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Incorporation of a controlled-release glass into a calcium phosphate cement

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A so-called controlled-release glass was synthesized occurring in the system $CaO\text{-}Na_2O\text{-}P_2O_5$. A certain sieve fraction of this glass was incorporated in a calcium phosphate cement, of which the powder contained α-tricalcium phosphate (α-TCP), dicalcium phosphate (DCP) and precipitated hydroxyapatite (HA). The glass appeared to retard the cement setting slightly and it reduced considerably the compressive strength after aging in aqueous solutions which were continuously refreshed. Scanning electron microscope (SEM) pictures and X-ray diffraction (XRD) patterns of the samples after 5 weeks of aging showed that the glass was not dissolved but that large brushite crystals were formed. Thereby, aging in $CaCl_2$ solutions resulted in more brushite formation than aging in NaCl solutions. The brushite crystals did not reinforce the cement. Neither was the aged glass-containing cement weaker than it was before the brushite formation right after complete setting. In conclusion, the incorporation of controlled-release glasses into a calcium phosphate cement and subsequent aging in aqueous solutions did not result in the formation of macropores in the cement structure, but that of brushite crystals. This incorporation reduced the compressive strength of the cement considerably.

1. Introduction

In the early *in vivo* evaluation of calcium phosphate ceramics it was not clear yet which role in their resorption was played by their composition and crystal structure on one hand and what importance their density and, hence, their porosity had on the other hand [1]. Soon it became clear that in bone histology studies β-tricalcium phosphate (β-TCP) is resorbed and replaced by new bone (a property which we will call osteotransductivity) but that hydroxyapatite ceramic (HA) is not resorbed but incorporated in the bone [2, 3], no matter whether these ceramics were dense [2] or porous [3]. When HA was made macroporous and covered with bone marrow cells, bone tissue grew into the pores, even when the ceramic was implanted subcutaneously in rats [4]. However, the bone growth stimulus comes from the bone marrow cells and not from the ceramic [3, 4]. So it seems that for implantation in bone it does not make much difference whether the calcium phosphate ceramic is β-TCP or HA or a mixed β-TCP–HA. However, manufacturers have a preference for making their market products macroporous in order to speed-up the osteointegration of their products [5]. Thereby, it is questionable whether for that purpose the porosity needs to be interconnected, as the main feature of the implanted ceramic must be a rough surface open for bone ingrowth.

Another reason for having porosity in HA ceramics may be to have the possibility to incorporate drugs into their structure which can be released after implantation, e.g. in order to prevent infection [6]. For such purposes the newly developed calcium phosphate cements [7] are even more attractive. Contrary to ceramics they can be molded during the operation and they set at body temperature. They are microporous and the pore volume is about 40% at the usual powder to liquid ratios. Incorporation of drugs into and their release from calcium phosphate cements has been shown to be very effective [8, 9] which is due to the easy incorporation during the mixing of cement powder and liquid and to the interconnectedness of the micropores. It has even been shown that bone morphogenetic protein can be incorporated into and released from such a material upon implantation, whereby the protein activated the transformation of the cement into new bone tissue [10].

However, some calcium phosphate cements [11] do not need this activation, as they undergo osteotransduc-

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tion spontaneously when implanted in bone [12, 13, 14]. As the amount of microporosity of such materials can be increased by the decrease of the powder/liquid ratio and as microporosity promotes the rate of dissolution in buffers [15], this approach may be taken to try to increase the rate of osteotransduction. Some authors [16] even suggest that it would be of help if such cements were made to contain macropores in addition to the unavoidable micropores. They succeeded in introducing macropores by mixing the cement powder with granules of either Na_2HPO_4 or $NaHCO_3$ or sugar.

In this study some types of so-called controlled release glasses [17, 18] will be used for that purpose. These are glasses occurring in the system $CaO - Na_2O - P_2O_5$. In contact with aqueous solutions like body fluids they dissolve slowly, whereby Ca^{2+}, Na^+ and phosphate ions are released.

Another purpose of this study was to investigate whether our calcium phosphate cement [11] could be reinforced by incorporation of such a glass and subsequent immersion in a solution of $CaCl_2$, which was refreshed continuously.

2. Materials and methods

α-tricalcium phosphate (α-TCP) was prepared by heating an appropriate mixture of dicalcium phosphate (DCP, $CaHPO_4$) (Merck, Darmstadt) and $CaCO_3$ (Merck) for at least 6 h at 1300 °C, and quenching it in air down to room temperature. The controlled-release glass was made of a mixture of $NH_4H_2PO_4$ (Panreac), Na_2CO_3 (Panreac) and $CaCO_3$ (Panreac). It was melted in a platinum crucible at a temperature of 1100 °C and quenched on a metallic plate preheated at 350 °C and subsequently annealed. The chemical composition of the glass is P_2O_5 61.5%, Na_2O 7.7%, CaO 30.8% in terms of molar ratio, and has a density of 2.80 g cm^{-3}. After crushing of the glass a sieved fraction was selected with diameters ranging from 105 to 400 μm. The calcium phosphate cement called Biocement F consisted of 63.2 wt % α-TCP, 27.7 wt % (DCP, $CaHPO_4$) and 9.1 wt % of precipitated hydroxyapatite (PHA, Merck, Darmstadt). The glass was to F cement at 10 wt %. The samples were prepared at a liquid/powder ratio (L/P = 0.32 ml g^{-1}) and the value chosen for the liquid concentration was a 2.5 wt % solution of Na_2HPO_4 (Merck) in water. The setting times initial t_I and final t_F were determined with Gillmore needles. 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 4 days, 2 and 5 weeks in Ringer's solution and 0.5% $CaCl_2$ at 37 °C (the solutions were refreshed every 3 days) prior to determination of the compressive strength CS using a Universal Testing Machine Instron-4507 at 1 mm min^{-1} crosshead speed. Scanning electron microscopy (SEM) was used for microstructural analysis. Finally, the samples were crushed in a mortar by hand for X-ray powder diffraction analysis. XRD patterns of the samples were recorded by step-scanning using a microprocessor-controlled diffractomer system (Siemens D500) with Ni-filtered CuK_α. The step-scanning was performed with an integration time of 3 s at intervals of 0.05 ° (2θ).

3. Results

In Table I the initial setting time t_I and the final setting time t_F of Biocement F alone and of the F cement containing 10% of the glass are given. It appears that the addition of the glass retarded the setting of the cement somewhat.

The data for the compressive strength CS after 4 days, 2 weeks and 5 weeks of aging in solutions of NaCl or $CaCl_2$ which were refreshed every 3 days, are also given in Table I. For Biocement F it did not make any difference whether aging was done in $CaCl_2$ or NaCl solutions. As far as the compressive strength is considered the values did not differ either for the Biocement F-Glass combinations. However, the glass incorporation resulted in a considerable decrease of the strength right after complete setting (4 days) and the strength did not change upon subsequent immersion for 2 or 5 weeks in NaCl or $CaCl_2$ solutions.

In Figs 1 through 6 SEM pictures are shown of the Biocement F-Glass combination after 4 days of aging (Figs 1 and 2), 2 weeks (Figs 3 and 4) and 5 weeks (Figs 5 and 6). It is observed that the structure of the glass is amorphous after 4 days or even after 2 weeks of aging. However, after 5 weeks the structure has become crystalline.

Fig. 7 shows the XRD pattern of the Biocement F-Glass combination after 4 days, 2 weeks and 5 weeks of aging in 0.5% $CaCl_2$ solution. After 5 weeks the peaks of

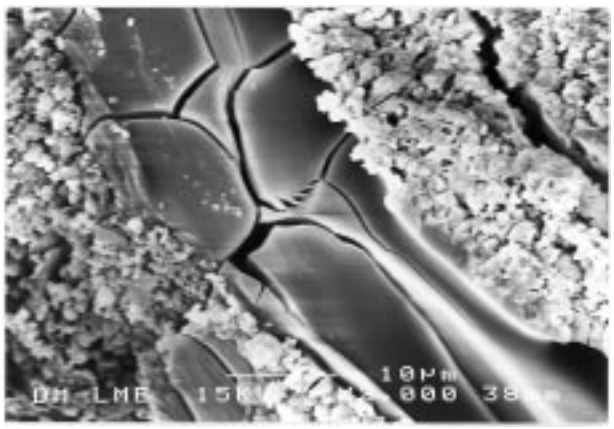

Figure 1 SEM picture of the Biocement F-Glass combination after 4 days of aging in 0.9% NaCl solution.

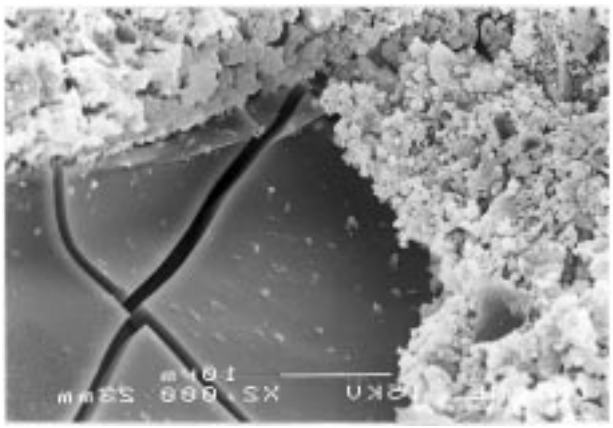

Figure 2 SEM picture of the Biocement F-Glass combination after 4 days of aging in 0.5% $CaCl_2$ solution.

TABLE I Initial setting time t_I, final setting time t_F and compressive strength CS of Biocement F and of the Biocement F-Glass combination after 4 days, 2 weeks and 5 weeks of aging in solutions of 0.9% NaCl or 0.5% $CaCl_2$

Cement	t_I (min)	t_F (min)	CS-4d (MPa)	CS-2w (MPa)	CS-5w (MPa)
F (NaCl or $CaCl_2$)	6–6.5	10.5	36 (5)*	33 (4)	32 (4)
F-Glass (NaCl)	7–7.5	11.5	19 (3)	19 (3)	22 (3)
F-Glass ($CaCl_2$)	7–7.5	11.5	23 (3)	19 (3)	19 (3)

*Standard deviation between brackets ($n = 8$).

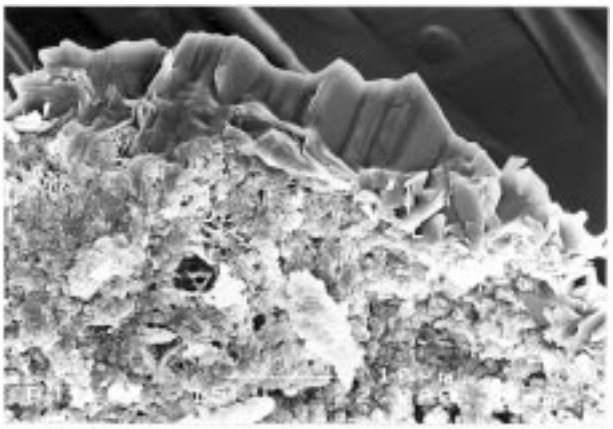

Figure 3 SEM picture of the Biocement F-Glass combination after 2 weeks of aging in 0.9% NaCl solution.

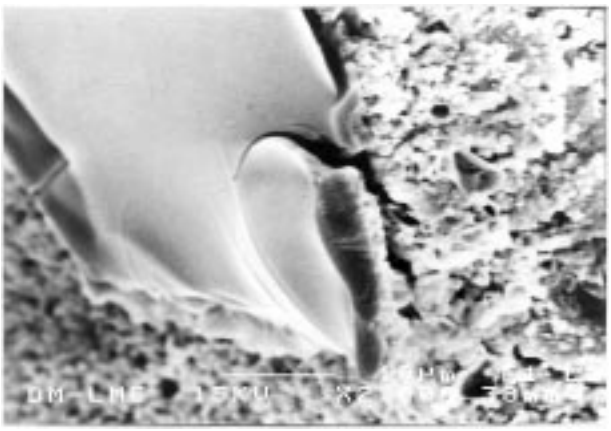

Figure 4 SEM picture of the Biocement F-Glass combination after 2 weeks of aging in 0.5% $CaCl_2$ solution.

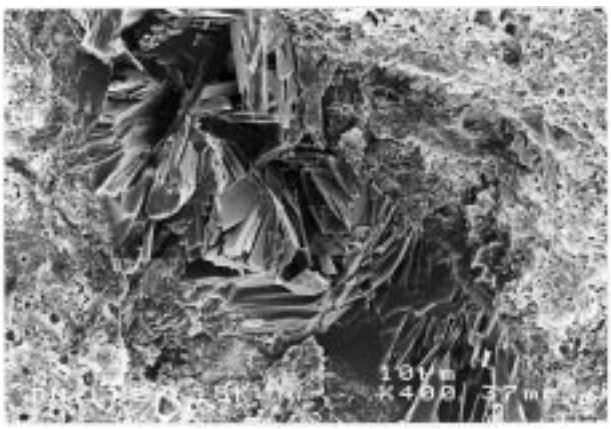

Figure 5 SEM picture of the Biocement F-Glass combination after 5 weeks of aging in 0.9% NaCl solution.

brushite are superimposed on the apatite pattern of the Biocement F. Fig. 8 shows the XRD pattern of Biocement F (lower curve) and the Biocement F-Glass combination (upper curve) after 5 weeks of aging in 0.9% NaCl solution. Both curves show the apatite pattern of Biocement F. However, the upper curve has the brushite pattern superimposed, although less intense than the upper curve of Fig. 7.

4. Discussion and conclusions

According to Figs 7 and 8 the glass released sodium and phosphate ions during aging both in 0.9% NaCl solution and in 0.5% $CaCl_2$ solution, because in both cases brushite was formed. But Fig. 8 (upper curve) showed less brushite than Fig. 7 (upper curve) so that during aging in 0.5% $CaCl_2$ solution even accumulation of calcium ions may have occurred.

Implantation studies [18] have shown that under *in vivo* conditions the biodegradable controlled-release glass is completely resorbed within 3 months, after implantation in bone as well as in soft tissue. In bone the glass seemed to shrink first and simultaneously there was ongrowth of new bone. It seemed as if the degradation of the glass took place by the passive process of dissolution, which is not surprising, as the solubility of these controlled-release glasses is higher than the calcium and phosphate concentration in the body fluids [19–21]. In these implantation studies [18] it is quite possible that before degradation first a transformation of the glass into brushite has occurred, similar to the brushite formation of the present experiment. But implantation of brushite on itself also results in complete resorption [22], also because the solubility of brushite in body fluids is higher than the actual concentration of calcium and phosphate [19–21].

The behavior of Biocement F upon implantation is quite different. After subcutaneous implantation under exclusion of direct cellular contact, but open contact with body fluids the material remained stable [23] meaning that the calcium deficient hydroxyapatite which has formed after the setting in Biocement F is in physico-chemical equilibrium with the body fluids [19–21]. However, implantation in bone resulted in resorption of the cement and formation of new bone [12, 13]. This transformation of the material into new bone was shown to be regulated by the activity of osteoclasts [24] and osteoblasts [25] as is the natural remodeling of bone.

It is likely that after implantation of the Biocement F-Glass combination into bone the glass particles will also be transformed first into brushite. As this brushite will have a higher solubility than the calcium and phosphate concentration in the bone extracellular fluid, the brushite

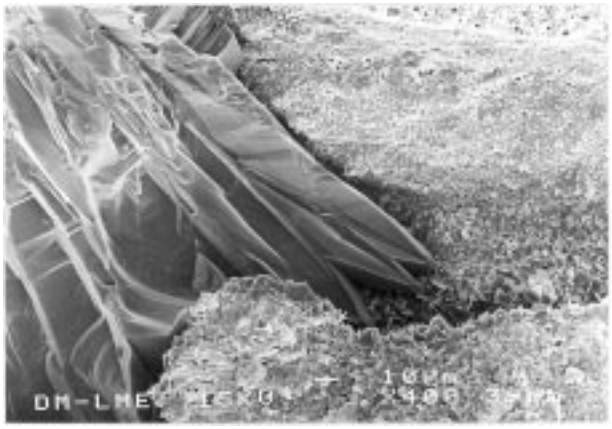

Figure 6 SEM picture of the Biocement F-Glass combination after 5 weeks of aging.

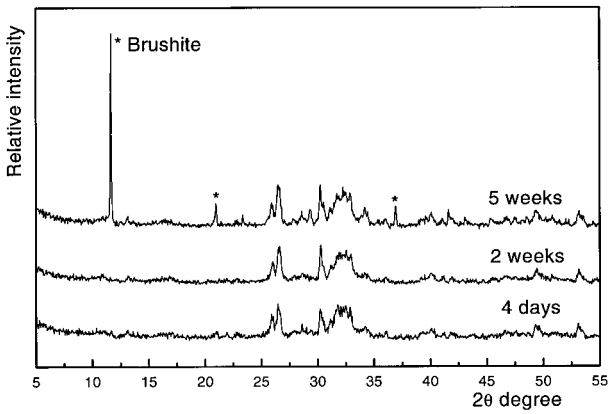

Figure 7 XRD pattern of the Biocement F-Glass combination after 4 days, 2 weeks and 5 weeks of aging in 0.5% $CaCl_2$ solution, (*) Brushite peaks.

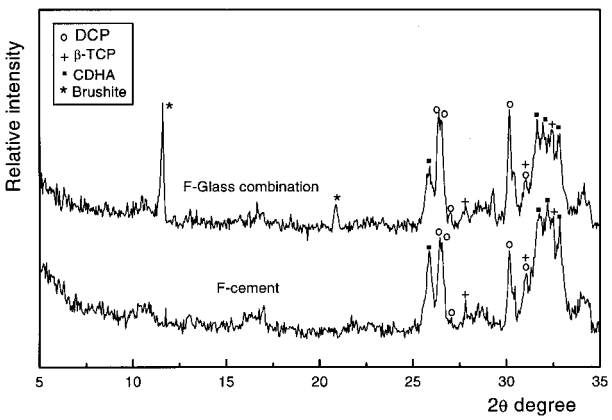

Figure 8 XRD pattern of Biocement F (lower curve) and of the Biocement F-Glass combination after 5 weeks of aging in 0.9% NaCl solution, (*) Brushite peaks.

particles will keep dissolving, a process which will be enhanced by the 40% microporosity in the Biocement F structure. So, it is expected that after some time the structure of the implanted Biocement F-Glass combination will show up some macropores. Whether this accelerates the osteotransduction (the transformation of the cement into new bone), will be investigated in a subsequent study. In any way, the present study has shown that the intermediate transformation of the glass particles into brushite did not reinforce the Biocement F, nor did it weaken the structure.

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