Effect of various additives and temperature on some properties of an apatitic calcium phosphate cement

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The effect of additives and temperature on setting time, swelling time and compressive strength of a previously developed apatitic calcium phosphate cement was investigated. Setting was faster at body temperature than at room temperature. Early contact with aqueous solutions resembling blood and other body fluids had no effect. Deliberate additions of soluble carbonates, pyrophosphate or magnesium salts to the cement powder retarded or even inhibited setting. However, additions of calcium pyrophosphate, β-tertiary calcium phosphate or sintered hydroxyapatite to the cement powder in amounts up to 10% had no effect on the cement properties. Several organic substances were used as additives. They all retarded the setting and decreased the strength of the cement considerably.

1. Introduction

In a previous study [1] the development of a new apatitic calcium phosphate bone cement has been described. In the meantime this cement has been optimized with its combined properties as a function of the working variables so that now it complies with all short-term clinical requirements of bone surgery, orthopaedics and dentistry [2, 3]. In the present study the effect of various additives and of the temperature on the initial and final setting times, on the so-called swelling time [4] and on the compressive strength are determined. The first objective was to determine whether the material would be suitable right from the time of implantation under the influence of components of blood and other body fluids. The second objective was to evaluate the influence that some deviations from stoichiometry of the starting powder (α-tricalcium phosphate, α-TCP) and its possible contamination with its allotromorphic phase β-tricalcium phosphate (β-TCP) could have on the setting and mechanical characteristics of the cement. This was done by adding sintered hydroxyapatite, calcium pyrophosphate and β-TCP. The third objective was to find out whether the properties concerning the compliance of the material with short-term clinical requirements could be improved by certain additives.

2. Materials and methods

The cement formulation as worked out previously [1–3] consists of a powder (containing 83% α-tricalcium phosphate, 15% β-tricalcium phosphate and 2% precipitated calcium-deficient hydroxyapatite) and a liquid (mostly a 2.5% aqueous solution of disodium hydrogen phosphate). Either the powder or the liquid was used in this study as a vehicle for the additive. In each case the initial setting time I and the final setting time F were determined with Gillmore needles, following the C266-89 ASTM standard as described elsewhere [5]. In most cases this procedure could be combined with an estimate of the upper or lower limit of the swelling time S as previously indicated [4] with the method of direct observation of desintegration either or not occurring upon immersion in Ringer's solution (or another aqueous solution to which certain components of the body fluids were added).

After final setting, cylindrical samples of cement having a height of 12 mm and diameter of 6 mm were immersed in Ringer's solution at 37 °C for 1 day, while still retained in their teflon mould. They were removed from the mould after polishing their top and bottom planes, and their compressive strength C was determined using an Instron Universal Testing Machine type 4507 at a crosshead speed of 1 mm/min.

3. Results

First, the effect of the temperature on the setting times I and F was determined as a function of the amount of accelerator (Na_2HPO_4) in the cement liquid. The results for a liquid/powder ratio of 0.32 ml/g are given in Fig. 1a and 1b, respectively. They confirm that Na_2HPO_4 in the cement liquid accelerates the setting, as found elsewhere [2], and indicate that after implantation the material will set somewhat faster than without implantation.

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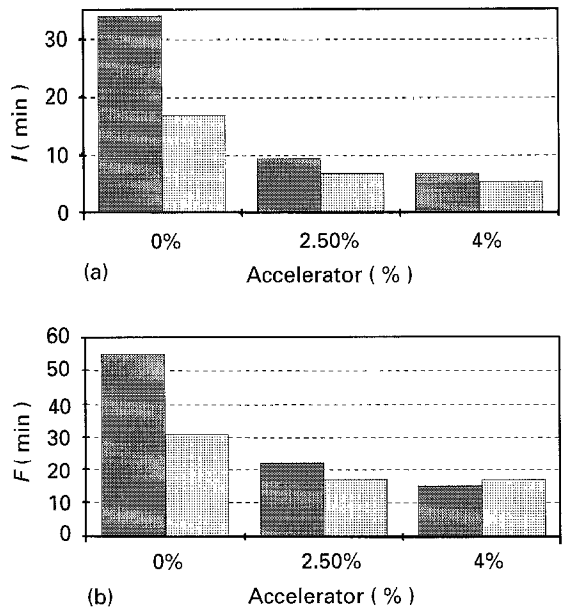

Figure 1 Effect of the temperature on: (a) the initial setting time I; and (b) the final setting time F as a function of the amount of accelerator (Na_2HPO_4) in the cement liquid (■ 22 °C; ▤ 37 °C).

TABLE I Effect of additions of Na_2CO_3 to the cement liquid on the setting times I and F

Temperature (°C)	%Na_2CO_3	%Na_2HPO_4	I (min)	F (min)
22	0	2.5	9.5	22
	0.25	2.5	24.5	35
	0	4	7.0	15
	0.25	4	14.5	24
37	0	2.5	7.0	17
	0.25	2.5	9.0	17
	0	4	5.5	17
	0.25	4	6.0	15

TABLE II Effect of simulated body fluid SBF on the initial and final setting time I and F and on the swelling time S and the compressive strength C

Cement liquid	Soaking fluid	I (min)	F (min)	S (min)	C(MPa)
2.5% Na_2HPO_4	0.9% NaCl	9.0	23	< 24	30.8 (3.1)[b]
	SBF[a]	9.0	23	< 24	29.6(1.7)
SBF + Na_2HPO_4	SBF[a]	12.5	21	< 22	36.7 (2.5)

[a] SBF containing also 2.5% Na_2HPO_4
[b] Standard deviation between brackets

In order to simulate body fluids or the possible effect of contact with body fluids 0.25% Na_2CO_3 was added to the cement fluids mentioned in Fig. 1. The results are given in Table I. It is observed that carbonate has a deleterious effect on the setting of the cement at room temperature. However, at body temperature there is no effect. In order to obtain a broader view on the possible effects of contact with body fluids we used a simulated body fluid (SBF) [6] of the following composition:

$$\begin{gathered} 0.105\ \mathrm{M\ NaCl} \\ 0.035\ \mathrm{M\ NaHCO_3} \\ 0.002\ \mathrm{M\ MgSO_4 \cdot 7H_2O} \\ 0.004\ \mathrm{M\ K_2CO_3} \end{gathered}$$

so that calcium and phosphate were not used and their possible interaction with the cement was avoided (all calcium and phosphate ions occurring in the soaking liquid were thus dissolved from the cement itself). Not only the setting times I and F were determined at room temperature, but also the swelling time S and the compression strength after 18 h of soaking at 37 °C. The results are given in Table II. SBF in the cement liquid appears to have a slightly deleterious effect on the setting, like carbonate alone, but it improves the compressive strength.

However, body fluids like blood serum contain not only inorganic ions but also organic substances. These were simulated by preparing a special fluid (SF) which was 0.105 M NaCl, 0.024 M $NaHCO_3$, 0.015 M Na_2CO_3, and which also contained 0.1% of each of the chemicals mentioned in Table III. This was used as the soaking fluid: the cement fluid contained the Na_2HPO_4 accelerator. The results are given in Table IV. They show that the combination of inorganic and organic substances of the SF has no effect on the compressive strength, i.e. the simulation of blood and other body fluids.

As mentioned earlier, the third objective was to investigate whether certain additives had an advantageous effect on the properties of the cement. First, the effect of carbonate was further explored, either as $NaHCO_3$ or Na_2CO_3 or K_2CO_3, either dissolved in the cement liquid or as an addition to the cement powder. A summary of the results is given in

TABLE III Organic substances used for the preparation of the special fluid SF and some other organic substances used in this study

Substance	Abbreviation	Brand	Catalogue number	Remarks
Agar	AG	Merck	1615	
Alginic acid	AL	Sigma	A-7003	
Casein alkalihöslich	CA	Merck	2241	
Polypep	PP	Sigma	P-5115	
Polyvinylpyrrolidon	PV	Merck	7443	
Sodium dodecylsulfate	SD	Merck	12012	
Hexadecyl trimethyl ammonium chloride	HAC	Merck	814087	50% solution
Gelatin powder		Merck	4078	
Glutardialdehyde		Merck	814393	50% solution

TABLE IV Compressive strength C as a function of the amount of accelerator Na_2HPO_4 and retardor Na_2CO_3 in the cement liquid after soaking for 18 h at 37 °C in either Ringer's solution or the special fluid SF

Cement liquid	Soaking fluid	C (MPa)
2.5% Na_2HPO_4 + 0.25% Na_2CO_3	0.9% NaCl	37.5 (5.3)[a]
	SF	35.2 (3.6)
4% Na_2HPO_4	0.9% NaCl	28.5 (3.5)
	SF	27.1 (2.6)

[a] Standard deviation between brackets

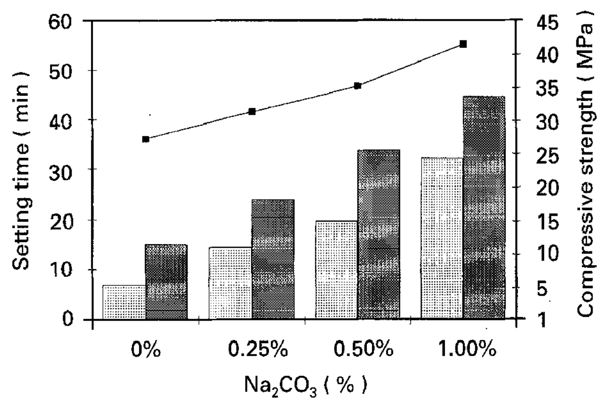

Figure 2 Effect of Na_2CO_3 in the cement liquid containing 4% Na_2HPO_4 on properties of the cement (soaking in special fluid SF for 18 h at 37 °C). ▦ *I*; ■ *F*; —■— *C*.

Table V and in Fig. 2. These data confirm that although Na_2HPO_4 in the cement liquid accelerates the setting, it also reduces the final compressive strength [2]. Moreover, they show that carbonates, either in the solid or in the cement liquid, retard the setting, increase the rate of strengthening and restore the final strength of the cement to the value which it originally had without the use of an accelerator.

TABLE VII Effect of additions of pyrophosphates to the cement powder on cement properties (liquid contained 2.5% Na_2HPO_4)

Powder	I (min)	F (min)	S (min)	C (MPa)
no addition	9	19	< 5	33.2 (2.2)
0.5% $Na_4P_2O_7$	53	n.d.[a]	> 55	0.3
0.5% $Mg_2P_2O_7$	8	17.5	< 10	29.6 (2.2)
0.5% $Ca_2P_2O_7$	9.5	17.5	< 10	30.3 (3.1)
5% $Ca_2P_2O_7$	11	21.5	< 7	37.6 (5.9)
10% $Ca_2P_2O_7$	12	23	< 7	38.4 (5.2)

[a] n.d. = not determined

Another constituent of body fluids which was studied in more detail was magnesium, either as MgO or as $MgHPO_4 \cdot 3H_2O$ in the cement powder (Table VI). It is observed that soluble magnesium compounds are disastrous for the cement, since they completely prevent strengthening of the cement paste.

Also pyrophosphate ions occur in body fluids. Therefore, additions of $Na_4P_2O_7$, $Ca_2P_2O_7$ and $Mg_2P_2O_7$ were also investigated (Table VII). Only the soluble form of $Na_4P_2O_7$ was detrimental. Additions of β-TCP to the powder were also investigated (Table VIII). Only large amounts of extra β-TCP have an effect (which is disadvantageous). Finally, sintered hydroxyapatite (SHA) was used as an inorganic additive: the results are given in Table IX. It appears that additions of SHA slightly retard the setting and increase the strength of the cement.

The effect of organic additives such as those listed in Table III is given in Table X. All substances tested increased the setting time and decreased the strength considerably. An attempt to incorporate gelatin and to cross-link its molecules by the addition of

TABLE V Effect of some carbonates in the cement powder on some properties of the cement

Cement liquid	Addition to the cement powder	Soaking time (h)	I (min)	F (min)	C (MPa)
2.5% Na_2HPO_4	0.5% $NaHCO_3$	18	12	30	30.7 (4.5)
	0.5% Na_2CO_3	18	47	> 60	44.7 (2.7)
		40	47	> 60	53.5 (5.0)
	0.5% K_2CO_3	18	35	> 60	42.3 (5.1)
2.5% Na_2HPO_4		18	9.5	22	30.8 (3.1)
		40	9.5	22	31.6 (2.6)
H_2O		18	34	55	33.2 (2.2)
		40	34	55	54.5 (3.5)

TABLE VI Effect of soluble magnesium-containing compounds on properties of the cement

Powder	Liquid	I (min)	F (min)	S (min)	C (MPa)
0.5% MgO	2.5% Na_2HPO_4	36	61	> 70	0.3
	4% Na2HPO4	37	> 65	> 300	0.3
1% MgO	2.5% Na_2H4PO_4	51	> 85	> 90	0.3
	4% Na_2HPO_4	n.d.[a]	n.d.	> 300	0.3
0.5% $MgHPO_4 \cdot 3H_2O$	2.5% Na_2HPO_4	> 50	n.d.	> 100	0.3
	4% Na_2HPO_4	> 50	n.d.	> 100	0.3

[a] n.d. = not determined

TABLE VIII Effect of additions of β-TCP to the cement powder (liquid without accelerator, soaking for 2 days in Ringer's solution)

Powder	*I* (min)	*F* (min)	*S* (min)	*C* (MPa)
0% β-TCP	34	55	> 100	54.5 (3.5)
10% β-TCP	37	61	> 65	47.4 (4.7)
20% β-TCP	33	58	> 65	45.1 (5.8)
30% β-TCP	28	40	> 40	i.s.[a]

[a] i.s. = inhomogeneous samples, not suitable for determination of the strength

TABLE IX Effect of sintered hydroxyapatite SHA on properties of the cement (2.5% Na_2HPO_4 in the liquid, soaking for 24 h at 37 °C in Ringer's solution)

Cement Powder	*I* (min)	*F* (min)	*S* (min)	*C* (MPa)
0% SHA	9	19	< 5	33.2 (2.2)
5% SHA	11	25	< 6	34.9 (5.3)
10% SHA	12.5	26	< 8	35.9 (4.0)
15% SHA	15.5	30	< 9	39.2 (6.8)

glutardialdehyde in order to obtain a three-dimensional organic network within the cement structure failed completely, as instead of a dense mass a granulate was obtained.

4. Discussion

The prospects for the suitability of the cement as developed earlier [1–3] are good. The effect of body temperature is positive, since at 37 °C the rate of the setting reaction responsible for the strengthening of the cement is higher than at room temperature. On the other hand, early contact with aqueous solutions resembling body fluids at body temperature has no effect on the setting characteristics nor on the compressive strength, as follows from Tables I to IV.

Deliberate additions of soluble carbonates and pyrophosphates to the cement powder are detrimental for the cement, since setting is clearly retarded. However, the effect of adding magnesium salts is even more deleterious. This is expected, since it is known that Mg^{2+} ions can retard or even inhibit the precipitation and growth of apatite in seeded calcium phosphate solutions supersaturated or slightly undersaturated with respect to OCP at neutral pH [6–8]. It has been shown that Mg^{2+} ions markedly retard the growth of apatite by blocking the active growth sites through adsorption at the surface of the apatite cristallites that are supposed to act as a seed.

In contrast, fairly large amounts of calcium pyrophosphate or sintered hydroxyapatite may be present in the cement powder without having a serious effect on the cement properties. This means that the cement does not depend rigorously on the way in which the α-tertiary calcium phosphate component of the cement powder is prepared. In fact, from the phase diagram of the system $CaO–P_2O_5–H_2O$ [9] it can be seen that any deviation from $Ca/P = 1.5$ would produce some contamination of the α-tertiary calcium phosphate with either hydroxyapatite or calcium pyrophosphate. As has been shown, this would not have negative consequences on the behaviour of the cement.

On the other hand, β-tricalcium phosphate can also be present in the starting powder of the cement without damaging its properties. As β-TCP is the stable phase of the tricalcium phosphate under 1180 °C, it is very difficult to avoid completely the presence of some β-TCP in α-TCP obtained by quenching. In fact, we have detected around 15% β-TCP in our α-TCP samples.

Even if it is not clear that the β-TCP, SHA or calcium pyrophosphate will behave the same way when they are added or when they are formed during preparation of the starting powder, the fact that their additions do not drastically modify the setting and mechanical properties of the cement is quite significant.

Finally, it appears that most organic additives have a deleterious effect on the properties of the cement.

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TABLE X The effect of organic additives to the cement powder on the properties of the resulting cement (soaking in Ringer's solution)

Cement powder	Liquid (% Na_2HPO_4)	Soaking (h)	*I* (min)	*F* (min)	*S* (min)	*C* (MPa)
0.25% SD	2.5	18	15.5	35	< 50	20.2 (1.9)
	4	18	10.5	27.5	< 40	17.3 (2.8)
0.25% HAC	2.5	72	12	40	< 45	27.4 (4.5)
	4	72	12	37	< 40	17.8 (2.0)
0.5% AG	2.5	18	10.5	22	< 30	25.2 (2.9)
0.5% AL	2.5	18	12	42	< 45	26.7 (2.1)
0.5% PV	2.5	18	11	25	< 30	24.1 (3.1)
0.5% CA	2.5	18	8	22	< 25	19.5 (2.1)
0.5% PP	2.5	18	9.5	26.5	< 30	23.9 (4.5)

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