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Synthesis of bioactive PMMA bone cement via modification with methacryloxypropyltrimethoxysilane and calcium acetate

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Bone cement consisting of polymethylmethacrylate (PMMA) powder and methylmethacrylate (MMA) liquid is clinically used for fixation of implants such as artificial hip joints. However, it does not show bone-bonding ability, i.e., bioactivity. The lack of bioactivity would be one of factors which cause loosening between the cement and the implant. The present authors recently showed the potential of bioactive PMMA-based bone cement through modification with γ-methacryloxypropyltrimethoxysilane (MPS) and calcium acetate. In this study, the effects of the kinds of PMMA powder on setting time, apatite formation and compressive strength were investigated in a simulated body fluid (Kokubo solution). The cement modified with calcium acetate calcined at 220 °C could set within 15 min when the PMMA powder had an average molecular weight of 100,000 or less. The addition of calcium acetate calcined at 120 °C in the PMMA powder required a much longer period for setting. The modified cements formed an apatite layer after soaking in the Kokubo solution within 1 day for cement starting from PMMA powder with a molecular weight of 100,000 or less. Compressive strengths of the modified cements were more than 70 MPa for cements starting from 100,000 and 56,000 in molecular weight. After soaking in Kokubo solution for 7 days, the modified cement consisting of PMMA powder of 100,000 in molecular weight showed a smaller decrease in compressive strength than that consisting of 56,000 in molecular weight. These results indicate that bioactive PMMA cement can be produced with appropriate setting time and mechanical strength when PMMA powders with a suitable molecular weight are used. Such a type of design of bioactive PMMA bone cement leads to a novel development of bioactive material for bone substitutes.

1. Introduction

Bone cement consisting of polymethylmethacrylate (PMMA) powder and methylmethacrylate (MMA) liquid is a popular bone-repairing material used for fixing artificial hip joints [1, 2]. A significant problem of the cement is the loosening between the cement and the implant. Several factors such as shrinkage of the cement and heat generation during polymerization are thought to cause the loosening. As one of these factors, we have focused our attention on lack of bone-bonding ability, i.e., bioactivity. In order to provide the cement with bioactivity, PMMA bone cement is often mixed with bioactive ceramic powders such as glass-ceramic A-W and sintered hydroxyapatite [3]. In this method, however, bioactive ceramic particles are hardly exposed to body fluid even after implanted in the body, since they are liable to be covered with PMMA matrix. As a result, it is difficult to provide the cements with bioactivity.

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The addition of a high content of bioactive powder into PMMA bone cement causes problems of limitation on its workability and mechanical properties.

The essential prerequisite for an artificial material to bond to bone is the formation of an apatite layer on its surface in a body environment [4, 5]. This apatite formation is well reproduced even in a simulated body fluid (Kokubo solution) with ion concentrations similar to those of human extracellular fluid [6]. It has been revealed from studies on bioactive glasses and glass-ceramics that formation of the apatite layer is initiated by heterogeneous nucleation of the apatite on the bioactive materials. Si-OH groups on their surfaces play an important role in the induction of the heterogeneous nucleation of the apatite and Ca^{2+} ions released from them into body fluid accelerate it by increasing the degree of supersaturation with respect to the apatite [7]. These findings make us think that modification of PMMA cements with Si-OH groups and Ca^{2+} ions is effective for obtaining bioactive PMMA cement. On the basis of this idea, the authors successfully synthesized PMMA cement with apatite-forming ability through chemical modification with alkoxysilane such as γ-methacryloxypropyltrimethoxysilane (MPS), as well as with calcium salts such as calcium chloride, calcium acetate and calcium hydroxide [8]. In this material design, the alkoxysilane is used as a compound which provides Si-OH groups after exposure to aqueous solution, while the calcium salts act as compounds which release Ca^{2+} ions. Several kinds of calcium salts (calcium chloride, calcium acetate and calcium hydroxide) are also suitable for modification of the PMMA cement to provide apatite-forming ability, while calcium carbonate and tricalcium phosphate are not. Among the calcium salts (calcium chloride, calcium acetate and calcium hydroxide), the addition of calcium chloride remarkably decreased the compressive strength of the modified cements after exposure to a simulated body fluid. On the other hand, the addition of calcium hydroxide shows a lower ability for apatite formation in the simulated body fluid than calcium chloride and calcium acetate. Based on these studies, we believe that modification of the cement with calcium acetate leads to moderate properties suitable for bioactivity, i.e., apatite formation, and for mechanical performance in a body environment. However the potential of the mechanical strength and bioactivity after the modification with calcium acetate was not revealed in detail. Therefore, this study focused on the investigation of the effect of calcium acetate and MPS on PMMA bone cement in regard to setting time, compressive strength and bone-bonding properties. The optimization of PMMA powder was also attempted preliminarily on several types of PMMA powders and on the treatment of calcium acetate powder.

2. Experimental procedure

A chemical reagent of calcium acetate monohydrate ($Ca(CH_3COO)_2 \cdot H_2O$; Wako Pure Chemical Industries Ltd. Osaka, Japan) was used as a starting material for the preparation of the modified cement. The thermal gravimetry (TG; WS002 TG-DTA 2000S, MAC Science Co., Ltd., Yokohama, Japan) of the calcium acetate monohydrate was performed at a rate of 5 °C/min up to 450 °C. Based on the results of TG curves, two conditions for heat-treatment of the powder of calcium acetate hydrate were applied: one is 120 °C for 12 h or more, the other is 220 °C for 2 h. The heat-treated powder was kept at 120 °C before preparation of the powder. The PMMA powders given in Table I were supplied from Sekisui Plastics Co., Ltd., Tokyo, Japan. Three types of the PMMA powder were subjected to the experiment, all of which have almost equal particle size on average, ranging from 10 to 20 μm, but have different molecular weights (M_w) on average, ranging from 56,000 to 200,000.

TABLE I Examined PMMA powders

Sample	Average particle size (μm)	Average molecular weight (M_w)
P20	14.0	200,000
P10	14.4	100,000
P05	16.8	56,000

The PMMA powder was mixed with the heat-treated calcium acetate powder, in addition to benzoyl peroxide (BPO; Wako Pure Chemical Industries Ltd.) as a polymerization initiator. MMA liquid (Wako Pure Chemical Industries Ltd.) was mixed with MPS (Chisso Industry Co., Ltd., Tokyo, Japan) and N,N-dimethyl-*p*-toluidine (NDT; Kanto Chemical Co., Inc., Tokyo, Japan) as a polymerization accelerator. These chemical agents were used without further purification. Detailed compositions of the examined cements are given in Table II. Reference was prepared by following the composition of commercially available PMMA bone cement. The powder to liquid (P/L) mass ratio was fixed at 1.0 g/0.5 g and was mixed at 23 $\pm$ 2 °C. Several cements were prepared as shown in Table III. Setting time of the mixed paste was measured in a simulated body fluid (Kokubo solution) with ion concentrations (Na^+ 142.0, K^+ 5.0, Mg^{2+} 1.5, Ca^{2+} 2.5, Cl^- 147.8, HCO_3^- 4.2, HPO_4^{2-} 1.0 and SO_4^{2-} 0.5 mM(=mol/m^3)) and pH (7.25). A weight of 300 g was loaded onto the mixed paste with a Vicat needle apparatus with a cross section of 1 mm^2. The setting time was defined as a time when a trace of the Vicat needle did not remain on the surface of the cements.

Apatite formation was examined for rectangular specimens of 10 $\times$ 15 $\times$ 1 mm^3 in size. The mixed paste was immersed in 35 mL of Kokubo solution before it was completely hardened. The specimens were kept at 36.5 °C in the solution for various periods. After soaking for predetermined intervals (1, 3 and 7 days), the cements were removed from the solution and were characterized by thin-film X-ray diffraction (TF-XRD; M18XHF^{22}-SRA, MAC Science Co., Ltd., Yokohama, Japan) and scanning electron microscopic (SEM; S-3500N, Hitachi Co., Ltd., Tokyo, Japan) observation.

The compressive strength of the cements was measured according to ISO5833. After the setting of the cement, it was kept for 24 h in air at room

TABLE II Constituents of the examined cements.

	Powder (mass ratio)				Liquid (mass ratio)		
Sample	PMMA	BPO	Calcium salt		MMA	MPS	NDT
Reference	0.971	0.029	0		0.496	0	0.004
CAL	0.777	0.029	0.194	Calcium acetate calcined at 120 °C	0.397	0.099	0.004
CA	0.777	0.029	0.194	Calcium acetate calcined at 220 °C	0.397	0.099	0.004

BPO: Benzoyl peroxide.
NDT: N,N-dimethyl-*p*-toluidine.
MPS: γ-methacryloxypropyltrimethoxysilane.

TABLE III Annotation of the examined cements

	P20	P10	P05
Reference	–	Reference(P10)	–
CAL	–	CAL(P10)	–
CA	CA(P20)	CA(P10)	CA(P05)

–: not examined.

temperature. A compressive load was applied at a crosshead speed of 20 mm/min normally to cylindrical specimens of 6 mm in diameter and 12 mm in length until fracture occurred. The compressive strength was calculated from the applied load and geometrical surface area of the specimens. The average compressive strength and standard deviation were calculated. Furthermore, the compressive strength of the cement after exposure to body fluid was also measured. The mixed paste was immersed in 35 mL of Kokubo solution before it was completely hardened. After the specimens were kept in the solution at 36.5 °C for 7 days, they were removed and their compressive strength was measured under the same condition.

3. Results

Fig. 1 shows the TG curve of the examined calcium acetate. Remarkable decreases in weight are observed at the ranges from 100 to 120 °C and from 140 to 220 °C. These decreases in weight are attributed to loss of water from the powder of the calcium acetate. The former decrease gives a loss of approximately half of the hydrate from the starting material

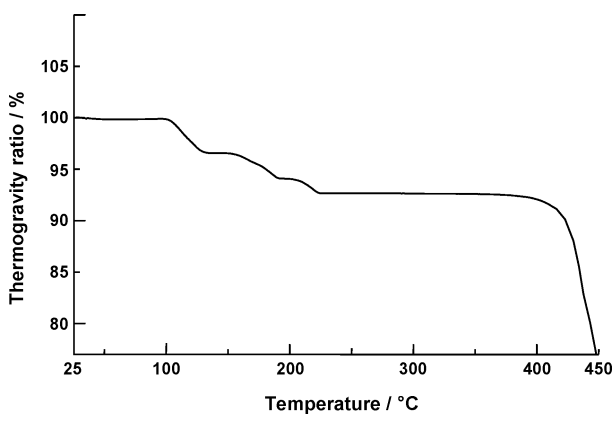

Figure 1 TG curve of the examined calcium acetate.

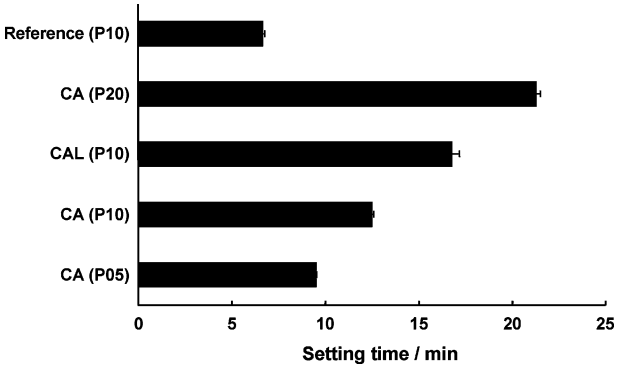

Figure 2 Setting time of the examined cements.

to form $Ca(CH_3COO)_2 \cdot 1/2H_2O$. The total loss (approximately 10 mass%) after the heat treatment up to 220 °C is consistent with the release of water molecules from the starting material to form calcium acetate anhydrate. Calcium acetate decomposes to calcium oxide and carbon dioxide when it is heated at 400 °C and more. Therefore, the powder of calcium acetate heated at 120 °C has water of crystallization, while the powder heated at 220 °C does not. Fig. 2 shows the setting time of the cements; Reference(P10), CAL(P10), CA(P10), CA(P20) and CA(P05). The addition of MPS and calcium acetate leads to a prolongation in the setting time of the cement. Specimens with added calcium acetate calcined at 120 °C (CAL(P10)) show longer setting times than specimens with added calcium acetate powder calcined at 220 °C (CA(P10)) when the molecular weight of the PMMA powder was fixed. This result supports the view that calcium acetate powder calcined at 220 °C is suitable for the modification of the cement. Comparing the difference of the molecular weight of the examined PMMA powders, it is clear that an increase in molecular weight of the PMMA prolongs the setting time of the cement. A molecular weight of 100,000 or less is suitable for the PMMA powder of the modified cements, even when calcium acetate is added to it. The incorporation of calcium acetate calcined at 220 °C with PMMA powder having a molecular weight of 200,000 shows longer periods of setting time than that which is needed in ISO5833, that is, ranging from 3 to 15 min. From these experiments, CA(P10) and CA(P05) were subjected to evaluation of their apatite-forming ability, i.e., bioactivity.

Fig. 3 shows SEM images of the Reference(P10), CA(P10) and CA(P05) cements after soaking in

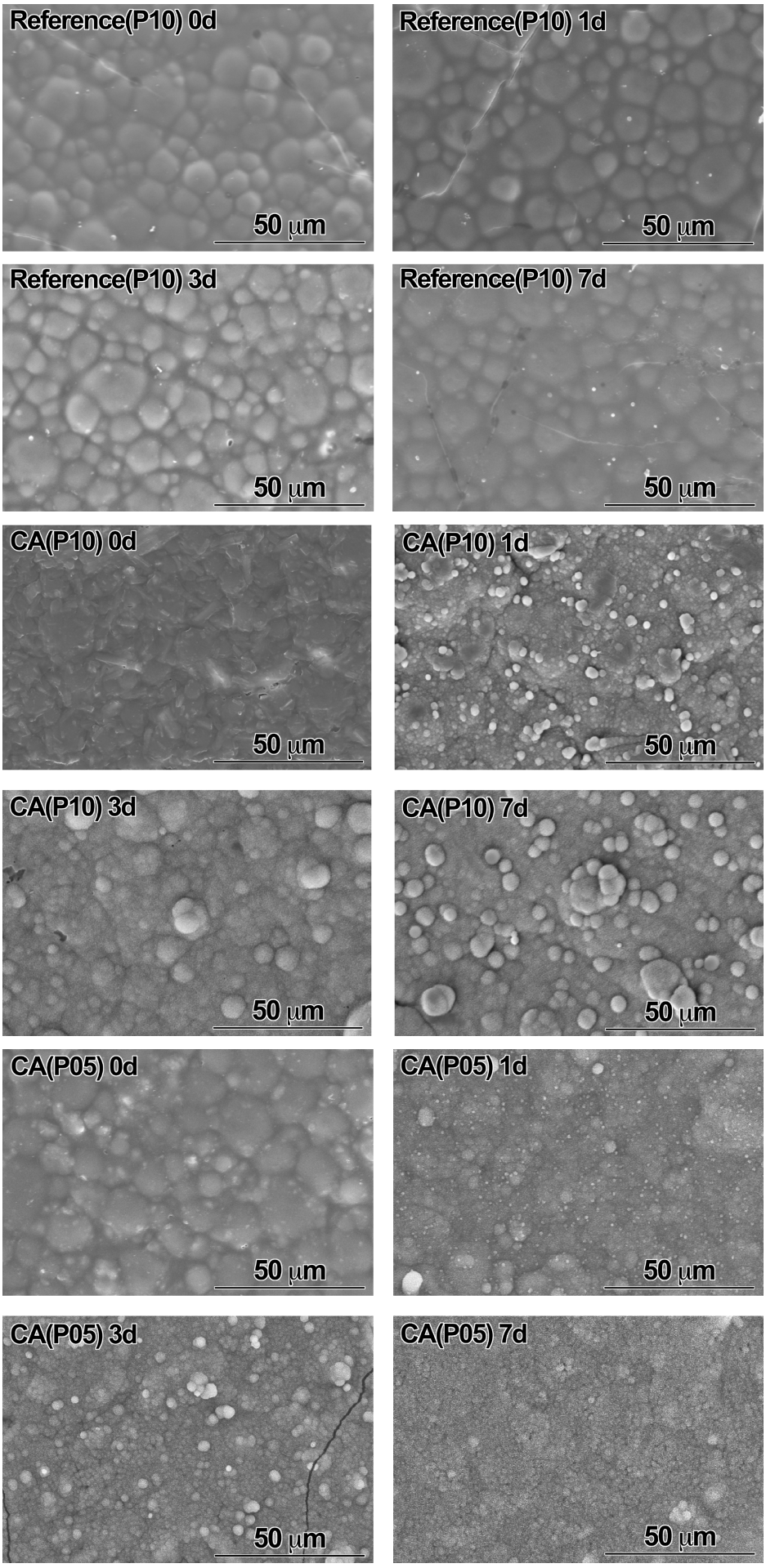

Figure 3 SEM images of the Reference(P10), CA(P10) and CA(P05) cements after soaking in Kokubo solution for various periods. "0d" denotes the specimens without soaking in Kokubo solution.

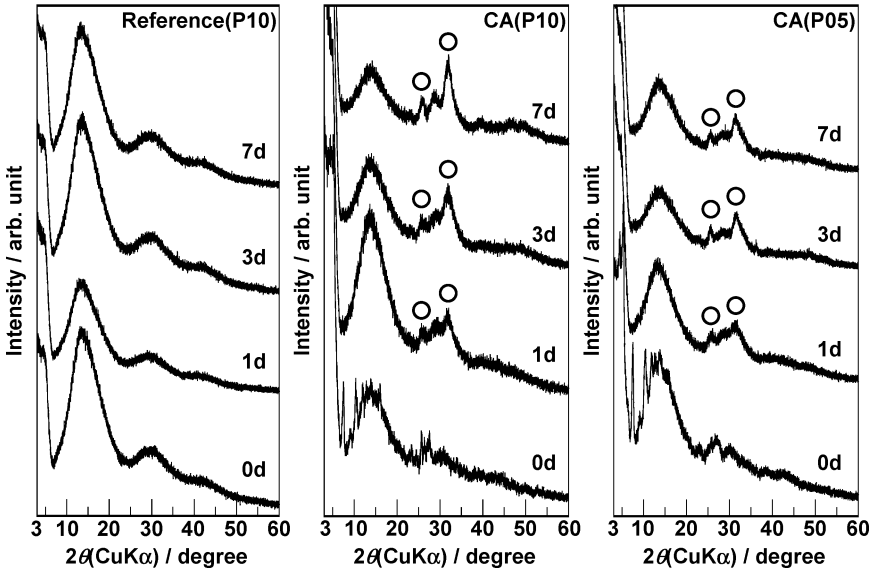

Figure 4 Thin-film X-ray diffraction patterns of the surface of the Reference(P10), CA(P10) and CA(P05) cements after soaking in Kokubo solution for various periods. "0d" denotes the specimens without soaking in Kokubo solution. White circle: Apatite

Kokubo solution for various periods. "0d" denotes the specimens without soaking in Kokubo solution. The examined cement showed a smooth surface when it did not contain MPS and calcium acetate. The mixture of MPS and calcium acetate gives the cements a somewhat rough surface on some regions. After exposure of the specimens to Kokubo solution, assemblies of fine particles were observed on some types of the modified cements (CA(P10) and CA(P05)) for 1 day, but not on Reference(P10). The morphology of the deposited particles on the surface is quite similar to that of the hydroxyapatite layer formed on bioactive glasses and glass-ceramics after soaking in Kokubo solution [9]. Fig. 4 shows TF-XRD patterns of the surface of Reference(P10), CA(P10) and CA(P05) cements after soaking in Kokubo solution for various periods. Peaks assigned to hydroxyapatite (JCPDS#15-0876) with low crystallinity were detected at about 26 ° and 32 ° for the specimen modified with MPS and calcium acetate, irrespective of the molecular weight of the PMMA powder, while they were not for Reference(P10). These results indicate that apatite crystals were deposited on the surface of the modified cement, irrespective of the molecular weight of PMMA powders in Kokubo solution. The rate of apatite deposition on CA(P10) cement was almost equal to that on CA(P05) cement.

Fig. 5 shows the compressive strength of Reference(P10), CA(P10) and CA(P05) cement with and without soaking in Kokubo solution for 7 days. The compressive strength of the cement without soaking in Kokubo solution was denoted as "0d". These three types of examined cement are adequate to satisfy the requirement of ISO5833(70 MPa), although the modified cements with MPS and calcium acetate showed a lower compressive strength than those without the modification. After soaking in Kokubo solution for 7 days, the compressive strength of the modified cements decreased. The degree of the decreased strength is much larger for CA(P05) than for CA(P10). The compressive strength of CA(P10) was kept at around 70 MPa, even after soaking.

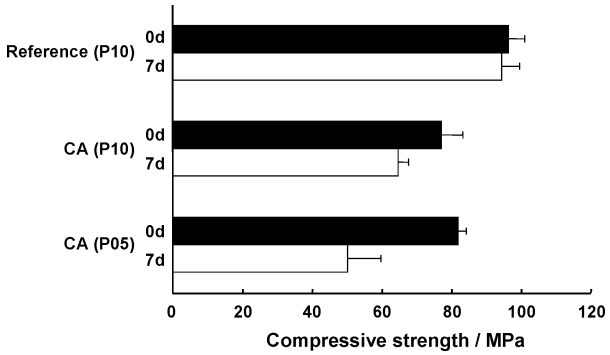

Figure 5 Compressive strength of the Reference(P10), CA(P10) and CA(P05) cements with and without exposure to Kokubo solution for 7 days.

4. Discussion

The present results indicate that prolongation of the setting time of the modified cements is reduced by removal of water of crystallization in calcium acetate hydrate by heat-treatment. The existence of water may decrease the rate of radical formation from BPO. A reduced amount of water in calcium acetate powder is also expected to give a reduction in porosity volume of the modified cement after reaction with body fluid. A higher molecular weight of PMMA powders results in prolongation of the setting time. PMMA powder with a high molecular weight may show less swelling against MMA monomers [10], which results in a longer setting time.

Apatite formation on the cements modified with MPS and calcium acetate was observed within 1 day after soaking in Kokubo solution, irrespective of the molecular weight of the PMMA powder, whereas the conventional type of PMMA cement did not show any apatite formation. This means that these modified cements

have high potential for osteoconduction, that is, bone-bonding ability, when they are used with implants in bone defects.

Apatite formation is triggered by the reaction of calcium acetate and MPS with surrounding fluid. This causes a decrease in the mechanical strength of the cements. Actually, the compressive strength of the modified cements decreased after soaking in Kokubo solution. The decrease in compressive strength was significant for the cement prepared by a PMMA powder of lower molecular weight (56,000). The usage of higher-molecular-weight (100,000) PMMA powder results in less decrease in compressive strength. Cement prepared by lower-molecular-weight PMMA powder may set with a structure that allows for a higher dissolution of calcium acetate and MPS after exposure to the fluid, although detailed differences in the morphology of the set cement could not be distinctly observed. These results indicate that optimized molecular weight of PMMA powder can be one of the important parameters for developing a bioactive cement with suitable workability and with mechanical strength, through modification with calcium salt and MPS.

5. Conclusion

Modification with γ-methacryloxypropyltrimethoxysilane (MPS) and calcium acetates can provide PMMA bone cement with apatite-forming ability, and hence the modified cements are expected to show bone-bonding ability when implanted in the body. Setting time can be appropriate after calcination of the calcium acetate compounds at 220 °C. Less decrease in the compressive strength of the cement after soaking in the simulated body fluid was achieved when the PMMA powder is 100,000 in molecular weight. This type of modified cement is expected to be a novel bone-repairing material with bioactivity as well as workability close to conventional PMMA bone cement.

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References

1. K. J. HERPER, *Proc. Inst. Mech. Eng. Part H* **212** (1998) 113.
2. K. D. KÜHN, "Bone Cements" (Springer, Berlin, 2000) p. 21.
3. S. SHINZATO, M. KOBAYASHI, W. F. MOUSA, M. KAMIMURA, M. NEO, Y. KITAMURA, T. KOKUBO and T. NAKAMURA, *J. Biomed. Mater. Res.* **51** (2000) 258.
4. T. KOKUBO, *J. Ceram. Soc. Japan (Seramikkusu Ronbunshi)* **99** (1991) 965.
5. H.-M. KIM, *J. Ceram. Soc. Jpn* **109** (2001) S49–S57.
6. T. KOKUBO, H. KUSHITANI, S. SAKKA, T. KITSUGI and T. YAMAMURO, *J. Biomed. Mater. Res.* **24** (1990) 721.
7. C. OHTSUKI, T. KOKUBO and T. YAMAMURO, *J. Non-Cryst. Solids* **143** (1992) 84.
8. C. OHTSUKI, T. MIYAZAKI, M. KYOMOTO, M. TANIHARA and A. OSAKA, *J. Mater. Sci.: Mater. Med.* **12** (2001) 895.
9. C. OHTSUKI, H. KUSHITANI, T. KOKUBO, S. KOTANI and T. YAMAMURO, *J. Biomed. Mater. Res.* **25** (1991) 1363.
10. S. SHINZATO, T. NAKAMURA, T. KOKUBO and Y. KITAMURA, *ibid.* **59** (2002) 225.

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