CHEMICAL AND BIOMATERIALS ASPECTS OF CALCIUM PHOSPHATE CEMENT

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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.

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INTRODUCTION

Materials in the systems CaO-Al$_2$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 Ca$_{10}$(PO$_4$)$_6$ (OH)$_2$, nonstoichiometrically Ca$_{10-x}$[(HP O$_4$)$_x$(OH)$_{2-x}$] · $n$H$_2$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 $\alpha$-Ca$_3$(PO$_4$)$_2$ powder was found$^{11}$. Nearly the same time a Ca$_3$(PO$_4$)$_2$O·CaHPO$_4$·2H$_2$O mixed type cement was developed$^{2}$. 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 αTCP cement. Left 3 blocks: Hydration-hardening bodies, Right 2 blocks: Ceramics obtained by sintering hydration-hardening bodies.

Fig. 2 Solubility curves of calcium phosphates with respect to pH (calculated). 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, Ca₄(PO₄)₂O or CaHPO₄ · 2H₂O dissolves for maintaining the singular point until either of Ca₄(PO₄)₂O or CaHPO₄ · 2H₂O disappears. Under such a thermodynamic consideration, this mixed type cement was developed. Similarly the pH of the system αTCP- CaHPO₄ · 2H₂O must be automatically kept at 8 (point C). And the hardening was experimentally confirmed.

CaHPO₄ · 2H₂O - CaCO₃ and βTCP - Ca(H₂PO₄) · H₂O 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 αTCP and Ca₄(PO₄)₂O as the main constituent. Only αTCP hardens without any other additives. Other CP cements are made by combinations of at least two components.

2. In the case of Ca₄(PO₄)₂O-CaHPO₄ · 2H₂O mixed type cement, solubility
**aTCP-based cements**

Chemical reactivity of the high tempera

Table 1  CP cement compositions and their hardened properties

<table>
<thead>
<tr>
<th>Main-component</th>
<th>Combinated-components</th>
<th>Hydration-hardened body</th>
<th>Organic acid-hardened body</th>
</tr>
</thead>
<tbody>
<tr>
<td>αTCP</td>
<td>None</td>
<td>t = 4-30, p = 55-80, σ = 3-18</td>
<td>t = 2-8, σ = 20-150</td>
</tr>
<tr>
<td>αTCP</td>
<td>CaHPO₄•2H₂O</td>
<td>t = 9-10, p = 48-56, σ = 14-19</td>
<td></td>
</tr>
<tr>
<td>αTCP</td>
<td>CaHPO₄</td>
<td>t = ca. 100</td>
<td></td>
</tr>
<tr>
<td>Ca₃(PO₄)₂O</td>
<td>None</td>
<td>t = 9-10, p = 48-56, σ = 14-19</td>
<td></td>
</tr>
<tr>
<td>Ca₃(PO₄)₂O</td>
<td>CaHPO₄•2H₂O</td>
<td>t = ca. 9</td>
<td></td>
</tr>
<tr>
<td>Ca₃(PO₄)₂O</td>
<td>CaHPO₄</td>
<td>t = 5-7, σ = 5-9</td>
<td></td>
</tr>
<tr>
<td>Ca₃(PO₄)₂O</td>
<td>CaHPO₄•2H₂O, HAp</td>
<td>t = 7-8, σ = 19-40</td>
<td></td>
</tr>
<tr>
<td>Ca₃(PO₄)₂O</td>
<td>αTCP</td>
<td>t = ca. 130, σ = 2-20</td>
<td></td>
</tr>
<tr>
<td>CaHPO₄•2H₂O</td>
<td>CaCO₃</td>
<td>t = 60-120, p = 64-68, σ = 2-3</td>
<td></td>
</tr>
</tbody>
</table>

a) Poly-carboxylic acids, lactic polymer, citric acid, malic acid, etc.
b) Compressive strength of 80% -hardened bodies : 3-30 MPa
c) Dilute H₃PO₄ solution used as mixing solution

ture α-form of TCP is larger than the low temperature βTCP. This fact is reasonable since the α-form must be thermodynamically metastable at room temperature. Reactions of αTCP with H₂O are summarized as follows depending on pH,

In acidic region :

\[
\text{Ca}_3(\text{PO}_4)_2 + \text{H}_2\text{O} \\
\rightarrow 2\text{CaHPO}_4 \cdot 2\text{H}_2\text{O} + \text{Ca(OH)}_2 \quad (1)
\]

In neutral region :

\[
3\text{Ca}_3(\text{PO}_4)_2 + 7\text{H}_2\text{O} \\
\rightarrow \text{Ca}_9\text{H}_2(\text{PO}_4)_6 \cdot 5\text{H}_2\text{O} + \text{Ca(OH)}_2 \quad (2)
\]

In basic region :

\[
(1-x)\text{Ca}_3(\text{PO}_4)_2 + 3(2+n-x)\text{H}_2\text{O} \\
\rightarrow 3\text{Ca}_{10-(2+n-x)}(\text{PO}_4)_{2-n}((\text{OH})_{2-n}} \cdot n\text{H}_2\text{O} + 2(1-x)\text{H}_3\text{PO}_4 \quad (3)
\]

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 \((0 < x < 1, 1.50 < \text{Ca/P} < 1.67)\). That is, the products are closed to biological apatite rather than so far developed stoichiometric HAp \((\text{Ca/P} = 1.67)\) biomaterials. The hydration-hardening is accelerated or retarded by additives in the following order \(^7,8\) : 

\[
\text{NH}_4 \text{ salts} > \text{Na salts} > (\text{none}) > \text{Ca salts} \approx \text{Mg salts} \quad (4)
\]

The αTCP 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 αTCP single component cement, compared with data on HAp sintered ceramics.

- αTCP-2CaHPO₄•2H₂O mixed type
cement\(^5\) hardens with the formation of octacalcium phosphate resembling compositionally and structurally HAp. This combination has comparatively good hardening properties, \(e.g.,\) 10 min in 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.

\[
2\text{Ca}_3(\text{PO}_4)_2 + 2\text{CaHPO}_4 \cdot 2\text{H}_2\text{O} + \text{H}_2\text{O} \rightarrow \text{Ca}_8\text{H}_2(\text{PO}_4)_6 \cdot 5\text{H}_2\text{O} \quad (5)
\]

The reaction rate is larger than that of \(\alpha\)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.

### Table 2 CP cement bone paste developed\(^{12}\).

<table>
<thead>
<tr>
<th>Main-component</th>
<th>Combined-components</th>
<th>Hydration-hardened body(^a)</th>
<th>Final product Features</th>
<th>Commercial name</th>
<th>Maker</th>
</tr>
</thead>
<tbody>
<tr>
<td>(\alpha)TCP</td>
<td>(\text{Ca}_3(\text{PO}_4)_2\cdot\text{CaHPO}_4\cdot 2\text{H}_2\text{O}\cdot\text{H}_2\text{O})</td>
<td>(t = 6-10) (\sigma = 60-90)</td>
<td>HAp Bio-resorbable High strength</td>
<td>Biopex</td>
<td>Pentax (Japan)</td>
</tr>
<tr>
<td>(\alpha)TCP</td>
<td>(\text{CaCO}_3, \text{Ca}(\text{H}_2\text{PO}_4)_2)</td>
<td>(t = 8-9) (\sigma = 28-38)</td>
<td>HAp Bio-resorbable High initial strength</td>
<td>Norian SRS</td>
<td>Norian (USA)</td>
</tr>
<tr>
<td>(\alpha)TCP</td>
<td>(\text{Ca}_3(\text{PO}_4)_2\cdot\text{CaHPO}_4\cdot \text{H}_2\text{O})</td>
<td>(t = 16-18) (\sigma = 6-10)</td>
<td>HAp Low viscosity paste</td>
<td>Cementek</td>
<td>Teknimed (France)</td>
</tr>
<tr>
<td>(\alpha)TCP</td>
<td>(\text{Ca}_3(\text{PO}_4)_2\cdot\text{CaHPO}_4\cdot \text{CaCO}_3\cdot \text{HAp})</td>
<td>(t = 6-7) (\sigma = 79-87)</td>
<td>HAp Biocement</td>
<td>Merk GmbH (German)</td>
<td></td>
</tr>
<tr>
<td>(\text{Ca}_3(\text{PO}_4)_2\cdot\text{CaHPO}_4\cdot \text{HAp})</td>
<td>(t = 5-20) (\sigma = 50)</td>
<td>HAp Little bio-resorbable</td>
<td>BoneSource</td>
<td>Libinger (USA)</td>
<td></td>
</tr>
<tr>
<td>(\text{Ca}_3(\text{PO}_4)_2\cdot\text{CaHPO}_4\cdot \text{HAp})</td>
<td>(t = 18-20) (\sigma = 3-5)</td>
<td>HAp (\alpha)-BSM</td>
<td>Cerapaste</td>
<td>NGK (Japan)</td>
<td></td>
</tr>
<tr>
<td>ACP(^b)</td>
<td>(\text{CaHPO}_4\cdot 2\text{H}_2\text{O})</td>
<td>(t = 18-20) (\sigma = 3-5)</td>
<td>HAp (\alpha)-BSM</td>
<td>ETEX (USA)</td>
<td></td>
</tr>
</tbody>
</table>

\(a\) \(t\) and \(\sigma\) mean hardening time (min) and compressive strength (MPa).
b) Amorphous calcium phosphate, \( \text{Ca}_3(\text{PO}_4)_2 \cdot n\text{H}_2\text{O} \)

\[
\begin{align*}
\text{Ca}_3(\text{PO}_4)_2\text{O}-\text{based cements}^{2,4)} \\
\text{and others}^{15)}
\end{align*}
\]

\( \text{CaHPO}_4 \) or \( \text{CaHPO}_4 \cdot 2\text{H}_2\text{O} \) as a combined component and HAp seed crystals are mixed, and dilute \( \text{H}_3\text{PO}_4 \) solution is used as a mixing liquid. The reaction is given as

\[
2\text{Ca}_4(\text{PO}_4)_2\text{O} + 2\text{CaHPO}_4 \cdot 2\text{H}_2\text{O} + \text{H}_2\text{O} \rightarrow 
\text{Ca}_{10}(\text{PO}_4)_{6}(\text{OH})_2 + 4\text{H}_2\text{O} \quad (6)
\]

Many other cement combinations have been studied, e.g., \( \text{CaHPO}_4 \cdot 2\text{H}_2\text{O-CaCO}_3 \) system (37-\( \beta \)-hardening time: 1-2 h, wet compressive: ca. 1 MPa, porosity: 70-80%, product: carbonated HAp), \( \beta \text{TCP-Ca(H}_2\text{PO}_4)_2 \cdot \text{H}_2\text{O} \) 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 materials\(^{14)}\). Increasing the hydration temperature increases the mechanical strength of hardened bodies. The 80-\( \beta \)-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 \( {\circ}\text{C} \).

\[
\begin{align*}
\text{Ca}_{10-\alpha}(\text{HPO}_4)_{\alpha}(\text{PO}_4)_{6-\alpha}(\text{OH})_{2-\alpha} \cdot n\text{H}_2\text{O} \\
\rightarrow (1-\alpha)\text{Ca}_{10}(\text{PO}_4)_{6}(\text{OH})_2
\end{align*}
\]

Therefore, the produced ceramics are composed of HAp single phase or HAp+TCP mixed phases or \( \beta \text{TCP single phase} \) 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 \( \mu \text{m} \) in pore diameter and 100-500 MPa in compressive strength are prepared. By using polymer beads porous HAp with 20-500 \( \mu \text{m} \) in pore size and 30-65\% in porosity could be easily prepared. By using \( \alpha \text{TCP} \) cement with albumin as a pore forming reagent, HAp bodies with large pores of 100-500 \( \mu \text{m} \) are prepared\(^{15)}\).

**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, drag delivery system (DDS) carrier and so forth.

![SEM photographs of HAp porous materials. A: \( \alpha \text{TCP} \) cement r.t.-hardened body, B: \( \alpha \text{TCP} \) cement 80-\( \beta \)-hardened body.](image)
Fig. 5  SEM photographs of HAp porous materials. C: Sintered body prepared by using αTCP cement and polymer beads, D: HAp crystals formed on sintered αTCP ceramics.

Fig. 6  SEM photographs of HAp porous materials. E and F: Tubular HAp and βTCP prepared by using gypsum hardened body.

CLOSING

The chemistry and characteristics of cement of the system CaO-P$_2$O$_5$ have been described briefly. The systems CaO-Al$_2$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, $^{13}$Si, $^{13}$P and $^{16}$S have just lined up. Furthermore various studies on the newly coming CaO-P$_2$O$_5$ cement are desired to be going on.

REFERENCES