CHEMICAL AND BIOMATERIALS ASPECTS OF CALCIUM PHOSPHATE CEMENT

Hideki Monma*

(*Corresponding author: monma@cc.kogakuin.ac.jp)

Department of Materials Science and Technology,
Faculty of Engineering, Kogakuin University
2665 Nakano-cho, Hachioji-shi, Tokyo 192-0015

Keywords: Hydroxyapatite, Calcium phosphate cement, Bone paste, Porous ceramics, Scaffold

Calcium phosphate cements and the resulting porous hardened bodies are noticed as injectable bone pastes and scaffolds for bone ingrowth or bone cell culture, respectively. The present paper provides various calcium phosphate cement combinations, chemistry and hardened properties.

(Received May 5, 2006; Accepted December 15, 2006)

INTRODUCTION

Materials in the systems $\text{CaO-Al}_2\text{O}_3$, CaO-SiO_2 and CaO-SO_3 are well-known as typical cement constituents, *i.e.*, the first two systems are for Portland cement and the third one for gypsum. In 1970's, hydroxyapatite (referred to as HAp, stoichiometrically $\text{Ca}_{10}(\text{PO}_4)_6(\text{OH})_2$, nonstoichiometrically $\text{Ca}_{10-x}(\text{HPO}_4)_x(\text{PO}_4)_{6-x}(\text{OH})_{2-x} \cdot n\text{H}_2\text{O}$) had been noticed as a future promising biomaterial for bone and tooth restorations, and many preparative and materials researches on HAp have been continued. And in 1976, a unique hydration and hardening property of $\alpha\text{-Ca}_3(\text{PO}_4)_2$ powder was found¹⁾. Nearly the same time a $\text{Ca}_4(\text{PO}_4)_2\text{O-CaHPO}_4 \cdot 2\text{H}_2\text{O}$ mixed type cement was developed²⁾. Each of the two cementing calcium phosphates (CP cements) was a pioneer for succeeding developments of various CP cements. Presently some CP cements are already applied to the medical treatment of bone and tooth. On the other hand, recently

porous calcium phosphate ceramics have become of interest as a structural morphology with good bioactivity, *i.e.*, scaffolds for bone ingrowth or for bone cell culture. Such porous ceramics could be easily prepared by using CP cements. In the present paper, CP cements are introduced from chemical and biomaterial aspects.

CP CEMENTS

Chemistry of CP cement

CP cements harden with the formation of mainly HAp by mixing with aqueous solution. Many types of CP cements have been created by various combinations of components. And properties of CP cements have been examined with respect to hardening mechanism, hardened microstructure, mechanical strength and so forth. **Fig.1** shows examples of CP cement hardened bodies and sintered ceramics prepared by using CP cement. Such porous materials have an excellent

biocompatibility, and are expected as scaffolds for bone ingrowth

Fig.1 HAp porous blocks prepared by using α TCP cement. Left 3 blocks : Hydration-hardening bodies, Right 2 blocks: Ceramics obtained by sintering hydration-hardening bodies.

and bone cell culture. The hydration-hardening of CP cements occurs according to the dissolution-precipitation mechanism, *i.e.*, by the entanglement of formed microcrystals such as HAp, as well as the hardening mechanism of gypsum hemihydrate $\text{CaSO}_4 \cdot 0.5\text{H}_2\text{O}$. HAp is the most stable phase in a wide pH region³⁾ as shown in **Fig. 2**. Possibilities of the hydration-hardening of CP cement compositions could be predicted by comparing the solubility of calcium phosphates, which were already discussed in detail in the literature⁴⁾. In other words, all compounds being over the solubility curve of HAp tend to change into HAp.

The cement hardening reaction must proceed without stirring and with approximate rates for the entanglement of formed HAp microcrystals. For example, the change of acidic $\text{CaHPO}_4 \cdot 2\text{H}_2\text{O}$ into basic HAp causes pH decreases with the reaction, therefore the reaction must stop at the point A (*e.g.*, singular point) in Fig.

2. In the case of $\text{Ca}_4(\text{PO}_4)_2\text{O}$ - $\text{CaHPO}_4 \cdot 2\text{H}_2\text{O}$ mixed type cement²⁾, solubility

Fig.2 Solubility curves of calcium phosphates with respect to pH (calculated)³⁾.

curves of the two components are crossing at pH 6.8 (point B), and the point is above the solubility of HAp. So, when the pH of the two component system shifts from the point, $\text{Ca}_4(\text{PO}_4)_2\text{O}$ or $\text{CaHPO}_4 \cdot 2\text{H}_2\text{O}$ dissolves for maintaining the singular point until either of $\text{Ca}_4(\text{PO}_4)_2\text{O}$ or $\text{CaHPO}_4 \cdot 2\text{H}_2\text{O}$ disappears. Under such a thermodynamic consideration, this mixed type cement was developed²⁾. Similarly the pH of the system α TCP- $\text{CaHPO}_4 \cdot 2\text{H}_2\text{O}$ must be automatically kept at 8 (point C). And the hardening was experimentally confirmed⁵⁾.

$\text{CaHPO}_4 \cdot 2\text{H}_2\text{O}$ - CaCO_3 and β TCP - $\text{Ca}(\text{H}_2\text{PO}_4) \cdot \text{H}_2\text{O}$ systems have also been developed. **Table 1** summarized various CP cement compositions and hardened properties. At present medically applied CP cements are two types consisting of α TCP and $\text{Ca}_4(\text{PO}_4)_2\text{O}$ as the main constituent. Only α TCP hardens without any other additives. Other CP cements are made by combinations of at least two components.

α TCP-based cements¹⁾

Chemical reactivity of the high tempera

Table 1 CP cement compositions and their hardened properties⁶⁾.

Main-component	Combined-components	Hydration-hardened body Hardening time, t /min porosity, p / % Compressive, σ / MPa	Organic acid-hardened body ^{a)} Hardening time, t /min Porosity, p / % Compressive, σ / MPa
α TCP	None	$t = 4-30, p = 55-80, \sigma = 3-18$ ^{b)}	$t = 2-8, \sigma = 20-150$
α TCP	$\text{CaHPO}_4 \cdot 2\text{H}_2\text{O}$	$t = 9-10, p = 48-56, \sigma = 14-19$	
α TCP	CaHPO_4	$t = \text{ca. } 100$	
$\text{Ca}_4(\text{PO}_4)_2\text{O}$	None		$t = 2-8, \sigma = 40-110$
$\text{Ca}_4(\text{PO}_4)_2\text{O}$	$\text{CaHPO}_4 \cdot 2\text{H}_2\text{O}$	$t = \text{ca. } 9$	
$\text{Ca}_4(\text{PO}_4)_2\text{O}$	CaHPO_4	$t = 5-7, \sigma = 5-9$	
$\text{Ca}_4(\text{PO}_4)_2\text{O}$	$\text{CaHPO}_4 \cdot 2\text{H}_2\text{O}, \text{HAp}^{\text{c)}$	$t = 7-8, \sigma = 19-40$	
$\text{Ca}_4(\text{PO}_4)_2\text{O}$	α TCP	$t = \text{ca. } 130, \sigma = 2-20$	$t = 2-20, \sigma = 30-150$
$\text{CaHPO}_4 \cdot 2\text{H}_2\text{O}$	CaCO_3	$t = 60-120, p = 64-68, \sigma = 2-3$	

a) Polycarboxylic acids, lactic polymer, citric acid, malic acid, etc.

b) Compressive strength of 80 °C-hardened bodies : 3-30 MPa

c) Dilute H_3PO_4 solution used as mixing solution

ture α -form of TCP is larger than the low temperature β TCP. This fact is reasonable since the α -form must be thermodynamically metastable at room temperature. Reactions of α TCP with H_2O are summarized as follows depending on pH,

In acidic region :

In neutral region :

In basic region :

where the product in Reaction (3) is a general formula ($x = 0-1$) of HAp. Hardening is observed according to Reactions (2) and (3). Reaction (1) might be too fast to harden due to the entanglements of produced particles with

each other. The resulting hydration-hardening bodies are porous materials with 55-80% in porosity, below 20 μm in pore size, and nonstoichiometric compositions near biological HAp ($0 < x < 1, 1.50 < \text{Ca}/\text{P} < 1.67$). That is, the products are closed to biological apatite rather than so far developed stoichiometric HAp ($\text{Ca}/\text{P} = 1.67$) biomaterials. The hydration-hardening is accelerated or retarded by additives in the following order^{7,8)};

The α TCP single component cement was a base of the first medical application to the tooth restoration in Japan in 1986. **Fig. 3** shows mechanical strength vs. porosity plots for hardened bodies prepared from α TCP single component cement, compared with data on HAp sintered ceramics.

α TCP- $2\text{CaHPO}_4 \cdot 2\text{H}_2\text{O}$ mixed type

cement⁵⁾ hardens with the formation of octacalcium phosphate resembling compositionally and structurally HAp. This combination has comparatively good hardening properties, *e.g.*, 10 min in 37 °C setting time. The hardening occurs as a result of the following continuous reaction kept automatically at the crossing point C (*ca.* pH 8) as shown in Fig. 2.

The reaction rate is larger than that of α TCP single component cement. Wet compressive strengths of thus obtained bodies were *ca.* 20 MPa at the beginning and finally 50-60 MPa. Nowadays 70-90 MPa values have been achieved, and the cement is an recent topic as injectable bone and medically applied.

pastes¹⁰⁻¹²⁾. **Table 2** lists medical CP cement bone pastes developed so far

Fig. 3 Relationships between compressive strength and porosity of HAp porous bodies⁹⁾. (dots : α TCP cement hardened bodies, solid lines : HAp ceramics)

Table 2 CP cement bone paste developed¹²⁾.

Main-component	Combined-components	Hydration-hardened body ^{a)}	Final product Features	Commercial name	Maker
α TCP	$\text{Ca}_4(\text{PO}_4)_2\text{O}$, $\text{CaHPO}_4 \cdot 2\text{H}_2\text{O}$, HAp	$t = 6-10$ $\sigma = 60-90$	HAp Bio-resorbable High strength	Biopex	Pentax (Japan)
α TCP	CaCO_3 , $\text{Ca}(\text{H}_2\text{PO}_4)_2$	$t = 8-9$ $\sigma = 28-38$	HAp Bio-resorbable High initial strength	Norian SRS	Norian (USA)
α TCP	$\text{Ca}_4(\text{PO}_4)_2\text{O}$, $\text{Ca}(\text{H}_2\text{PO}_4)_2$	$t = 16-18$ $\sigma = 6-10$	HAp Low viscosity paste	Cementek	Teknimed (France)
α TCP	$\text{Ca}_4(\text{PO}_4)_2\text{O}$, CaHPO_4 , CaCO_3 , HAp	$t = 6-7$ $\sigma = 79-87$	HAp	Biocement	Merk GmbH (German)
$\text{Ca}_4(\text{PO}_4)_2\text{O}$	CaHPO_4 ,		HAp Little bio-resorbable	BoneSource	Libinger (USA)
$\text{Ca}_4(\text{PO}_4)_2\text{O}$	CaHPO_4 ,	$t = 5-20$ $\sigma = 50$	HAp	Cerapaste	NGK (Japan)
ACP ^{b)}	$\text{CaHPO}_4 \cdot 2\text{H}_2\text{O}$	$t = 18-20$ $\sigma = 3-5$	HAp	α -BSM	ETEX (USA)

a) t and σ mean hardening time (min) and compressive strength (MPa).

b) Amorphous calcium phosphate, $\text{Ca}_3(\text{PO}_4)_2 \cdot n\text{H}_2\text{O}$

*Ca₄(PO₄)₂O-based cements^{2,4)}
and others¹³⁾*

CaHPO_4 or $\text{CaHPO}_4 \cdot 2\text{H}_2\text{O}$ as a combined component and HAp seed crystals are mixed, and dilute H_3PO_4 solution is used as a mixing liquid. The reaction is given as

Many other cement combinations have been studied, e.g., $\text{CaHPO}_4 \cdot 2\text{H}_2\text{O}$ - CaCO_3 system (37 °C-hardening time: 1-2 h, wet compressive: ca. 1 MPa, porosity: 70-80%, product: carbonated HAp), βTCP - $\text{Ca}(\text{H}_2\text{PO}_4)_2 \cdot \text{H}_2\text{O}$ system, and cement compositions above over 400 varieties.

*HAp porous bodies prepared
by using CP cement*

Recently calcium phosphate porous ceramics have become of great interest as an excellent scaffold structure for osteoblast culture and bone ingrowth. CP cements are available for producing such porous materials¹⁴⁾. Increasing the hydration temperature increases the mechanical strength of hardened bodies. The 80 °C-hydrated HAp hardened bodies are machinable. By heating the products crack-free sintered apatite ceramics are prepared. During the heat-treatment, the following thermal change occurs over 700-800 °C.

Therefore, the produced ceramics are composed of HAp single phase or HAp+TCP mixed phases or βTCP single phase depending on the degree (x) of the nonstoichiometry of reactant HAp. When the Ca/P molar ratio of the CP cement used could be adjusted with the addition of appropriate calcium salts, HAp single phase ceramics with 4-20% in porosity, 2-5 μm in pore diameter and 100-500 MPa in compressive strength are prepared. By using polymer beads porous HAp with 20-500 μm in pore size and 30-65% in porosity could be easily prepared. By using αTCP cement with albumin as a pore forming reagent, HAp bodies with large pores of 100-500 μm are prepared¹⁵⁾. **Figs.4-6** show microstructures of HAp porous materials prepared by using hydration reactions. These porous materials are applicable not only to medical engineering materials but also to catalyst support, ion-exchanger, adsorbent of smelling gasses, drug delivery system (DDS) carrier and so forth.

Fig. 4 SEM photographs of HAp porous materials. A: αTCP cement r.t.-hardened body, B: αTCP cement 80 °C-hardened body,

C

D

Fig. 5 SEM photographs of HAp porous materials. C: Sintered body prepared by using α TCP cement and polymer beads, D: HAp crystals formed on sintered α TCP ceramics,

E

F

Fig. 6 SEM photographs of HAp porous materials. E and F: Tubular HAp and β TCP prepared by using gypsum hardened body¹⁶⁾.

CLOSING

The chemistry and characteristics of cement of the system $\text{CaO-P}_2\text{O}_5$ have been described briefly. The systems $\text{CaO-Al}_2\text{O}_3$ and CaO-SiO_2 are well-known for the base of Portland cement, and CaO-SO_3 for gypsum. Namely, hydraulic cement materials consisting of Ca salts of ^{13}Al , ^{14}Si , ^{15}P and ^{16}S have just lined up. Furthermore various studies on the newly coming $\text{CaO-P}_2\text{O}_5$ cement are desired to be going on.

REFERENCES

1. H.Monma, T.Kanazawa, *J. Ceram. Soc. Japan.*, **84**(4), 209-213(1976); **108**(8), S75-S80(2000).
2. W.E.Brown, L.C.Chow, *J. Dent. Res.*, **62**(Spec. Issue), 672(1983); *U.S.Pat.* 4518430(1985); L.C.Chow, *Adv. Dent. Res.*, **2**(1), 181-186(1988).
3. H.Monma, *Biomaterials*, **15**(1), 24-30 (1997).
4. W.E.Brown, L.C.Chow, *Cements Res. Progress*, 351-379(1986).
5. H.Monma, A.Makishima, M.Mitomo, Y.Ikegami, *J. Ceram. Soc. Japan.*, **96**(8), 878-880(1988).
6. H.Monma, *FC Report*, **6**(12), 475-480 (1988).
7. H.Monma, Y.Goto, T.Kohmura, *J. Soc. Inorg. Mater. Japan*, No.188, 11-16 (1984).
8. C.Durucan, P.W.Brown, *J. Mater. Sci.*, **37**(5), 963-969(2002).
9. H.Monma, *Kogyo Zairyo*, **28**(10), 90-102 (1980).
10. H.Takeuchi, *J. Soc. Inorg. Mater. Japan*, No.240, 52-59(1992).
11. M.Hirano, *New Ceramics*, No.5, 55-59 (1993).
12. H.Takeuchi, *Spin & Spinal Cord*, **15**(11), 1056-1063(2002).
13. O.Bermudez, J.A.Boltung, F.C.M. Driessens, *J. Mater. Sci.:Mater. Med.*, **5**(3), 144-146(1994).
14. H.Monma, *Zairyo Gijutsu*, **13**(5), 143-147(1995).
15. J.A.Delgado, I.Harr, A.Almirall, S.del Valle, J.A.Planell, M.P.Ginebra: *Key Eng. Mater. (Bioceramics 17)*, **284-286**, 157-160(2005).
16. H.Monma, Y.Moriyoshi, T.Urano, T. Okura, S.Takahashi, *Phos. Res. Bull.*, **19**, 166-171(2005).