Limited compliance of some apatitic calcium phosphate bone cements with clinical requirements

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Clinical requirements for calcium phosphate bone cements were formulated in terms of the initial setting time, the final setting time, the cohesion time and the ultimate compressive strength. Two cements were tested. Biocement H was made of a powder containing α-tertiary calcium phosphate and precipitated hydroxyapatite. Biocement F was made of a powder containing, in addition, some monetite. The liquid/powder (L/P) ratio was varied over the range 0.30–0.40 ml g^{-1}, whereas the accelerator concentration in the liquid was varied from 0%–4% Na_2HPO_4 in water. For Biocement H there was no combination L/P ratio and % Na_2HPO_4 for which all clincal requirements were satisfied. However, Biocement F had a certain area where this was the case. Therefore, it is expected that Biocement F can be applied in clinical situations such as orthopaedics, plastic and reconstructive surgery and oral and maxillofacial surgery, even when early contact with blood is inevitable.

1. Introduction

Calcium phosphate bone cements (CPBCs) are materials consisting of a liquid (water or an aqueous solution) and a powder containing one or more solid compounds of calcium and/or phosphate salts, so that if liquid and powder are mixed in an appropriate ratio, they form a paste which at room or body temperature sets by precipitation of one or more other solid compounds, of which at least one is a calcium phosphate. They have the advantage over calcium phosphate bioceramics that they do not need to be delivered in prefabricated forms or as granules, but that they can be molded during the operation or simply injected into the bone defect [1].

Since the first CPBC was synthesized in 1983 [2], some 20 different formulations have been published which set at room or body temperature into solid bodies with considerable mechanical strength [3] so that, at the moment, four types are known, depending on the type of calcium phosphate formed during setting. This can be either dicalcium phosphate dihydrate ($CaHPO_4 \cdot 2H_2O$ or DCPD), calcium-deficient hydroxyapatite, ($Ca_9(HPO_4)(PO_4)_5OH$ or CDHA), hydroxyapatite ($Ca_{10}(PO_4)_6(OH)_2$ or HA), or amorphous calcium phosphate (ACP) having no fixed stoichiometry.

The CPBCs investigated in this study are both of the CDHA type. Biocement H was developed earlier [4]. Its powder consists of alpha-tertiary calcium phosphate (αTCP) and some precipitated hydroxyapatite (PHA). Its liquid is an aqueous solution of disodium hydrogen phosphate (Na_2HPO_4). It has been proven that its properties do not depend critically on the stoichiometry or the temperature treatment of the α-TCP preparation used [5]. Further, the setting characteristics and the strength are considerably improved when going from room temperature to body temperature [6]. During setting, there is no dimensional change nor any detectable thermal effect [7].

Biocement F is also of the CDHA type [8] although originally it was thought to be of the OCP type. Here OCP means octocalcium phosphate ($Ca_8(HPO_4)_2(PO_4)_4 \cdot 5H_2O$) [9]. OCP seems to precipitate relatively easy [10] at least in the range $5.5 < pH < 7$. However, none of the calcium phosphate cements synthesized up to now is of the OCP type, contrary to previous reports [11]. The liquid of Biocement F is either water or an aqueous solution of Na_2HPO_4, whereas the powder is a mixture of dicalcium phosphate or monetite ($CaHPO_4$), α-TCP and HA. During setting, the α-TCP is transformed into CDHA according to the reaction [8]

$$3\,\alpha\text{-}Ca_3(PO_4)_2 + H_2O \rightarrow Ca_9(HPO_4)(PO_4)_5OH \quad (1)$$

which also occurs in Biocement H as the setting reaction. In Biocement F, the monetite does not participate in the setting reaction [8].

As for dental stone, the so-called *Gillmore needles* are suitable for measuring the setting times of CPBCs. The light and thick needle is used to measure the initial setting time, *I*, the heavy and thin needle for the final setting time, *F* [12]. The clinical meaning of *I* is that it indicates the time from whence the paste may not be deformed without damaging the structure of

the solidifying cement. F indicates the time from when the cement can be touched without scratching it. So the cement must be applied before I and the wound may be closed after F.

In the early stage of our investigation we noticed that some CPBCs desintegrate upon early contact with water, aqueous solutions and body fluids such as blood. So we designed a test to measure the so-called cohesion time, CT, of a CPBC, i.e. the time from which it no longer disintegrates when immersed in Ringer's solution [13]. From this definition it is clear that a CPBC must be applied to a wound after CT but before I.

The first serious attempt to formulate clinical requirements for the CPBCs in terms of setting times and cohesion times came from our working group [14, 15]. At the moment we have had some practical experience with clinicians. On the basis of that experience we can express the following handling requirements:

$$3 \leqslant I < 8 \tag{2}$$

$$I - CT \geqslant 1 \tag{3}$$

$$F \leqslant 15 \tag{4}$$

in which the numbers express minutes. Requirement (3) means, in effect, that CT must be at least 1 min before I, so that the clinician has at least 1 min to apply and to mold the material. As the mixing in a mortar is about 1 min, the shortest CT that can be allowed is about 2 min, so that the clinician has at least 1 min to collect the paste from the mortar and to put it on the pallet knife or in the syringe with which it is to be transferred to the wound after CT and before I. For dental applications, I must be close to 3 min, whereas for orthopaedic applications it must be close to 8 min. However, in no case is it tolerable for the clinician that F is longer than 15 min.

For many dental cements and also for CPBCs it is suitable to measure the compressive strength, CS, and the diametral tensile strength DTS, after immersion of the cement in Ringer's solution at 37 °C during some time [16]. Usually CPBCs reach ultimate strength within 5 d immersion [8]. Because in most clinical applications the CPBCs are applied in direct contact with human trabecular bone, it can be stated as a mechanical requirement that the stregth of a CPBC must be at least as high as that of human trabecular bone. As, in most applications, the CPBC will be occluded between bone and metal implant surfaces, one may presume that the compressive strength, CS, is most relevant. As the maximum compressive strength of human trabecular bone is 30 MPa [17] the main mechanical requirement for CPBCs is expected to be

$$CS \geqslant 30\,\text{MPa} \tag{5}$$

From the previous studies on Biocement H and Biocement F [4–8] it was presumed that there were certain areas for the liquid/powder ratio (L/P) and the accelerator concentration (% Na_2HPO_4) in the cement liquid for which requirements 2–5 were simultaneously satisfied. The purpose of the present study was to investigate the limitations of this area in order to draw conclusions on whether

1. a clinically suitable high-viscosity paste can be formulated which can be applied as a dough;

2. a clinically suitable low-viscosity paste can be formulated which can be applied by injection from a syringe; and

3. both a high-viscosity and a low-viscosity paste can be formulated using the same cement powder but eventually using different L/P ratios and/or accelerator concentrations in the liquid.

2. Materials and methods

α-TCP was prepared by using an appropriate mixture of $CaHPO_4$ (Merck, Darmstadt, Catalog number 2144) and $CaCO_3$ (Merck 2076), heating it at 1300 °C for at least 6 h and quenching it in air down to room temperature. The PHA was a commercial product called Tri-calcium phosphate (Merck 2143) but in fact being apatitic. The powder of Biocement H contained 98% α-TCP and 2% PHA. The powder of Biocement F was composed of 64% α-TCP, 27% $CaHPO_4$ and 9% PHA.

The liquid/powder ratio L/P of both cements was taken to be either 0.30 or 0.32 or 0.35 or 0.40 ml g^{-1}. The values chosen for the accelerator concentration were 0%, 1%, $2\frac{1}{2}$% and 4% Na_2HPO_4 in water. The setting times I and F were determined as usual [12] and the cohesion time, CT, with the method developed previously [13]. Teflon molds were used to prepare cement cylinders with a height of 12 mm and a diameter of 6 mm, and soaking was carried out during 1, 2 and 5 d in Ringer's solution at 37 °C prior to determination of the compressive strength, CS, with an Instron Universal Testing Machine Type 4507 at a compression rate of 1 mm min^{-1}. The results were screened on their area of compliance with each of the requirements 2–5. For those conditions, for which requirements 2–5 were satisfied simultaneously, it was investigated whether the paste was of a sufficiently low-viscosity type to be injectable at time CT.

3. Results

For Biocement H the results are given in Tables I–VI. For none of the combinations of L/P and % Na_2HPO_4 investigated was there compliance with requirements 2–5 simultaneously. This means that Biocement H is not suitable for clinical applications.

For Biocement F, the results are given in Tables VII–XII. Table XIII indicates, for which combinations of L/P and % Na_2HPO_4 there is full compliance with requirements 2–5. Further investigations of the pastes in question showed that all three can be handled as doughs, and none of them is really injectable. So, in conclusion, Biocement F is suitable for clinical applications as a biomaterial to repair bone, but only for those applications where a dough consistency is required.

TABLE I The initial setting time I for Biocement H as a function of the L/P ratio (ml g^{-1}) and the accelerator concentration % Na_2HPO_4

Na_2HPO_4 (%)	L/P (ml g^{-1})	Initial setting time (min)			
		0.30	0.32	0.35	0.40
0		28	32	35	38
1		10	8.5	12	20
$2\frac{1}{2}$		7	6.5	9	11
4		$4\frac{1}{4}$	5	6.5	9

TABLE II The final setting time F for Biocement H as a function of the L/P ratio and the accelerator concentration % Na_2HPO_4

Na_2HPO_4 (%)	L/P (ml g^{-1})	Final setting time (min)			
		0.30	0.32	0.35	0.40
0		70	76	78	80
1		28	28	30	58
$2\frac{1}{2}$		15	17	28	35
4		22	17	30	56

TABLE III The initial setting time I minus the cohesion time CT for Biocement H as a function of the L/P ratio and the accelerator concentration % Na_2HPO_4

Na_2HPO_4 (%)	L/P (ml g^{-1})	$I - CT$ (min)			
		0.30	0.32	0.35	0.40
0		9.5	13	14	15
1		4.5	3	4	9
$2\frac{1}{2}$		0	0.5	4	7
4		−21	0	1.5	4.5

TABLE IV The 1 d compressive strength $CS - 1$ of Biocement H ($n = 7$) as a function of the L/P ratio and the accelerator concentration % Na_2HPO_4

Na_2HPO_4 (%)	L/P (ml g^{-1})	$CS - 1$ (MPa)			
		0.30	0.32	0.35	0.40
0		44[a]	38	41	36
1		37	38	39	30
$2\frac{1}{2}$		32	29	32	23
4		26	27	27	25

[a]On average, the standard deviation of the compressive strength values was 15%.

TABLE V The 2 d compressive strength $CS - 2$ of Biocement H ($n = 7$) as a function of the L/P ratio and the accelerator concentration % Na_2HPO_4

Na_2HPO_4 (%)	L/P (ml g^{-1})	$CS - 2$ (MPa)			
		0.30	0.32	0.35	0.40
0		54	57	55	46
1		41	47	48	35
$2\frac{1}{2}$		38	31	32	30
4		27	32	27	28

TABLE VI The 5 d compressive strength $CS - 5$ of Biocement H ($n = 7$) as a function of the L/P ratio and the accelerator concentration % Na_2HPO_4

Na_2HPO_4 (%)	L/P (ml g^{-1})	$CS - 5$ (MPa)			
		0.30	0.32	0.35	0.40
0		50	50	51	35
1		44	52	50	39
$2\frac{1}{2}$		47	51	35	34
4		n.d.[a]	39	n.d.	28

[a]n.d. = not determined.

TABLE VII The initial setting time I of Biocement F as a function of the L/P ratio and the accelerator concentration % Na_2HPO_4

Na_2HPO_4 (%)	L/P (ml g^{-1})	I(min)			
		0.30	0.32	0.35	0.40
0		14.5	20	27	28
1		8	7.5	10	12.5
$2\frac{1}{2}$		3.5	4	4.5	5.5
4		$2\frac{3}{4}$	3	4	$4\frac{1}{4}$

TABLE VIII The final setting time F of Biocement F as a function of the L/P ratio and the accelerator concentration % Na_2HPO_4

Na_2HPO_4 (%)	L/P (ml g^{-1})	F(min)			
		0.30	0.32	0.35	0.40
0		32	43	57	60
1		16	15	20	29
$2\frac{1}{2}$		7	9	10	11.5
4		4	6	8	9.5

TABLE IX The initial setting time I minus the cohesion time CT of Biocement F as a function of the L/P ratio and the accelerator concentration % Na_2HPO_4

Na_2HPO_4 (%)	L/P (ml g^{-1})	$I - CT$ (min)			
		0.30	0.32	0.35	0.40
0		2.5	10	16	13
1		2	1.5	2	2.5
$2\frac{1}{2}$		0	$1\frac{1}{4}$	1	0.5
4		0	1	2	0.5

TABLE X The 1 d compressive strength $CS - 1$ of Biocement F as a function of the L/P ratio and the accelerator concentration % Na_2HPO_4

Na_2HPO_4 (%)	L/P (ml g^{-1})	$CS - 1$ (MPa)			
		0.30	0.32	0.35	0.40
0		36	30	28	22
1		29	35	29	22
$2\frac{1}{2}$		32	31	23	20
4		30	28	26	17

TABLE XI The 2 d compressive strength $CS-2$ of Biocement F as a function of the L/P ratio and the accelerator concentration % Na_2HPO_4

Na_2HPO_4 (%)	L/P ($ml\,g^{-1}$)	$CS-2$ (MPa)			
		0.30	0.32	0.35	0.40
0		42	33	32	24
1		37	32	33	22
$2\frac{1}{2}$		30	29	29	20
4		35	31	25	20

TABLE XII The 5 d compressive strength $CS-5$ of Biocement F as a function of the L/P ratio and the accelerator concentration % Na_2HPO_4

Na_2HPO_4 (%)	L/P ($ml\,g^{-1}$)	$CS-2$ (MPa)			
		0.30	0.32	0.35	0.40
0		37	32	27	n.d.
1		35	31	27	n.d.
$2\frac{1}{2}$		32	30	31	n.d.
4		25	26	28	n.d.

[a]n.d. = not determined.

TABLE XIII Compliance (+) with the four requirements 2–5 for Biocement F as a function of the L/P ratio and the accelerator concentration % Na_2HPO_4

Na_2HPO_4 (%)	L/P ($ml\,g^{-1}$)	Initial setting time (min)			
		0.30	0.32	0.35	0.40
0		–	–	–	–
1		–	+	–	–
$2\frac{1}{2}$		–	+	+	–
4		–	–	–	–

4. Discussion

It was shown that Biocement H is not suitable for clinical applications. The main cause is that requirement 3 is not fulfilled: the cohesion time, CT, coincided practically with the initial setting time, I, for the most promising combinations of the L/P ratio and accelerator concentration % Na_2HPO_4.

According to Miyamoto *et al.* [18], the HA type cement invented by Brown and Chow [2] has the same problem, even when phosphate solutions are used as accelerator. Ishikawa *et al.* [19] solved this problem by the addition of sodium alginate to the cement liquid. This addition does not adversely affect the biocompatibility of this material [20].

In our case, Biocement H set faster at body temperature than at room temperature [6]. Further, we found that early contact with aqueous solutions resembling blood and other body fluids, had no effect on its setting behavior [5]. Yet, Jansen *et al.* [21] noticed some problems with early blood contact of Biocement H during animal experimentation. No such problems occur with Biocement F.

The histology of CPBC implants in bone shows a very good osteointegration (which is a question of days) followed by a gradual osteotransduction, i.e. the cement is transformed into new bone tissue [21]. The osteotransduction is a question of months in rabbits [22, 23] whereas in goats it takes longer [21]. On the other hand, when the CPBC is implanted subcutaneously in rats so that cellular contact is inhibited while contact with extracellular fluid is provided [24], it is mechanically and chemically stable during several months, which means that the CDHA is in physico-chemical equilibrium with the extracellular fluid.

This *in vivo* behavior of CDHA-type CPBCs suggests that the osteotransduction is due to the same mechanism as that causing the normal bone remodeling, whereby osteoclasts decrease the pH in their environment and, hence, dissolve the mineral and the matrix of old bone, after which the osteoblasts deposit new matrix and increse the local pH so that this new matrix becomes mineralized [10].This hypothesis is being tested in *in vitro* cell culture experiments. It is already proven that osteoclasts resorb CDHA type CPBCs [25].

Experiments with osteoblasts and osteoprogenitor cells are still on-going. The biocompatibility of CDHA-type CPBCs is excellent [26], mainly due to the fact that their pH during and after setting is close to 7.4. A further advantage is that there is no dimensional change nor any heat effect during setting [7]. For these reasons, it is concluded that Biocement F has good potential value for use in orthopaedics, plastic and reconstructive surgery and oral and maxillofacial surgery, where the cement is exposed to blood. But obviously this exposition must take place after CT and before I.

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