudnicki (1989) found that the reaction (2.15) occurred at temperature higher than $1300^\circ C$, and ran rapidly at temperatures higher than $1350^\circ C$.

Fig. 2.4 shows that if the ambient atmosphere contains no water, various calcium phosphates could be found at high temperatures, such as tetracalcium phosphate (C_4P), α-tricalcium phosphate ($\alpha-C_3P$), monetite (C_2P), and mixtures of calcium oxide (CaO) and C_4P. Hydroxyapatite (HA) was not stable under these conditions. If the partial water pressure was increased from 0 to 500 mmHg, as shown in Fig.2.3, then the situation was quite different : HA could be found. If the ratio Ca/P was not exactly equal to 10/6, a wide range of apatite- containing mixtures was thermodynamically stable, e.g., tetracalcium phosphate, tricalcium phosphate and calcium oxide (CaO).

Fig. 2.3 and 2.4, the two phase diagrams stress the importance of temperature, exact Ca/P ratio, and partial pressure of water vapor in the ambient atmosphere in the determination of stable phases (β-tricalcium phosphate is considered to be stable in the range 700 to $1200^\circ C$ and turns into α-tricalcium phosphate around $1200^\circ C$.)

The diagram in Fig. 2.2 showed clearly the importance of partial water pressure. This phase diagram shows, for example, that for a Ca/P

ratio higher than 10/6, at a temperature of $1300^{\circ}C$ ($10^4/T = 6.40$, if T is expressed in $^{\circ}K$), the stable phase is $C_3P + C_4P$ if the vapor pressure is 1 mmHg (log $pH_2O = 0$). The stable phase is Ap + C_4P at 10 mmHg (log $pH_2O = 1$). At pressure of around 100 mmHg mixtures of Ap +CaO are stable. Thus, with a Ca/P ratio exceeding that of apatite by only a few percent, stable phase can vary from $C_3P + C_4P$ (log $pH_2O = 0$), Ap+ C_4P (log $pH_2O = 1$), and Ap + CaO (log $pH_2O = 2$). The part of the Ca/P phase diagram that is most crucial is shown in Fig. 2.1. As in Fig. 2.2, T_1 and T_2 are water vapor pressure–dependent phase transitions, showing that, besides temperature and Ca/P ratio, this pressure is also of utmost importance in the determinaton of stable phases. It is not always easy to predict which phase, stable at high temperatures, will remain so at room temperature because several phase transitions may take days or longer, especially at temperatures below $1000^{\circ}C$.

In the previous paragraphs, it discussed that the phases brushite (at pH 4.2) and hydroxyapatite (at pH > 4.2) were the only stable phases at room temperature in an aqueous environment. Hence, except for hydroxyapatite, most phases stable at high temperature will gradually undergo a phase transition to hydroxyapatite, if the pH is physiological.

It is not surprising that β–tricalcium phosphate had been shown to transform into HA after incubation in aqueous solution at body temperature.

2.5.3 Thermal changes

$Ca_4P_2O_9$ reacts easily with water vapor in air at high temperatures and forms HA as follows. (Kanazawa., 1989)

$$3Ca_4P_2O_9 \xrightarrow{1100-1420^{\circ}C} HA + 2CaO \qquad (2.17)$$
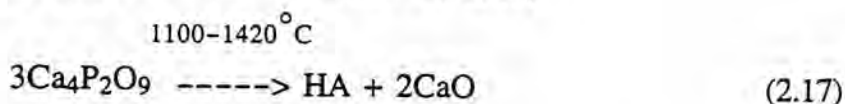
This conversion has been followed in detail by TG , x–ray diffraction and IR methods. Fig. 2.10 shows repeated heating and cooling TG curves of

synthetic $Ca_4P_2O_9$. Increases in weight reflect the reaction of the phosphate with H_2O in air, and the following changes have been clarified.

$$Ca_4P_2O_9 \xrightarrow[420^\circ C]{B\rightarrow C} HA + 2CaO \xrightarrow[850^\circ C]{C\rightarrow D} (H.O)Ap + 2CaO \xrightarrow[1200^\circ C]{D\rightarrow E} TTCP$$

$$G\leftarrow F, <1050^\circ C, \text{gradual cooling}$$
$$\text{rapid cooling}$$
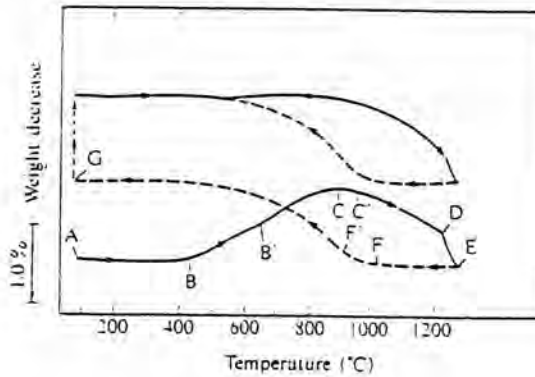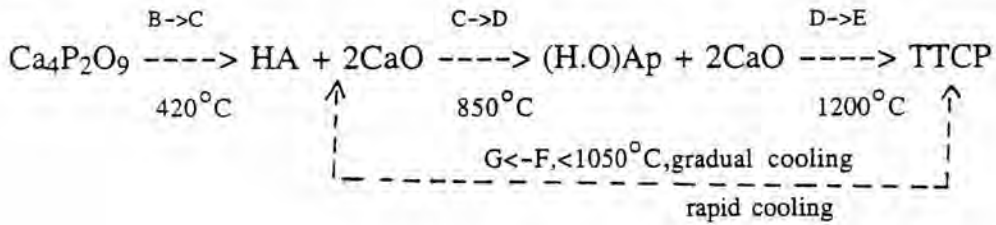

Fig. 2.10 Repeated heating TG (solid lines) and cooling TG (dashed lines) for synthetic TTCP in air, heating and cooling rate $10^\circ C/min$, sample weight 80 mg.

When (H.O)Ap is hydroxyapatite suggested from decreases in weight without changes in phase between C and D. (Kanazawa., 1989)

2.5.4 Chemical properties (Kanazawa., 1989)

$Ca_4P_2O_9$ was related structurally or chemically to HA and α-TCP. Hydration reactivity followed the order β-TCP < TTCP < α-TCP. $Ca_4P_2O_9$ as a catalyst was more basic than the stoichiometric HA, and had high catalytic activity and selectivity for alcohol decomposition.

Other calcium phosphates included $Ca(H_2PO_4)_2 \cdot H_2O$, $Ca(H_2PO_4)_2$, $CaHPO_4 \cdot 2H_2O$ and $CaHPO_4$. Almost all calcium phosphate had the

possibility of converting finally to HA in solution through the formation of intermediates such as OCP and ACP.

$CaHPO_4 . 2H_2O$ (DCPD) was gradually dihydrated in water at $60-100^\circ C$ and changes to $CaHPO_4$.(DCPA). DCPD converted to OCP or HA in solutions under controlled pH conditions of nearly neutral to alkaline. DCPA was also able to react as well as, although its reactivity was considerably lower than, its dihydrate. In air, DCPD changes as followed.

$$CaHPO_4.2H_2O \xrightarrow{120^\circ C} CaHPO_4 \xrightarrow{270-750^\circ C} \gamma-Ca_2P_2O_7 \xrightarrow{500-750^\circ C} \beta-Ca_2P_2O_7$$

$$\xrightarrow{1165^\circ C} \alpha-Ca_2P_2O_7 \tag{2.19}$$
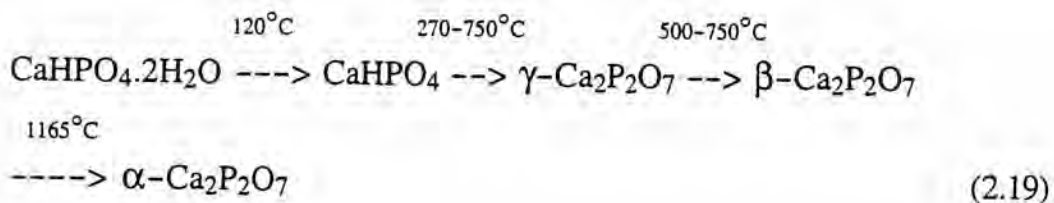
Temperatures for such thermal changes were affected by atmosphere. The α-form $Ca_2P_2O_7$ was easily prepared by rapid cooling.

2.6. Application : self-setting calcium phosphate cements.

Tetracalcium phosphate (TTCP) was first proposed by Brown and Chow as a possible pulp-capping agent in 1975. Self-setting calcium phosphate cements could be even more ideal because they had the unique combination of the following properties :   (LeGeros., 1991)

  a) components of chemical compatibility with the enamel and dentine material (i.e., apatite Ca-P and collagen)

  b) would not promote the leaching out of ions, e.g., Zn^{2+}, foreign to the tooth mineral.

  c) adjustability of the composition of the Ca-P cement. (e.g., with or without F^-, Mg^{2+}, Sr^{2+}, etc.)

  d) aesthetics

An equimolar mixture of TTCP and dicalcium phosphate dihydrate (DCPD) is hardened into a phase of HA cement isothermally at almost neutral pH when mixed with dilute phosphoric acid. Self–setting calcium phosphate cements (CPC) have been a subject of considerable interest in recent years. Materials that are totally biocompatible and also harden like a cement at the site of application are highly desirable in a wide range of biomedical applications. In these materials,one or more ambient–temperature reactions involving phase transformation of the calcium phosphate compounds cause the hardening of the cement. A summary of the physical chemistry of calcium phosphate compounds is first given to provide a background for understanding the setting reactions in CPC.

2.6.1 Solution chemistry of calcium phosphates (Chow., 1991)

Orthophosphate salts, which have PO_4^{3-} groups, were distinguished from metaphosphates and pyrophosphates, which have PO_3^- and $P_2O_7^{4-}$ groups.

The principle calcium phosphate salts given in table 2.3 are listed in the order of increasing Ca/P molar ratio. This is also the order of increasing basicity. Except of fluorapatite (FAp), all are members of the ternary system, $Ca(OH)_2-H_3PO_4-H_2O$.

Table 2.2 Calcium (ortho) phosphate compounds and their solubility product constants. (Chow., 1991)

Compound	Formula	Ca/P	log(Ksp) at 25 °C	log(Ksp)* at 37 °C
Monocalcium phosphate monohydrate (MCPM)	$Ca(H_2PO_4)_2 \cdot H_2O$	0.5	highly soluble	
Monocalcium phosphate anhydrous (MCPA)	$Ca(H_2PO_4)_2$	0.5	highly soluble	
Dicalcium phosphate dihydrate (DCPD)	$CaHPO_4 \cdot 2H_2O$	1.0	6.59[3]	6.63
Dicalcium phosphate anhydrous (DCPA)	$CaHPO_4$	1.0	6.90[46]	7.02
Octacalcium phosphate (OCP)	$Ca_8H_2(PO_4)_6 \cdot 5H_2O$	1.33	96.6[47]	95.9
σ-Tricalcium phosphate (σ-TCP)	$\sigma\text{-}Ca_3(PO_4)_2$	1.5	25.5[48]	25.5
ß-Tricalcium phosphate (ß-TCP)	$\text{ß }Ca_3(PO_4)_2$	1.5	28.9[49]	29.5
Hydroxyapatite (OHAp)	$Ca_5(PO_4)_3OH$	1.67	58.4[50]	58.6
Fluorapatite (FAp)	$Ca_5(PO_4)_3F$	1.67	60.5[51]	
Tetracalcium phosphate (TTCP)	$Ca_4(PO_4)_2O$	2.0	38[1] to 44[2]	42.4

* log(Ksp) values used in calculation of the isotherms shown in Figures 1 through 3.

(a) Solubility product constants.

It is the solubility that determines the direction of nearly all ambient–temperature chemical reactions (usually dissolution, precipitation or phase transformation in nature) in while calcium phosphate is involved.

Gravimetric solubility, i.e., the mass of a solid that can dissolve into a unit volume of the solution, is a simple way of describing solubility. However, this quantity can change significantly with other solution parameters such as the pH , the concentrations of other components , etc.,and is not considered suitable for describing the solubility properties of a calcium phosphate salt under a broad range of conditions. (Chow., 1991)

The thermodynamic solubility product constant, Ksp, a quantity related to the Gibbs free energy of the solid, is expressed in a form related to the formula of the compound, e.g., for HA,

$$K_{Sp} \text{ (HA)} \quad = \quad (Ca)^5(PO_4)^3(OH) \tag{2.20}$$

Where quantities in ( ) on the right hand side of the equation denote activities. Table 2.3 lists the K_{Sp} values for the salts at 25 and 37°C. Measurements of the solubility of tetracalcium phosphate (TTCP) have been somewhat hampered by the high reactivity of TTCP with water, and studies have yielded K_{Sp} values ranging from 10^{-38} to 10^{-44}.

(b) Solubility phase diagrams

Based on Gibbs phase rule, a ternary system with two phases, a solution and a solid, in equilibrium at a fixed temperature and pressure has a single degree of freedom. (Chow., 1991)

Thus a line , known as a solubility isotherm, in the phase diagram (Figs.2.11 (a) and 2.11(b)) defines the compositions of all solutions that are saturated with respect to that salt.
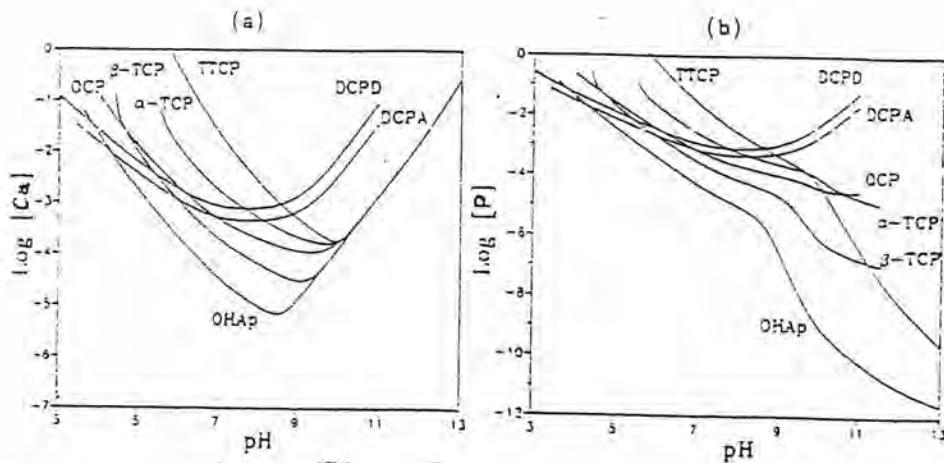
Fig. 2.11 Solubility phase diagram for the ternary system, Ca(OH)$_2$–H$_3$PO$_4$–
H$_2$O, at 37°C : (a) solubility isotherms showing log[Ca] and pH of
solutions in equilibrium with various salts; (b) solubility isotherms
showing log[P] and pH of solutions. (Laurence., 1991)

Fig. 2.11(a) shows calculated isotherms (37°C) of seven salts :
dicalcium phosphate dihydrate (DCPD), dicalcium phosphate anhydrous
(DCPA), octacalcium phosphate (OCP), α-tricalcium phosphate (α-TCP),
β-tricalcium phosphate (β-TCP),and hydroxyapatite (HA), in the form of
the logarithm of the total calcium concentrarion, log[Ca], of the saturate
solution as a function of pH. Fig. 2.11(b) shows the isotherms for the same
compounds in the form of the logarithm of the total phosphate concentration,
log[P], of the saturate solution as a function of pH.

The isotherms in both figures have negative slopes in the neutral and
acidic regions, i.e., pH below about 7, of the phase diagram. This reflects
the fact that all of these compounds are more stable as the pH decreases.
The slope of the isotherm is an indication of how rapidly the (gravimetric)
solubility of the salt increases with decreasing pH. The acidic salts, DCPD
and DCPA, have smaller negative slopes than do the basic salts, TTCP, HA
and the two TCPs.

It may be concluded that the solubility behavior of a calcium phosphate salt is principally determined by two factors : the thermodynamic solubility product constant and the basicity of the compounds.

The solubility phase diagrams shown in Figs2.11(a) and (b) are quite useful because they reveal the relative stabilities of salts at various pHs. At a given pH a salt whose isotherm lies below that of another salt is less soluble (more stable) than the other. Thus, it is readily seen from the phase diagrams that at 37°C HA is the least soluble among all salts until the pH falls below approximately 4.2 where DCPA becomes the least soluble.

Similarly, TTCP is the most soluble salt for pH below 8.5 ; above that DCPD is the most soluble. The relative stabilities of the various salts are the major driving forces for the reactions that occur in calcium phosphate cements.
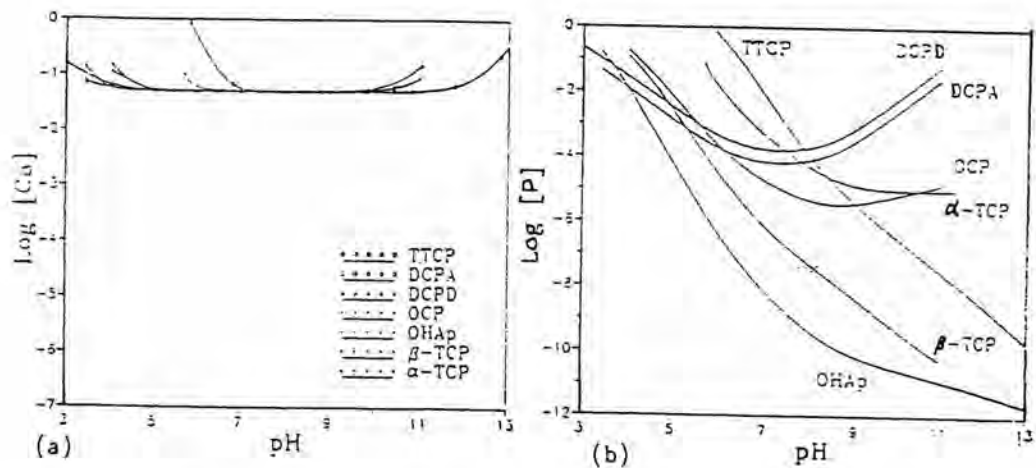

Fig. 2.12 Solubility phase diagram for the quaternary system, Ca(OH)$_2$–
H$_3$PO$_4$–HCl–H$_2$O, at 37°C and a fixed HCl concentration of 0.1
mol/l: (a) solubility isotherms showing log[Ca] and pH of solutions
in equilibrium with various salts; (b) solubility isotherms showing
log[P] and pH of the solutions (Laurence, 1991)

Fig. 2.12(a) and 2.12(b) show phase diagrams for the system $Ca(OH)_2-H_3PO_4-HCl-H_2O$ in while the isotherms are for a fixed concentration of HCl at 0.1 mol/l. It can be seen that the primary effects of HCl, while does not form stable ion-pairs or insoluble salts with calcium or phosphate ions, are to shift the loci of the isotherms. The Ca concentrations of all points on all the isotherms are increased from the corresponding values in the ternary system by approximately 0.05 mol/l, simply to balance the negative charges carried by the Cl^- ions. This results in a collapse of the separations between the isotherms plotted in the form of log[Ca] vs. pH (Fig. 2.12(a)).
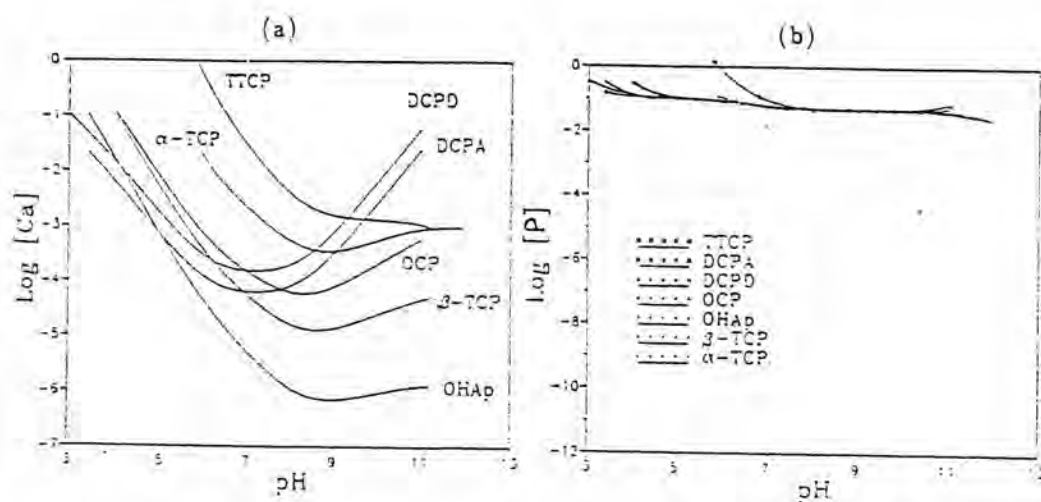
Fig. 2.13 Solubility phase diagram for the quaternary , $Ca(OH)_2-H_3PO_4-$ NaOH-H₂O, at 37°C and a fixed NaOH concentration of 0.1 mol/l: (a) solubility isotherms showing log[Ca] and pH of solutions in equilibrium with various salts; (b) solubility isotherms showing log[P] and pH of the solutions. (Laurence, 1991)

Shown in Figs. 2.13(a) and 2.13(b) are isotherms for the $Ca(OH)_2-$ $H_3PO_4-NaOH-H_2O$ systems in while the concentration of NaOH is fixed at 0.1 mol/l. The effects of NaOH are opposite to those of HCl, e.g., to lower

the Ca concentration and increase the P concentration compared to the corresponding solutions in the ternary system. The isotherms in the log[P] vs. pH phase diagram become superimposed because all solutions below pH 12 would have a minimum P concentration of 0.05 mol/l to balance the changes of the Na^+ ions.

When the isotherms for various calcium phosphate are plotted on the same axes, their solubility behavior relative to each other may be determined, as shown in Fig.2.5. Specifically, a calcium phosphate whose isotherm lies above the isotherm of another calcium phosphate at a given pH is metastable with respect to the latter.

The point where the isotherms of the two calcium phosphates interest is known as a singular point. In a solution that is saturated with respect to the two calcium phosphates, both calcium phosphates will be in equilibrium with the saturated solution at the singular point. This means that neither calcium phosphate will precipitate out of solution, but another calcium phosphate whose isotherm lies below the singular point can precipitate. The present invention relates to combinations of calcium phosphates that form singular point solutions that precipitate hydroxyapatite.

Three additional considerations that limit the choice of calcium phosphate (Doi. et al., 1988):

1. The combination of calcium phosphates should contain $Ca_4(PO_4)_2O$ in order to possess the desired remineralization properties.

2. The singular point of the two calcium phosphates must lie above the isotherm for HA. Thus, HA can precipitate out of the solution and be available for remineralization.

3. The singular point for the pair of calcium phosphates should preferably not lie too far above the isotherm for $CaHPO_4 . 2H_2O$, since the singular point of such a combination might be too unstable for use as a remineralizer or cement.

The reason that a singular point combination has such desirable properties as a remineralizer and cement is that it resists changes in the pH

or composition of the solution by driving itself back to the singular point whenever the composition or pH changes, for example, if two calcium phosphates that possess a singular point were present in excess in a solution that is more acidic than the pH of the singular point, the more basic phosphate will dissolve and cause the more acidic phosphate to precipitate.

This process will continue until the pH and the composition are forced back to the singular point, where the two calcium phospates present in excess will both be in equilibrium with the solution and neither would precipitate out of solution. The reverse process will occur if the composition starts at a point more basic than the singular point pH. Furthermore, the solution will only be in equilibrium at the singular point. However, the precipitation of a third salt , such as HA , may drive the composition in the direction of the third salt's isotherm. The degree of deviation depends upon the relative rates of dissolution and precipitation of the three salts.
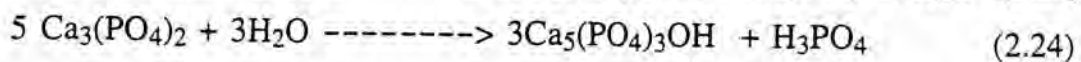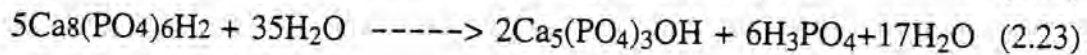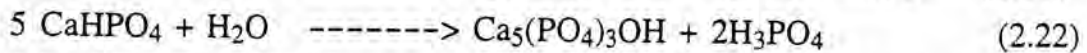
2.6.2 Chemistry of CPC setting reactions

The cementation can occur in mixtures containing a variety of calcium phosphate compounds with or without additional acidic or basic components. The products formed in these systems include DCPD, DCPA, OCP and HA. Although a large number of parameters affecting the direction of these reactions may be understood by analyzing the solubility behavior of the various salts, discussion on cement setting reactions are organized by the type of calcium phosphate salts present in the mixtures.

(a) Cement setting reaction in systems that form HA

Formation of HA through hydrolysis of a single calcium phosphate salt. Because HA is the least soluble phase in the pH range of approximately 4.2 and above, other calcium phosphate salts when suspended in an aqueous solution in this pH range tend to dissolve and reprecipitate as HA.

With the exception of TTCP, all non-apatite calcium phosphate salts have Ca/P ratios lower than that of HA. (de Groot., 1991) As a result, H_3PO_4 will be released into solution as a byproduct of the hydrolysis reaction, e.g., eqs.2.21 to 2.24 (Chow., 1991)

$$5\ Ca(H_2PO_4)_2 \cdot H_2O \ \text{------>}\ Ca_5(PO_4)_3OH + 7H_3PO_4 + 4H_2O \qquad (2.21)$$
$$5\ CaHPO_4 + H_2O \ \text{-------->}\ Ca_5(PO_4)_3OH + 2H_3PO_4 \qquad (2.22)$$
$$5Ca_8(PO_4)_6H_2 + 35H_2O \ \text{----->}\ 2Ca_5(PO_4)_3OH + 6H_3PO_4 + 17H_2O \quad (2.23)$$
$$5\ Ca_3(PO_4)_2 + 3H_2O \ \text{-------->}\ 3Ca_5(PO_4)_3OH + H_3PO_4 \qquad (2.24)$$
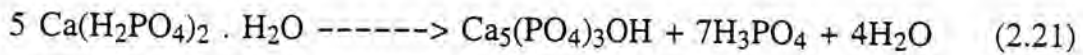
For TTCP, the hydrolysis reaction produces $Ca(OH)_2$ as a by-product (eq. 2.25).
$$3\ Ca_4(PO_4)_2O + 3\ H_2O \ \text{------->}\ 2Ca_5(PO_4)_3OH + 2Ca(OH)_2 \qquad (2.25)$$
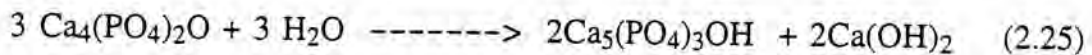
This would increase the pH which also causes the solution to become less supersaturated with respect to HA (Fig 2.11(a) and (b)). Although adding a base such as $Ca(OH)_2$ or NaOH would neutralize the H_3PO_4 by-product in reactions described by eqs. (2.21) to (2.24). The initial high pH may produce two problems :

a) The degree of supersaturation with respect to HA may become diminished at higher pH values.

b) The Ca and/or P concentrations at high pHs are lower and the reaction would occur more slowly. Monma et al. (1984) showed that conversion of α-TCP to non-stoichiometric HA could occur in solutions at pH 7.5 or higher, but the reaction rate was very slow.

(b) CPC systems containing TTCP and other calcium phosphate.

TTCP is the only calcium phosphate salt that has a Ca/P ratio higher than that of HA. Thus, only TTCP can be combined with one or more other calcium phosphate salts (with lower Ca/P ratio) to form the stoichiometry of HA.

Formation of HA in such a mixture will not release acidic or basic by-product, e.g.,

$$Ca_4(PO_4)_2O + CaHPO_4 \ ----> Ca_5(PO_4)_3OH \qquad (2.26)$$
$$Ca_4(PO_4)_2O + CaHPO_4 .2H_2O \ ----> Ca_5(PO_4)_3OH + 2H_2O \qquad (2.27)$$
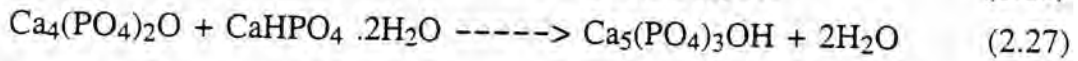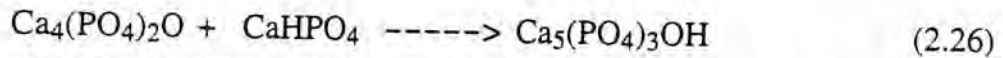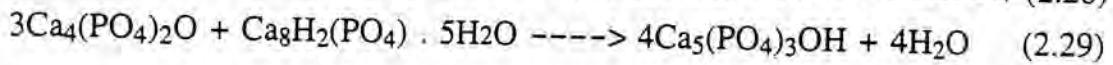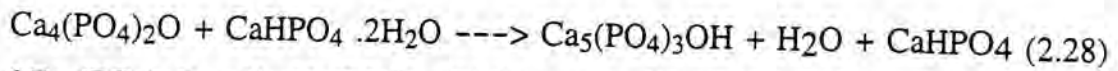
Brown and Chow (1985) recently patented a process of preparing Ca-P cement by the following reactions :

$$Ca_4(PO_4)_2O + CaHPO_4 .2H_2O \ ---> Ca_5(PO_4)_3OH + H_2O + CaHPO_4 \quad (2.28)$$
$$3Ca_4(PO_4)_2O + Ca_8H_2(PO_4) . 5H2O \ ----> 4Ca_5(PO_4)_3OH + 4H_2O \qquad (2.29)$$

The TTCP + DCPA and TTCP + DCPD systems have the advantage that the singular point pH values are near the physiological pH, and this contributes to the high biocompatibility that is essential for biomedical application. During this period the cement setting reaction proceeds, at a near-constant rate, indicating that it may have followed zero order reaction kinetics. This will suggest that the reaction rate is limited by factors that are unrelated to the amounts of the starting materials and the reaction products present in the system at any given time. Such factors can be related to the surface area of DCPD or TTCP to the diffusion distances over which the calcium and phosphate ions must migrate in order to form HA. It can be seen from Fig. 2.11(b) that the singular points of TTCP with OCP, α-TCP and β-TCP are not as well separated from the HA isotherm as are the TTCP-DCPD and TTCP-DCPA singular points. This indicates that the former compositions have lower degrees of supersaturation with OCP, α-TCP and β-TCP, hence do not react as fast to produce a setting cement. Since TTCP structure is similar to HA, it will promotes the rate of HA crystal growth.

(c) CPC setting reactions that form OCP.

Since the compositions on a lage section of the DCPA, DCPD, α-TCP, and TTCP isotherms are also supersatureted with respect to OCP (Fig. 2.11(a) and (b)), OCP may also precipitate from slurries of those salts. Although OCP is more soluble than HA so that formation of HA is favored as the stable final product, Brown (1962) reported that OCP formed more rapidly than HA. Matsuya (1991) reported that OCP was also the major product of TTCP hydrolysis reaction when the pH was kept constant at 6 by titration with H_3PO_4.

2.6.3 Composition and preparation on calcium phosphate cements

Calcium phosphate cement comprises a solid phase and a liquid phase. The following composition of solid phase are definitely available as calcium phosphate cements : $CaHPO_4 .2H_2O$ with $Ca_4(PO_4)_2O$; $CaHPO_4$ with $Ca_4(PO_4)_2O$; $Ca_4(PO_4)_2O$ with $Ca_8H_2(PO_4)_6 . 5H_2O$; and $Ca_4(PO_4)_2O$ with β-TCP. Although water is sometimes a reactant or a product of the cement setting reactions (eqs. 2.21 to 2.24), its primary role is as a vehicle for dissolution of the reactants and precipitation of the products.

A dilute (e.g. 0.2%) phosphoric acid solution is most commonly used as the liquid phase for TTCP + DCPA (or DCPD) cements because the dilute acid solution allows rapid dissolution of the solids to obtains the singular point composition. In several earlier studies the CPC powder also contained HA seeds from 3 wt% to 40 wt% to produce cement with good setting and strength properties. Brown and Chow (1985) found that calcium fluoride (CaF_2), a sparingly soluble salt, had also been used as additive to the CPC powder for the purpose of increasing the rate of setting reaction and/or reducing the solubility of the set cement. The ratio $(Ca^{2+}) / (H^+)^2$ is constant at a given singular point, where the parentheses denote ion activities. Thus, the addition of an acid compound, such as HCl, $CaCl_2$ or $Ca(C_2H_3O_2)_2$, will increase the ionic activity of Ca^{2+}, increase the Ca/P

ratio of the singular point and cause the singular point to move to a lower pH. (Brown. et al., 1985) In addition, particle size is a factor since as particle size increases, the rate of mineralization decreases. Inert components such as barium hydroxyapatite or zirconia oxide were included in CPC powder for increasing its radiopacity, which is essential in some biomedical applications. (Chown., 1991)

2.6.4 Physicochemical properties of CPC

Brown and chow (1985) reported that setting times of CPC prepared from TTCP and DCPD mixtures ranged from 8 min to about 22 min. Some of the differences might be accounted for by the differences in the experimental conditions used. For those CPC systems that form HA as the major product, shorter setting times generally were obtained with CPC mixtures containing up to 40wt% HA seeds, while longer times were obtained for samples without HA seeds. Other factors that might influence the setting time included the particle sizes and shapes of powder and the powder- to-liquid ratio used.

The mean compressive strength of 36 MPa for the 24-hour specimens was abtained in the cement setting reaction of CPC consisting of TTCP and DCPA (Hamanishi. et al., 1996). Properties such as setting time or strength of cements appeared to be influenced by the added seed HA crystals. In the presence of 40 wt% of HA seed prepared at several temperatures ranging from $40^{\circ}C$ to $100^{\circ}C$. Doi. et al (1988) reported that the setting time was shorter than 9 min. Lower temperature HA (6 min for at $40^{\circ}C$) was more effectives as setting accelerator than higher temperature HA (9 min at $100^{\circ}C$).

2.6.5 Factors affecting strength

The relatively high porosity (when compared to ceramic HA) is likely

to be a major reason for the limited compressive strengths that have been obtained so far. Thus, reducing the porosity will seem to be a critical factor in improving the strength of CPC. The compressive strength of the set cements also strongly depends on the types of HA added. Doi. et al (1988) found that the compressive strength of the cements containing HA prepared at temperatures higher than $60^{\circ}C$ gradually weakened as HA preparation temperature increased. Since partical size of both DCPD and TTCP affected the dissolution rate, the crystal growth of HA during cement formation depended on the specific surface area of the raw materials. Otsuka. et al (1993) showed that the crushing strength of the cement after hardening increased with an increase of its surface area. Cement prepared from small TTCP and large DCPA particles produced samples of no measurable strength, whereas the highest compressive strength (51 MPa) was obtained from the mixture containing large TTCP and small DCPA particles.

2.6.6 Microstructure

The morphology of cement prepared from a TTCP + DCPA mixture, as a function of time after sample preparation, was studied by scanning electron microscopy (Kanazawa., 1989). The specimens obtained at 1 hour after mixing showed the outline of the reactant particles and the presence of amorphous-looking materials in inter-particle spaces. Micrographs of higher magnifications revealed that the "amorphous" materials consisted of small petal-like crystals. These appeared to be the products of the cement setting reaction that might be responsible for causing the particles to adhere to one another. Both the amount and the crystallinity of materials present in the interparticle spaces increased with time. In the 24-hour sample, the crystals present in areas adjacent to a void grew radially and were well-separated. The cement specimens appeared rather amorphous-looking under low magnifications ; however, under higher magnifications, it was apparent that the cement consisted of mostly crystalline materials.

2.6.7 In Vivo characteristics of CPC

Data on tissue reactions to CPC began to appear in the literature only recently. The discussions given below will focus on in vivo characteristics of TTCP+DCPA or TTCP+DCPD-based CPC materials because the bulk of the data have been obtained using these cements. Hamanishi. et al (1996)'s results from initial testing of CPC, showed that CPC was not mutagenic or toxic. Histologically, no inflamatory reaction was observed around cement. Bone conduction onto the cement or cement block was quick and aggressive and fragmentation and intrusion by the host bone occurred in the disks intercalated in the bony gaps as well as those incorporated into the bone marrow space.

CPC appears to be the first calcium-based cement that sets to resorbable HA and is replaced by bone in an approximate one to one relationship. Though it appears to be useful for the reconstruction of nonstress-bearing areas of the skeleton of as a dental cement, greater shear strengths will be required before CPC can be used for reconstruction of stress-bearing bone, such as these of extremities.

2.6.8 Conclusion

Yet the properties of CPC, including the setting time, compressive and tensile strengths, porosity, solubility, in vivo resorption rate, etc., may be affected by a large number of parameters. The strengths of CPC considerably lower than bone, teeth, and some dental cement. It is the combination of self-setting capability and high biocompatibility that makes CPC a unique material among the biomaterial currently available. However, much remains to be done to further improve its properties to meet the requirements for different applications.