JOURNAL OF MATERIALS SCIENCE: MATERIALS IN MEDICINE 5 (1994) 123–129

Effects of glass composition on compressive strength of bioactive cement based on $CaO–SiO_2–P_2O_5$ glass powders

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Mixtures of $CaO–SiO_2–P_2O_5–CaF_2$ glass powders with 3.7 M ammonium phosphate solution give bioactive cements which can set in a few minutes and bond to living bone in a few weeks. In the present study, the mechanical strengths of the mixtures, which were held in 100% humidity at 37 °C for 1 h and then soaked in a simulated body fluid (SBF) for 23 h, were investigated in terms of the glass composition. Their compressive strengths varied significantly with small changes in the $CaO/SiO_2/P_2O_5$ ratios under a constant CaF_2 content. Addition of CaF_2 to a $CaO–SiO_2–P_2O_5$ composition increased the compressive strength, whereas addition of MgO decreased it. The glass composition of CaO 47.1, SiO_2 35.8, P_2O_5 17.1, CaF_2 0.75 wt ratio gave the highest compressive strength among the compositions examined: 56 and 80 MPa, respectively, after soaking in the simulated body fluid for 23 h and 3 days. The variation of the compressive strength with the glass composition was well interpreted in terms of the amount of the hydroxyapatite formed at the intergranular spaces of the glass powders in the simulated body fluid.

1. Introduction

Some bioactive glasses and glass-ceramics, such as Bioglass and glass-ceramic A–W, bond not only to the bone, but also to themselves, when sited in the living body [1]. This bond is attributed to the formation of a biologically active bone-like apatite layer on their surfaces when sited in the body [2–4]. The same type of apatite layer is formed on their surfaces, even in an acellular simulated body fluid with ion concentrations nearly equal to those of human blood plasma [5]. This enables the glass and glass-ceramic to bond to themselves, even in the simulated body fluid [6].

According to studies by the present authors, the apatite layer on the surfaces of CaO, SiO_2-based glasses and glass-ceramics is formed by the following mechanism. The calcium ion dissolved from the glasses and glass-ceramics increases the ionic activity product of the apatite in the surrounding body fluid which is already supersaturated with respect to the apatite under normal conditions [7]. The hydrated silica on the surfaces of glasses and glass-ceramics provides favourable sites for apatite nucleation [8, 9]. As a result, a large number of apatite nuclei are rapidly formed on the surfaces of the glasses and glass-ceramics. The phosphate ion required for the formation of the apatite is supplied from the surrounding body fluid. Once the apatite nuclei are formed, they grow spontaneously by consuming the calcium and phosphate ions from the surrounding body fluid. On the basis of these findings, it is expected that a certain kind of CaO, SiO_2-based glass powder could be solidified in a few minutes by forming hydroxyapatite on their surfaces when mixed with an appropriate solution containing the phosphate ion, and could bond to living bone through the apatite. Such type of bioactive cement might be useful for bone fillers, drug carriers in drug delivery systems etc.

Hitherto, so-called bone cements of polymethylmethacrylate (PMMA) and sintered hydroxyapatite granules have mainly been used for such purposes. The former is solidified in a few minutes, but releases toxic monomers before polymerization, generates a harmful large amount of heat during polymerization, and does not bond to living bone [10]. The latter bonds to living bone, but does not bond to itself, and hence is liable to be lost from the implanted sites. Various attempts have been made to obtain bioactive cement using crystalline calcium phosphates [11, 12]. They still have, however, some problems in their setting time, inflammatory reaction, mechanical strength and/or stability in the body, and hence are hardly used clinically.

The present authors recently found that a $CaO–SiO_2–P_2O_5–CaF_2$ glass powder sets in a few minutes

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when mixed with an ammonium phosphate solution, and bonds to living bone when implanted into bone defect [13, 14]. In the present study, the mechanical strengths of mixtures of $CaO-SiO_2-P_2O_5-CaF_2$ glass powders with ammonium phosphate solution were investigated in terms of the glass composition, after they were held in 100% humidity conditions at 37 °C for 1 h and then soaked in simulated body fluid for 23 h. Effects of particle size of the glass powder and soaking time in the simulated body fluid on the compressive strength of the mixture were also studied.

2. Experimental procedures

2.1. Preparation of glass powder

Powder mixtures of the nominal compositions given in Table I were prepared from reagent-grade $CaCO_3$, SiO_2, $Ca_2P_2O_7$, CaF_2 and MgO. In compositions A to G, the ratios of the CaO, SiO_2 and P_2O_5 were varied and the CaF_2 content was held constant: they are located at points shown by the solid circles in Fig. 1. The dotted line in Fig. 1 shows the glass-forming regions in the system $CaO-SiO_2-P_2O_5$ containing CaF_2 in 0.75 wt ratio. In compositions E, H, I and J, the ratios of the CaO, SiO_2 and P_2O_5 were held constant and only the CaF_2 content was changed. In compositions E, K and L, the ratios of the CaO, SiO_2, P_2O_5 and CaF_2 were held constant and only the MgO content was changed. These powder mixtures were put into a platinum crucible and melted in a SiC furnace at 1500–1600 °C for 4 h. The melt was then quenched between water-cooled steel rollers and formed into thin ribbons. These glass ribbons were pulverized by an alumina ball mill into fine powders and their particle size distributions measured by a laser diffraction particle size analyser (Simadzu Model SALD-1000). Glass powders with an average size of 5.0 μm were used in the following experiments unless otherwise mentioned.

2.2. Preparation of liquid

Reagent-grade $(NH_4)_2HPO_4$ and $NH_4H_2PO_4$ in the amounts of 60.1 and 5.0 g, respectively, were dissolved into 100 ml of ion-exchanged water to form a 3.7 M ammonium phosphate solution with pH 7.4.

TABLE I Compositions of the glass powders and the maximum powder-to-liquid ratios (*P*/*L*) able to form homogeneous paste

Powder type	Composition (wt ratio)					*P*/*L*(g/ml)
	CaO	SiO_2	P_2O_5	MgO	CaF_2	
A	38.4	61.6	0	0	0.75	1/0.5
B	48.3	51.7	0	0	0.75	1/0.5
C	52.3	47.7	0	0	0.75	1/0.5
D	49.5	41.5	9.0	0	0.75	1/0.5
E	47.1	35.8	17.1	0	0.75	1/0.5
F	50.1	33.8	16.1	0	0.75	1/0.6
G	53.1	31.7	15.2	0	0.75	1/0.7
H	47.1	35.8	17.1	0	0	1/0.5
I	47.1	35.8	17.1	0	0.5	1/0.5
J	47.1	35.8	17.1	0	1.0	1/0.5
K	47.1	35.8	17.1	4.8	0.75	1/0.6
L	47.1	35.8	17.1	9.6	0.75	1/0.8

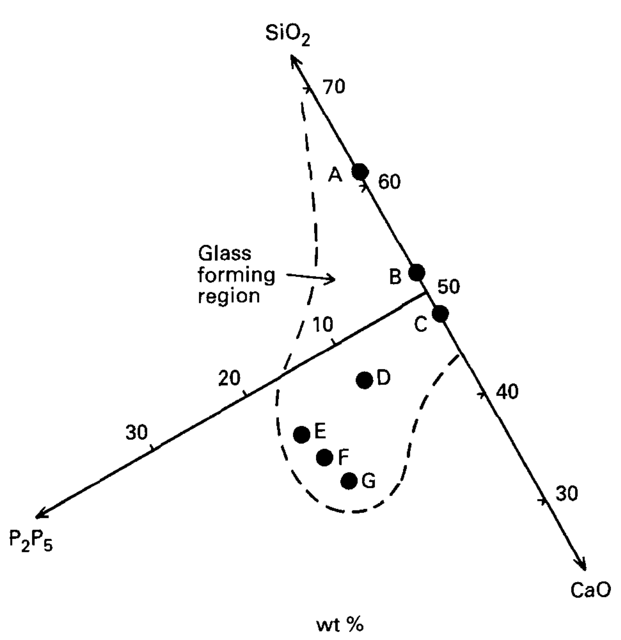

Figure 1 Compositions of examined glass powders. CaO + SiO_2 + P_2O_5: 100; CaF_2: 0.75 in wt ratio.

2.3. Preparation of mixture

The glass powders and the ammonium phosphate solution described above were mixed with a maximum powder-to-liquid ratio in which a homogeneous mixed paste was obtained. Their ratios are given in the right column of Table I. After mixing for 30 s, the paste was put into a 12 mm-high PMMA mould with a 6 mm internal diameter. The mould was put between two glass plates and tightly nipped by a "C"-clamp and then stored in 100% humidity conditions at 37 °C for 1 h. The cement was removed from mould and five pieces were immersed into 20 ml of a simulated body fluid (SBF) [15] with ion concentrations nearly equal to those of human blood plasma [16], as shown in Table II. The SBF was buffered at pH 7.25 with 50 mM tris (hydroxymethyl) aminomethane ($(CH_2OH)_3CNH_2$) and 45 mM hydrochloric acid (HCl), and its temperature maintained at 37 °C. According to a previous study [15], this SBF can reproduce fairly precisely the surface reaction of bioactive glasses and glass-ceramics in the living body.

2.4. Measurement of compressive strength

Compressive strengths of the mixtures were measured at a crosshead speed of 0.5 mm min^{-1}, using an Instron-type testing machine, before and after soaking in SBF, and while the test pieces were wet. The soaking time in SBF was 23 h unless otherwise mentioned. At least five measurements were taken for each data point.

2.5. Analysis of microstructure

Crystalline phases formed in the mixture were analysed by powder X-ray diffraction (Rigaku RAD series) with CuK_α before and after soaking in SBF. Scanning speed, tube current and tube voltage in this analysis were 2°/min, 40 mA and 30 kV, respectively.

TABLE II Ion concentrations of simulated body fluid (SBF) and human blood plasma

	Ion concentration (mM)							
	Na^+	K^+	Ca^{2+}	Mg^{2+}	Cl^-	HCO_3^-	HPO_4^{2-}	SO_4^{2-}
SBF	142.0	5.0	2.5	1.5	147.8	4.2	1.0	0.5
Human plasma	142.0	5.0	2.5	1.5	103.0	27.0	1.0	0.5

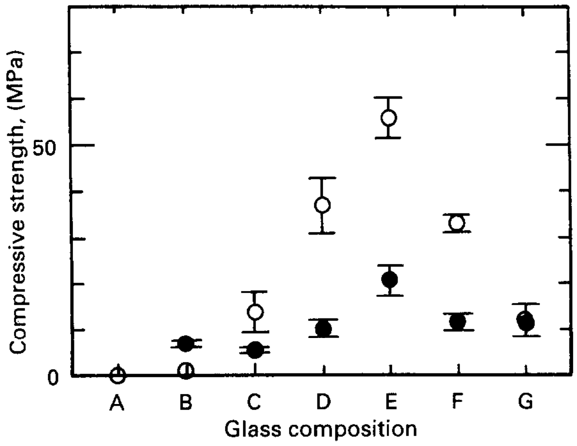

Figure 2 Compressive strengths of the mixtures composed of glass powders with different CaO, SiO_2 and P_2O_5 ratios and constant CaF_2 content. ● and ○: before and after soaking in SBF for 23 h, respectively.

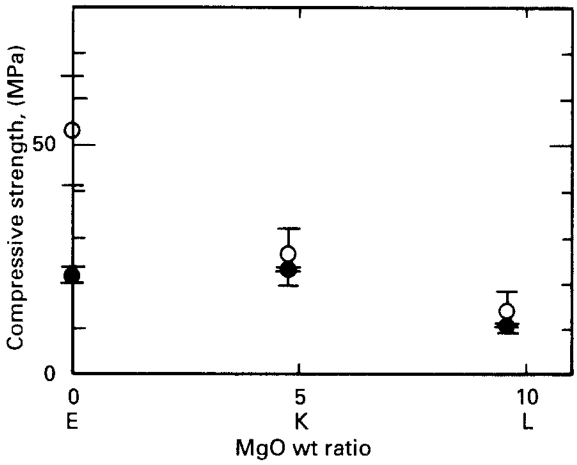

Figure 4 Compressive strengths of the mixtures composed of glass powders with different MgO additions to composition E. ● and ○: before and after soaking in SBF for 23 h.

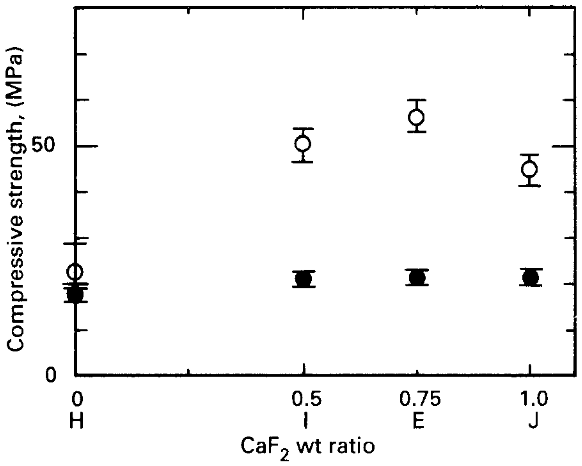

Figure 3 Compressive strengths of the mixtures composed of glass powders with different CaF_2 contents and constant CaO, SiO_2 and P_2O_5 contents. ● and ○: before and after soaking in SBF for 23 h.

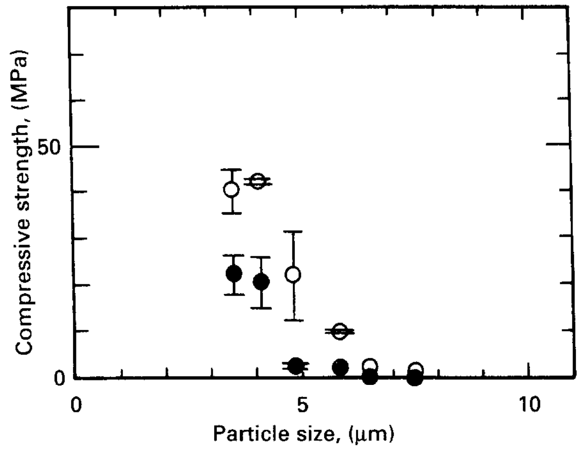

Figure 5 Compressive strengths of the mixtures composed of glass powder composition E with different average particle sizes. ● and ○: before and after soaking in SBF for 23 h.

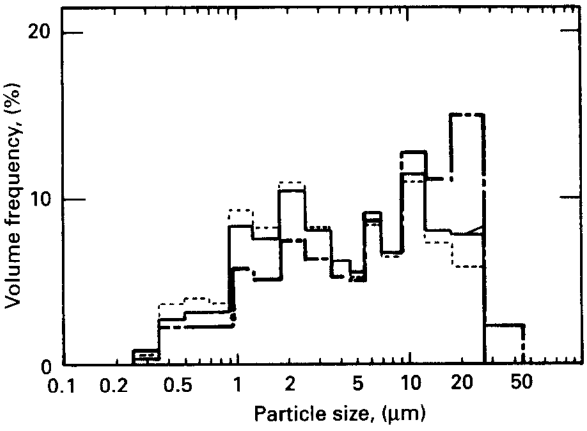

Figure 6 Particle size distributions of some glass powders having different average particle sizes. Average particle size: – – 7.5 µm; —— 5.0 µm; ---- 4.1 µm.

Morphological characteristics of the mixture were analysed by observing fracture surfaces of the mixtures before and after soaking in SBF using a scanning electron microscope (SEM) (Hitachi, Model S-2500CX). A platinum–gold film was coated on the surface and an accelerating voltage of 20 kV was used.

3. Results

3.1. Compressive strength

Fig. 2 shows the compressive strengths of the mixtures of glass powders with different CaO, SiO_2 and P_2O_5 ratios and constant CaF_2 content before and after soaking in SBF for 23 h. Generally, the latter results were higher than the former. Both of them varied significantly with CaO, SiO_2 and P_2O_5 ratios, giving maximum values of 23 and 56 MPa before and after

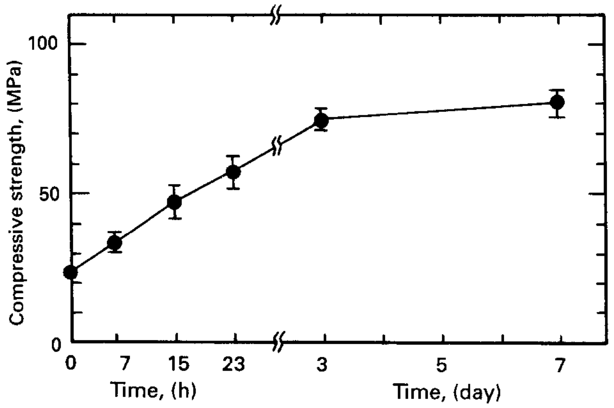

Figure 7 Compressive strength of the mixture composed of glass powder E, 5 μm average particle size, as a function of soaking time in SBF.

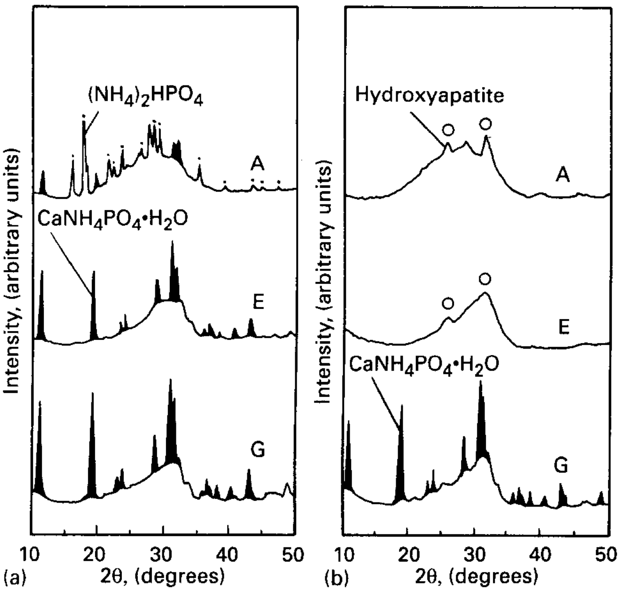

Figure 8 Powder X-ray diffraction patterns of some mixtures composed of glass powders with different CaO, SiO_2 and P_2O_5 ratios and constant CaF_2 content, (a) before and (b) after soaking in SBF for 23 h. Types A, E and G correspond to those given in Table I and Fig. 1.

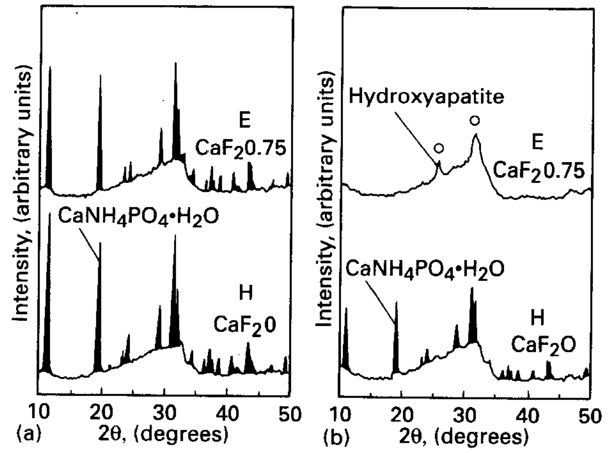

Figure 9 Powder X-ray diffraction patterns of the mixtures composed of glass powders containing (E) and not containing (H) CaF_2, before and after soaking in SBF for 23 h.

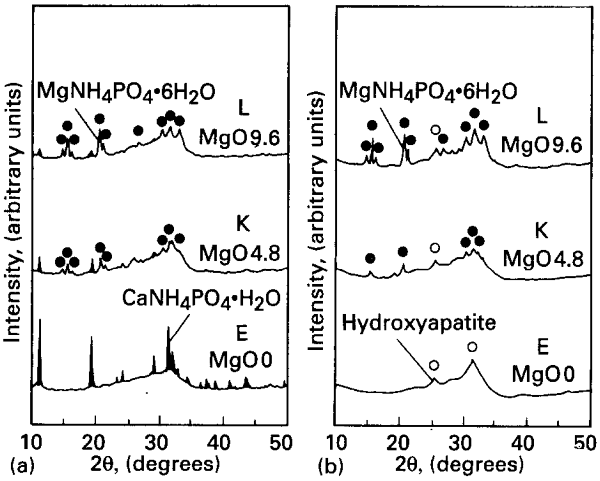

Figure 10 Powder X-ray diffraction patterns of the mixture composed of glass powders E with different MgO contents, before and after soaking in SBF for 23 h.

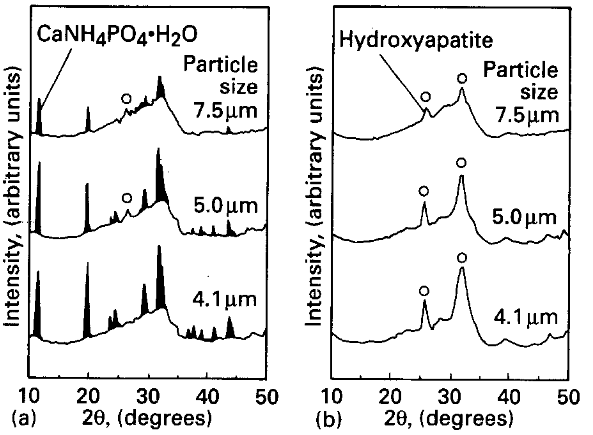

Figure 11 Powder X-ray diffraction patterns of the mixtures composed of glass powder E with different average particle sizes, before and after soaking in SBF for 23 h.

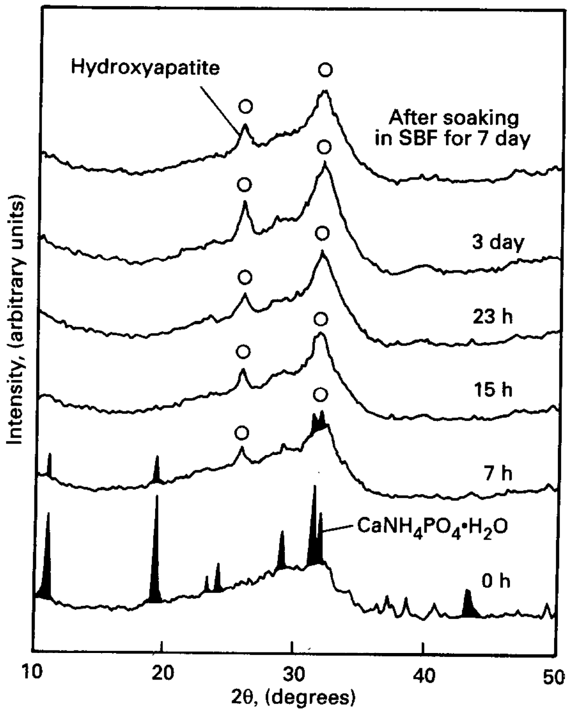

Figure 12 Powder X-ray diffraction patterns of the mixtures composed of glass powder E as a function of soaking time in SBF.

soaking, respectively, in SBF at the composition E, i.e. CaO 47.1, SiO_2 35.8, P_2O_5 17.1, CaF_2 0.75 wt ratio.

When the CaF_2 content of the glass powder was changed with constant CaO, SiO_2 and P_2O_5 contents, the compressive strengths of the mixtures increased with increasing content of CaF_2, at least up to 0.75 wt ratio, before as well as after soaking in SBF (shown in Fig. 3, which also gives the maximum values for composition E).

When different amounts of MgO were added to glass powder composition E, the compressive strengths of the mixtures decreased with increasing amount of MgO, before as well as after soaking in SBF (shown in Fig. 4, which also gives the maximum values for composition E).

Figure 5 shows the compressive strengths of the mixtures composed of glass powder composition E with different average particle sizes. Particle size distributions of some glass powders having different average particle sizes are shown in Fig. 6. A relatively low powder-to-liquid ratio of 1 g/0.6 ml was used for all the mixtures in this experiment, since glass powders with smaller average particle sizes required a larger amount of liquid to form a homogeneous mixed paste. It can be seen from Fig. 5 that the compressive strengths of the mixtures increase with decreasing average particle size of the glass powders, at least down to 4.1 μm. It should, however, be noted that the compressive strength of the mixture composed of glass powder with 4.1 μm average particle size and the

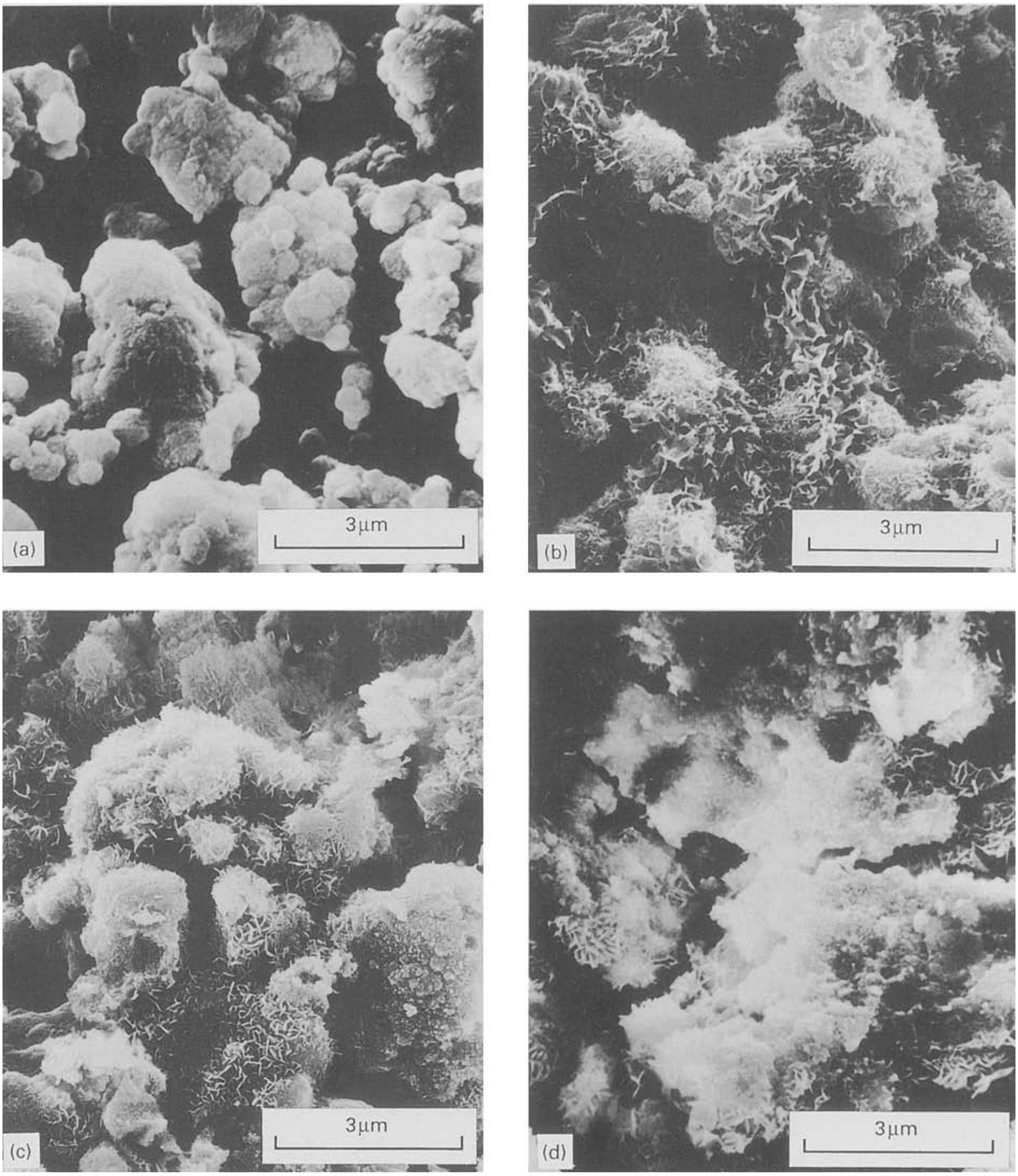

Figure 13 SEM photographs of the fractured surface of the mixtures composed of glass powder E as a function of soaking time in SBF: (a) 0 h, (b) 7 h, (c) 15 h and (d) 7 days.

present powder-to-liquid ratio is less than that of the mixture composed of glass powder with 5 μm size with a powder-to-liquid ratio of 1 g/0.5 ml (Figs 2, 3 and 4).

Figure 7 shows the change in compressive strength of the mixture composed of glass powder E, 5 μm average particle size, with soaking time in SBF. The compressive strength increased with increasing soaking time in SBF reaching over 80 MPa after 7 days.

3.2. X-ray diffraction

Powder X-ray diffraction patterns of some mixtures composed of glass powders with different CaO, SiO_2 and P_2O_5 ratios and constant CaF_2 content, before and after soaking in SBF for 23 h, are shown in Fig. 8. It can be seen that glass powders E and G form only crystalline calcium ammonium phosphate monohydrate ($CaNH_4PO_4 \cdot H_2O$) whereas powder A precipitates diammonium hydrogen phosphate ($(NH_4)_2HPO_4$) together with calcium ammonium phosphate monohydrate when mixed with ammonium phosphate solution. When soaked in SBF, powders A and E formed hydroxyapatite in place of calcium ammonium phosphate monohydrate, whereas G did not convert calcium ammonium phosphate into hydroxyapatite. The amount of the formed hydroxyapatite was larger for composition E than composition A.

Even when the $CaF_2$was eliminated from composition E, the glass powders formed calcium ammonium phosphate when mixed with ammonium phosphate solution as shown in Fig. 9. Glass powder E containing CaF_2, however, formed hydroxyapatite when soaked in SBF, whereas glass powder H not containing CaF_2 did not form hydroxyapatite.

When the MgO was added to glass composition E, the glass powders formed crystalline magnesium ammonium phosphate hexahydrate ($MgNH_4PO_4 \cdot 6H_2O$) together with calcium ammonium phosphate monohydrate, when mixed with ammonium phosphate solution, and hardly formed hydroxyapatite when soaked in SBF, as shown in Fig. 10

Figure 11 shows powder X-ray diffraction patterns of the mixtures composed of glass powder E with different average particle sizes. The amounts of both calcium ammonium phosphate monohydrate, which was formed by mixing with ammonium phosphate solution, and hydroxyapatite, which was formed by soaking in SBF, increased with decreasing average particle size.

Figure 12 shows powder X-ray diffraction patterns of the mixtures composed of glass powder E with average particle size 5 μm as a function of soaking time in SBF. When the mixture of glass powder E and ammonium phosphate solution was immersed in SBF, calcium ammonium phosphate monohydrate levels gradually decreased and hydroxyapatite increased in place of the calcium ammonium phosphate monohydrate with increasing soaking time.

3.3. SEM observation

Figure 13 shows SEM photographs of fracture surfaces of the mixtures composed of glass powder E as a function of soaking time in SBF. The glass powder formed agglomerates of fine particles around the raw glass particles when mixed with ammonium phosphate solution, and then formed platelet particles when soaked in SBF. The amount of the latter increased with increasing soaking time.

4. Discussion

It can be seen from the experimental results described above that the dependence of the compressive strengths of the mixtures after soaking in SBF on the CaO, SiO_2 and P_2O_5 ratios, the CaF_2 content, the MgO contents, average particle size of the glass powders, and soaking time of the mixtures in SBF, are all well correlated with the amount of hydroxyapatite formed in the mixtures. It can therefore be concluded that the compressive strength of the mixture soaked in SBF is determined by the amount of hydroxyapatite formed in the mixture. The platelet particles in Fig. 13 are considered to be hydroxyapatite.

Figures 8 to 11 show that those glass powders forming the larger amount of calcium ammonium phosphate monohydrate when mixed with ammonium phosphate solution generally form a larger amount of hydroxyapatite when soaked in SBF. The agglomerates in Fig. 13 are considered to consist of calcium ammonium phosphate monohydrate. The calcium ammonium phosphate monohydrate is considered to convert to hydroxyapatite by releasing the ammonium ion and taking up the calcium ion in SBF. All the calcium ammonium phosphate monohydrate, however, does not convert to hydroxyapatite in SBF, as seen for compositions G and H in Figs 8 and 9. It seems that the excessive calcium ion stabilizes the calcium ammonium phosphate monohydrate whereas the fluoride ion accelerates its conversion to hydroxyapatite. The calcium ammonium phosphate monohydrate is formed on the surface of the glass particles by the reaction of the calcium ion released from the glass particles with the ammonium phosphate solution. In the case of glass A, since only a small amount of calcium ion is released from the glass particles, a certain amount of diammonium hydrogen phosphate in the liquid is precipitated without reacting with the calcium ion. In the case of glass powders containing MgO, the magnesium ion is also released from the glass particles to form, preferentially, magnesium ammonium phosphate hexahydrate and hence hydroxyapatite is hardly formed in SBF, as seen in Fig. 10.

Acknowledgements

This work was supported by a Grant-in-Aid for Scientific Research, The Ministry of Education, Science and Culture, Japan.

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Received 11 March and accepted 2 June 1993