JOURNAL OF MATERIALS SCIENCE: MATERIALS IN MEDICINE 5 (1994) 103–107

Preparation and properties of some magnesium–containing calcium phosphate cements

M. P. GINEBRA, M. G. BOLTONG, F. C. M. DRIESSENS, O. BERMÚDEZ, E. FERNÁNDEZ, J. A. PLANELL
Department of Material Sciences and Metallurgy, Universitat Politècnica de Catalunya, Avda. Diagonal 647, E08028 Barcelona, Spain

Attempts were made to prepare magnesium-containing calcium phosphate cements. These were successful at the composition $CaMg_2(PO_4)_2xH_2O$. X-ray diffraction showed that such a compound is not formed but that the cement consists of magnesium phosphate precipitated on the calcium phosphate admixture. The pH of this formulation is around 10 during setting and after. The cement is injectable. Its setting time is about 10 min. In this study compressive strength values were as high as 11 MPa and the diametral tensile strength was over 2 MPa. Animal experiments must show whether it is suitable for replacement or augmentation of bone in non-load bearing situations.

1. Introduction

The biocompatibility of calcium phosphates has been well established [1–4]. Due to their good osteoconductivity calcium phosphate ceramics have been applied for bone replacements and augmentation. Ceramic blocks have the disadvantage that they must be used in prefabricated forms, whereas granules frequently drift away from the site of implantation. These disadvantages may be overcome with the use of calcium phosphates in the form of cements.

The term 'calcium phosphate cements' was introduced by Gruninger *et al.* [5]. Such a cement may be described as a powder or a mixture of powders which upon mixing with water or an aqueous solution to a paste, reacts around room or body temperature by the formation of a precipitate containing crystals of one or more calcium phosphates and sets by the entanglement of the crystals of that precipitate. In fact, up to now only orthophosphate cements have been presented in the literature. Brown and Chow [6] were the first who developed a calcium orthophosphate cement. They prepared mixtures of dicalcium phosphate dihydrate (DCPD) with tetracalcium phosphate (TTCP) and of dicalcium phosphate (DCP), TTCP and hydroxyapatite (HA) and reported setting times decreasing with increasing HA content from 22 to 8 min as measured with a Vicat needle. Fukase *et al.* [7] optimized such cements as derived from mixtures of DCP and TTCP. They added some fluoride to the aqueous solution and reported that the reaction product was HA and that the setting reaction was completed within 24 h, when the samples were kept under 100% relative humidity at 37 °C.

Another type of calcium orthophosphate cements has been developed by Lemaitre *et al.* [8]. They found that mixtures of monocalcium phosphate monohydrate (MCPM) and β-tricalcium phosphate (β-TCP) mixed with water into a paste set at room temperature within 2 min. Mirtchi *et al.* [9] reported that the reaction product in such cements was DCPD. Furthermore, Mirtchi *et al.* [10] measured the setting times of such cements with admixtures of calcium sulphate dihydrate, calcium sulphate hemihydrate and/or calcium pyrophosphate and found that these admixtures increased the setting time from about 1 up to 10 min, as measured with a Vicat needle.

Hardened products of calcium phosphates were developed by Monma [11]. They made pastes of water with mixtures of DCPD and calcium carbonate (they did not report which calcium carbonate) or of DCP with calcium carbonate and kept them at 50 or 80 °C for 16 to 40 h. By X-ray diffraction and IR spectroscopy they proved that either octocalcium phosphate (OCP) or carbonated hydroxyapatite or both were formed, but they could not report on any setting times. Earlier, Monma and Kanazawa [12] had reported that hardened bodies could be produced by keeping pastes of α-TCP with water at temperatures between 60 and 100 °C. The reaction product was a calcium deficient apatite with a Ca/P molar ratio near 1.50. These products can hardly be called cements because the setting temperatures are impractically high.

A third type of calcium orthophosphate cements was developed by Monma *et al.* [13]. They prepared mixtures of α-TCP with DCPD and added water to form pastes which appear to set within 9 to 30 min as measured with a Vicat needle. The reaction product in these mixtures was OCP.

Oonishi [14] reported that mixtures of α-TCP with collagen gels or of TTCP with collagen gels could set upon the implantation into the bones of animals. However, it is not clear what the reaction products are, so that it is unknown whether these products can be considered as calcium orthophosphate cements.

The development of a fourth calcium orthophosphate cement has been published by Nishimura *et al.* [15]. They prepared a glass from the system $CaO–SiO_2–P_2O_5–CaF_2$, fractured it and milled it to a particle size of 325 mesh, with an average of 5 μm. When mixed with a solution of diammonium hydrogen phosphate into a paste, this paste set in about 6 min at room temperature as measured with a Vicat needle, under the formation of calcium ammonium phosphate monohydrate. Upon inmersion of that cement in water the reaction product was transformed into hydroxyapatite within 1 week.

Brown and Chow [6] and later Fukase *et al.* [7] claimed that their powder mixture of DCP and TTCP reacted upon mixing with water to stoichiometric hydroxyapatite $Ca_{10}(PO_4)_6(OH)_2$. However, more recent investigations [16, 17] have shown that only the first nuclei consist of nearly stoichiometric hydroxyapatite whereas further growth of these nuclei occurs in the form of calcium deficient hydroxyapatite $Ca_9(HPO_4)(PO_4)_5OH$ with a Ca/P ratio of 1.50. Another hydroxyapatite cement was formed by Constantz *et al.* [18] who mixed water-free phosphoric acid with TTCP.

A prerequisite for calcium phosphate cements to be formed is that the calcium phosphate in question precipitates from the aqueous phase within the cement. Magnesium whitlockite $Ca_9Mg(HPO_4)(PO_4)_6$ is known to be formed by such precipitation reaction [19]. In the system $CaO–MgO–P_2O_5$ compounds like $Ca_4Mg_5PO_4)_6$ are also known [20], but it is as yet unknown whether they can be prepared by precipitation. In the present study it was investigated whether calcium phosphate cements containing magnesium could be obtained.

2. Materials and methods

The materials used in attempts to prepare cements in the present study are detailed in Table I. It was established by X-ray diffraction that they were pure and single-phase within the limits of error. In the first experiment attempts were made to prepare MWH cements (magnesium whitlockite) starting with $MgHPO_4·3H_2O$ as one of the components. In the second experiment a similar series of attempts was done starting with MgO as one of the components. In the third experiment formulations were used aiming at the formation of $CaMg_2(PO_4)_2$ cements. The ingredients were proportioned by weighing and homogenized by milling in an agate ball mill. The initial setting time *I* and the final setting time *F* were determined using Gilmore needles at suitable water/powder ratios. Cylinders were prepared with a diameter of 6 mm and a height of 12 mm. After soaking for 1 day in Ringer's solutions at 37 °C the compressive strength *C* and the diametral tensile strength *T* (MPa) were determined with an Instron Universal Testing Machine type 4507 operating at a cross-head speed of $1\ mm\ min^{-1}$.

TABLE I Compounds used as constituents in the attempts to synthesize magnesium containing calcium phosphate cements

Abbreviation	Formula	Name
MCPM	$Ca(H_2PO_4)_2·H_2O$	monocalcium phosphate monohydrate
DCP	$CaHPO_4$	dicalcium phosphate
DCPD	$CaHPO_4·2H_2O$	dicalcium phosphate dihydrate
α-TCP	$Ca_3(PO_4)_2$	alpha-tertiary calcium phosphate
β-TCP	$Ca_3(PO_4)_2$	beta-tertiary calcium phosphate
TTCP	$Ca_4(PO_4)_2O$	tetracalcium phosphate
–	$CaKPO_4$	calcium potassium phosphate
SP	Ca_2PO_4Cl	spodiosite
SWH	$Ca_{10}Na(PO_4)_7$	sodium whitlockite
CA	$Ca_{10}(PO_4)_6Cl_2$	chloroapatite
–	CaO	calcium oxide
–	$MgPHO_4·3H_2O$	magnesium hydrogen phosphate trihydrate
–	MgO	magnesium oxide

As only the third experiment was successful the rest of the experiment was devoted to optimization of the two most promising $CaMg_2(PO_4)_2$ cements. The fourth experiment was carried out with mixtures having a constant (Ca + Mg)/P ratio of 1.5, but with varying Ca/Mg ratios. A minimum in the setting time and a maximum in the strength were determined. At that composition the fifth experiment was carried out with variable W/P ratios, whereas the sixth experiment was done with variable milling times.

Finally, the pH of the cement mix was measured from the start of mixing the powder with water for a period of up to 3 days. Also the X-ray pattern of the resulting cements was recorded.

3. Results

The results of the first and the second experiment which were designed to obtain MWH cements are given in the Table II and Table III, respectively. Although in certain cases the setting times were promising, the strength values of the cement cylinders were very small. The attempts to prepare $CaMg_2(PO_4)_2$ cements were more successful as observed from Table IV. For this reason the other experiments in this study were devoted to optimization of the second and the third formulation mentioned in Table IV.

The ingredients were such that the formulations could be varied along the composition $Ca_{3-x}Mg_x(PO_4)_2$ for different values of *x*. The final setting times *F* for the second and the third formula as obtained in this way as a function of *x* are given in Figs 1 and 2, respectively, whereas those for the respective compressive strengths *C* can be seen in Figs 3 and 4. From these figures it is obvious that the optimal composition is $CaMg_2(PO_4)_2$ in both cases within the limits of error.

At this composition the W/P ratios of the two formulations were varied to observe their effect on the strength. The results are given in Tables V

TABLE II Attempts to prepare magnesium containing calcium phosphate cements of the MWH type using $MgHPO_4 \cdot 3H_2O$ as one of the reactants (Mg/P = 0.14, Ca/P = 1.28) and 10% of β-TCP added as nucleator

Other reactants	W/P	*I*	*F*	*C*	*T*
DCP, CaO	0.27	9.5	34	0.5	0.1
DCPD, CaO	0.30	5	27	0.6	0.1
MCPM, CaO	0.60	15	> 75	–	–
DCP, TTCP	0.30	7.5	21	1.2	0.2
DCPD, TTCP	0.33	7.5	30	0.7	0.1
MCPM, TTCP	0.35	4.5	42.5	–	–
α-TCP	0.30	30	57	< 0.3	< 0.1
$CaKPO_4$, SP	0.28	23	70	< 0.3	< 0.1
SWH, CA	0.27	11	44	0.8	0.2

W/P = water/powder ratio (g/g)
I = initial setting time (min)
F = final setting time (min)
C = compressive strength (MPa)
T = diametral tensile strength (MPa)

TABLE III Attempts to prepare magnesium containing calcium phosphate cements of the MWH type using MgO as one of the reactants (Mg/P = 0.14, Ca/P = 1.28) and 10% of β-TCP added as nucleator

Other reactants	W/P	*I*	*F*	*C*	*T*
DCP, CaO	0.30	11	37.5	0.5	0.1
DCPD, CaO	0.32	11.5	30	1.1	0.2
MCPM, CaO	0.50	17.5	60	1.0	0.2
DCP, TTCP	0.30	14.5	25	1.1	0.2
DCPD, TTCP	0.33	7.5	31	0.7	0.1
MCPM, TTCP	0.23	< 1	–	–	–
DCP, α-TCP	0.30	16.5	47.5	0.9	0.1
DCPD, α-TCP	0.33	15	47.5	< 0.3	< 0.1
MCPM, α-TCP	0.50	< 1	2	–	–
DCP, $CaKPO_4$, SP	0.25	20	55	1.7	0.4
DCPD, $CaKPO_4$, SP	0.30	19	50	1.0	0.2
MCPM, $CaKPO_4$, SP	0.40	1	3	–	–
DCP, SWH, CA	0.27	> 30	–	–	–
DCPD, SWH, CA	0.30	17.5	52.5	0.4	0.1
MCPM, SWH, CA	0.50	< 1	2	–	–

W/P = water/powder ratio (g/g)
I = initial setting time (min)
F = final setting time (min)
C = compressive strength (MPa)
T = diametral tensile strength (MPa)

TABLE IV Attempts to prepare $CaMg_2(PO_4)_2$ cements

Reactants	W/P	*I*	*F*	*C*	*T*
MCPM, MgO	0.5G[a]	4	10	6.8	1.4
DCP, MgO, $MgHPO_4 \cdot 3H_2O$	0.40	3.5	6	5.5	1.4
DCPD, MgO, $MgHPO_4 \cdot 3H_2O$	0.40	2.5	4.5	3.7	0.8
CaO, $MgHPO_4 \cdot 3H_2O$	0.30	21	50	0.8	0.2

[a] The liquid was not water, but a 50% aqueous solution of glycerol in order to slow down the reaction rate

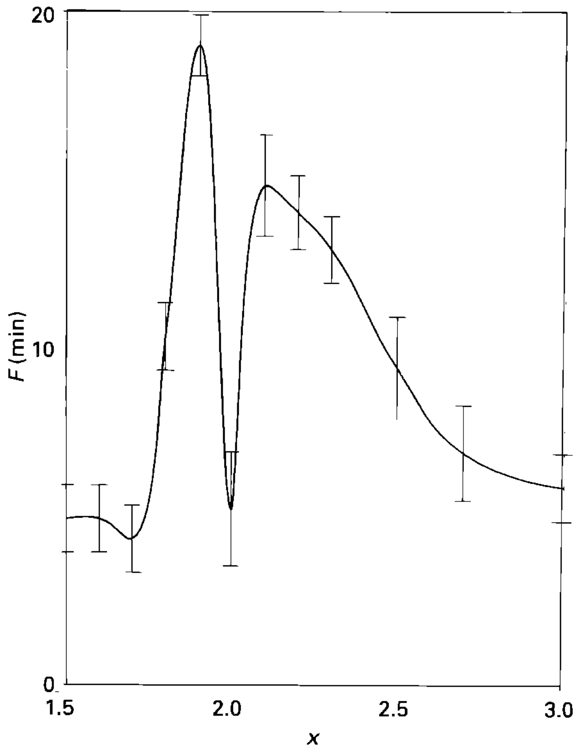

Figure 1 Final setting time *F* (min) as a function of the value *x* of $Ca_{3-x}Mg_x(PO_4)_2$ cements at a W/P ratio of 0.5, starting with DCP, MgO and $MgHPO_4 \cdot 3H_2O$ as the basic materials.

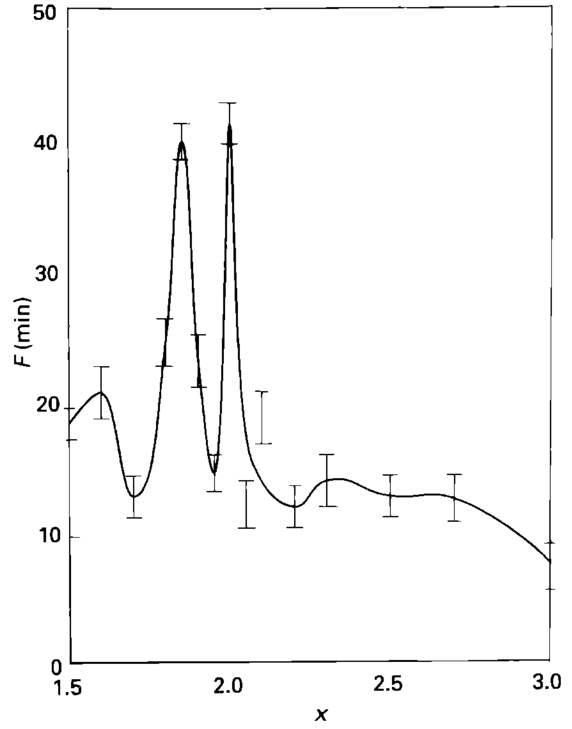

Figure 2 Final setting time *F* (min) as a function of the value *x* of $Ca_{3-x}Mg_x(PO_4)_2$ cements at a W/P ratio of 0.5, starting with DCPD, MgO and $MgHPO_4 \cdot 3H_2O$ as the basic materials.

and VI. At first sight the W/P ratios did not have a significant effect on the strength over the range $0.35 < W/P < 0.50$, although there were some indications that the strength of formulation 1 (obtained with DCP) was probably somewhat higher at W/P = 0.35.

Variations of the milling time were combined with variations in the W/P ratio for formulation 1 (see Table VII). It appeared that the optimum milling time was 50 min, at which strength values were high and their standard deviations low. It also was proven

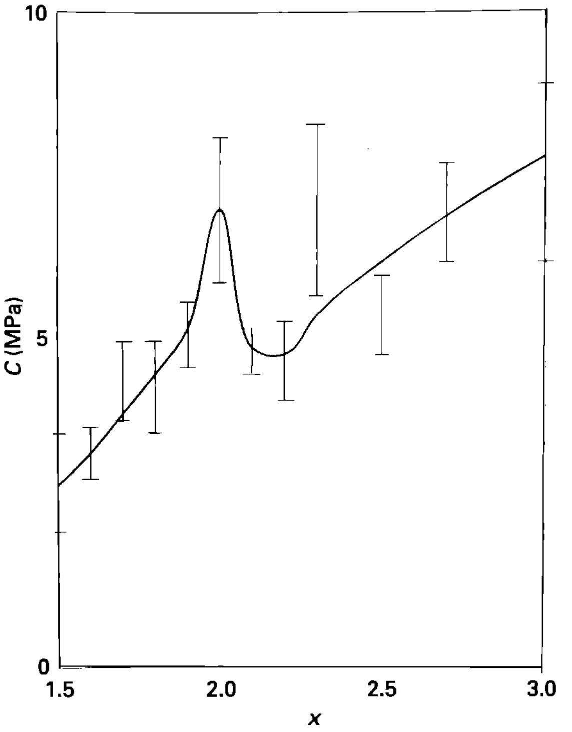

Figure 3 Compressive strength C as a function of x of $Ca_{3-x}Mg_x(PO_4)_2$ cements at a W/P ratio of 0.5, after soaking for 1 day in Ringer's solution at 37 °C. Basic materials were DCP, MgO and $MgHPO_4{\cdot}3H_2O$.

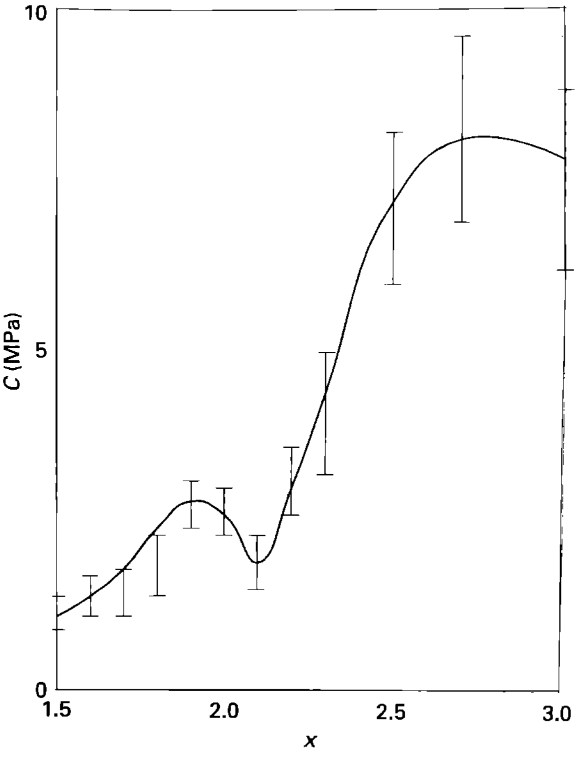

Figure 4 Compressive strength C as a function of x of $Ca_{3-x}Mg_x(PO_4)_2$ cements at a W/P ratio of 0.5, after soaking for 1 day in Ringer's solution at 37 °C. Basic materials were DCP, MgO and $MgHPO_4{\cdot}3H_2O$.

definitely that the strength was higher at W/P = 0.35. Milling times were also varied for formulation 2 (obtained with DCPD) (see Table VIII). Strength values may rise with very long milling times, but they remain far below the levels obtained for formulation 1.

TABLE V Effect of the W/P ratio on the compressive strength C and the diametral tensile strength T of $CaMg_2\ (PO_4)_2$ cements prepared from mixtures of DCP, MgO and $MgHPO_4{\cdot}3H_2O$ after milling for 30 min ($n = 6$) (standard deviation in parentheses)

W/P	*C*	*T*	*C*/*T*
0.50	7.0 (1.1)	1.5 (0.3)	4.7 (1.1)
0.45	6.6 (0.6)	1.2 (0.2)	5.5 (1.2)
0.40	6.0 (0.8)	1.3 (0.3)	4.6 (1.3)
0.35	9.2 (3.5)	1.9 (0.4)	4.8 (1.7)

TABLE VI Effect of the W/P ratio on the compressive strength C and the diametral tensile strength T of $CaMg_2\ (PO_4)_2$ cements prepared from mixtures of DCPD, MgO and $MgHPO_4{\cdot}3H_2O$ after milling for 30 min ($n = 6$) (standard deviation in parentheses)

W/P	*C*	*T*	*C*/*T*
0.50	2.7 (0.3)	0.6 (0.1)	4.5 (1.2)
0.45	2.9 (0.4)	0.5 (0.2)	5.8 (1.4)
0.40	4.3 (1.2)	0.9 (0.2)	5.6 (1.8)
0.35	2.7 (0.4)	0.9 (0.3)	3.0 (1.4)

TABLE VII Effect of the milling time of mixtures of DCP, MgO and $MgHPO_4{\cdot}3H_2O$ on the setting times and the strengths of the resulting $CaMg_2\ (PO_4)$ cements at W/P = 0.35 or 0.40 ($n = 6$) (standard deviation in parentheses)

W/P	Milling time (min)	*I*	*F*	*C*	*T*
0.40	30	–	–	6.0 (0.8)	1.3 (0.3)
	50	–	–	6.2 (0.6)	1.5 (0.2)
	70	–	–	6.1 (1.5)	1.2 (0.3)
0.35	00	16	28	8.3 (1.2)	1.3 (0.2)
	10	4	7	10.9 (2.4)	1.9 (0.3)
	30	1.5	3.5	9.2 (3.5)	1.9 (0.4)
	50	1	2.5	10.9 (0.4)	2.3 (0.3)
	70	1	2.5	9.0 (1.9)	2.2 (0.2)
	90	2	3	11.0 (1.9)	1.4 (0.4)

TABLE VIII Effect of the milling time of mixtures of DCPD, MgO and $MgHPO_4{\cdot}3H_2O$ on the setting times and the strengths of the resulting $CaMg_2\ (PO_4)_2$ cements at W/P = 0.40 ($n = 6$) (standard deviation in parentheses)

Milling time (min)	*I*	*F*	*C*	*T*
00	42	> 60	0.7 (0.3)	0.2 (0.1)
10	11	23	2.0 (0.3)	0.4 (0.1)
30	4	14	4.3 (1.2)	0.9 (0.2)
50	1.5	3.5	4.4 (0.8)	0.6 (0.2)
70	2	4.5	4.3 (0.1)	1.0 (0.2)
90	2.5	5	6.7 (1.7)	1.2 (0.3)

The pH of the two cement formulations was around 10 right after the start of mixing with water. It remained at this level during the 3 days of observation.

The X-ray diffraction pattern for the two formulations was different from any pattern published for the compound $Ca_4Mg_5(PO_4)_6$. For this reason the pattern of this cement is given in Table IX (for formula-

TABLE IX X-Ray diffraction pattern of the cements with composition $CaMg_2(PO_4)_2$ (formulation 1)

d	I/I_{100}	d	I/I_{100}	d	I/I_{100}
7.96	15	3.46[a]	20	2.49[a]	5
6.81	5	3.37[a]	100	2.24[a]	3
5.95	20	3.08	10	2.19[a]	5
5.34	20	3.04	10	2.11[a]	10
4.95	2	2.96[a]	80	1.91[a]	3
4.72	10	2.76[a]	10	1.85[a]	5
4.50	2	2.72[a]	40	1.80[a]	3
4.10	5	2.58	10	1.72[a]	15

[a] DCP peaks

tion 1). From this table it is clear that the original DCP had not reacted.

4. Discussion

It is evident from the data of Figs 1 to 4 that the optimum composition of the cements in this study is $CaMg_2(PO_4)_2$. However, a compound like that is not formed according to the X-ray pattern. This pattern rather indicates that a conglomerate of magnesium phosphate crystals is formed on the original DCP crystals as nucleators. The solubility of this conglomerate is unknown. Therefore, it would be mere speculation to hypothesize something about its behaviour *in vivo* upon implantation. The only thing which is probable is that its basic character during and long after setting promotes the precipitation of bone mineral from the body fluids [21, 22]. This is expected to happen whether or not the site of implantation is bone. For this reason a follow-up study is planned to investigate the effect of subcutaneous implantation of these cements in rats on ongrowth or ingrowth of bone-like mineral and whether this will change the mechanical properties of the cement. It will also be studied whether in the long run the cement is resorbed or transformed into another more bone-like mineral. The latter happened with rhenanite upon implantation [4].

A big advantage of the cements developed in this study is that they can be injected into the field of operation. Further their setting time is attractive for application as a filler in periodontal pockets or in alveolar holes (for the reduction of the shrinkage of alveolar ridges after extraction of the teeth). In order to establish these surgical techniques animal experiments have to be done first.

Acknowledgements

This study was supported by a grant from the Dirección Científica y Técnica of Spain. The authors would also like to thank the CICYT for funding this work through project MAT89-0277. They are indebted to Jorge Rovira for the X-ray diffractograms.

References

1. H. U. CAMERON, I. MACNAB and R. M. PILLIAR, *J. Biomed. Mater. Res.* **11** (1977) 179.
2. D. E. CUTRIGHT, S. N. BHASKAR, J. M. BRADY, L. GETTER and W. R. POSSEY, *Oral. Surg.* **33** (1972) 850.
3. M. JARCHO, *Clin. Orthop.* 157 (1981) 157.
4. F. C. M. DRIESSENS, M. M. A. RAMSELAAR, H. G. SCHAEKEN, A. L. H. STOLS, P. J. van MULLEM and J. R. de WIJN, *J. Mater. Sci. Mat. Med* **3** (1992) 413.
5. S. E. GRUNINGER, C. SIEW, L. C. CHOW, A. O'YOUNG, N. K. TSAO and W. E. BROWN, *J. Dent. Res.* **63** (1984) 200.
6. W. E. BROWN and L. C. CHOW, US Patent 4518430, May 21 (1985).
7. Y. FUKASE, E. D. EANES, S. TAKAGI, L. C. CHOW and W. E. BROWN, *J. Dent. Res.* **69** (1990) 1852.
8. J. LEMAITRE, A. MIRTCHI and A. MORTIER, *Silicates Industriels* (1987) 141.
9. A. A. MIRTCHI, J. LEMAITRE and N. TERAO, *Biomaterials* **10** (1989) 475.
10. A. A. MIRTCHI, J. LEMAITRE and E. MUNTING, *ibid.* **10** (1989) 634.
11. H. MONMA, *Yogyo Kyokai Shi* **95** (1987) 146.
12. H. MONMA, and T. KANAZAWA, *ibid.* **84** (1976) 209.
13. H. MONMA, A. MAKISHIMA, M. MITOMO and T. IKEGAMI, *Nippon Seramikkussu Kyokai Gakujutsu Ronbunshi* **96** (1988) 878.
14. H. OONISHI, *Biomaterials* **12** (1991) 171.
15. N. NISHIMURA, T. YAMAMUNO, Y. TAGUCHI, M. YKENAZA, T. NAKAMURA, T. KOBUBO and S. YOSHIHARA, *J. Appl. Biomaterials* **2** (1991) 219.
16. P. W. BROWN and M. FULMER, *J. Am. Ceram. Soc.* **74** (1991) 934.
17. P. W. BROWN, N. HOCKER and S. HOYLE, *ibid.* **74** (1991) 1848.
18. B. R. CONSTANTZ, B. BARR and K. McVICKER, US Patent 5053212, 1 October (1991).
19. F. C. M. DRIESSENS and R. M. H. VERBEECK, "Biominerals" (CRC Press, Boca Raton, 1990).
20. R. A. TERPSTRA, F. C. M. DRIESSENS and R. M. H. VERBEECK, *Z. anorg. allg. Chem.* **515** (1984) 213.
21. F. C. M. DRIESSENS and R. M. H. VERBEECK, *Z. Naturforsch.* **41C** (1986) 468.
22. F. C. M. DRIESSENS, G. SCHAAFSMA, E. C. M. van BERESTIJN and J. ROTGANS, *Z. Orthop.* **124** (1986) 599.

Received 15 April
and accepted 20 August 1993