JOURNAL OF MATERIALS SCIENCE: MATERIALS IN MEDICINE 12 (2001) 895–899

Development of bioactive PMMA-based cement by modification with alkoxysilane and calcium salt

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Poly (methyl methacylate) (PMMA) bone cement is one of the popular bone-repairing materials for fixation of artificial hip joints. Significant problems on the PMMA bone cement are caused by loosening at the interface between bone and the cement, since the cement does not show bone-bonding, i.e. bioactivity. Development of PMMA bone cement capable of bone-bonding has been therefore long desired. The prerequisite for an artificial material to show bone-bonding is the formation of a biologically active bone-like apatite layer on its surface when implanted in the body. The same type of apatite formation can be observed on bioactive materials even in a simulated body fluid (Kokubo solution) with ion concentrations nearly equal to those of human blood plasma. Fundamental researches for bioactive glasses and glass-ceramics revealed that the apatite deposition is initiated by release of Ca^{2+} ions from the material into the body fluid, and by catalytic effect of Si–OH groups formed on the surface of the material. These findings lead an idea that novel bioactive cement can be designed by incorporation of Si–OH groups and Ca^{2+} ion into PMMA bone cement. In the present study, PMMA bone cement is modified with 20 mass% of various kinds of alkoxysilanes and calcium salts, and its apatite-forming ability was evaluated in Kokubo solution. The apatite formation was observed on the surface of the modified cements containing 20 mass% of $CaCl_2$, irrespective of the kind of the examined alkoxysilane. On the other hand, the apatite formation was observed on the cement containing $CaCl_2$, $Ca(CH_3COO)_2$ or $Ca(OH)_2$, but not on the cement containing $CaCO_3$ or β-$Ca_3(PO_4)_2$, even when the cement contains 3-methacryloxypropyltrimethoxysilane (MPS). The results indicate that modification with alkoxysilane and calcium salts showing high water-solubility is effective for providing PMMA bone cement with bioactivity.

Introduction

Bone cement consisting of poly(methyl methacrylate) (PMMA) powder and methyl methacrylate (MMA) liquid, in which they are mixed and polymerized, is clinically used for the fixation of implants such as artificial hip joint [1, 2]. Significant problems on the PMMA bone cement are caused by loosening at the interface between bone and the cement, since the cement does not show bone-bonding, i.e. bioactivity. Several studies have been conducted to develop bioactive cement through a method by mixing powder of bioactive ceramics with PMMA cement [3]. In this method, large amounts of ceramic powder should be incorporated into the cement to show bioactivity, since the bioactive ceramic powder is almost covered with PMMA matrix and hardly exposed to body fluid. Novel strategies for obtaining bioactive PMMA bone cements should be therefore developed as the basis of fundamental study on bonding mechanism of artificial materials to living bone.

Previous studies reported that the prerequisite for an artificial material to show bioactivity is the formation of a biologically active bone-like apatite layer on its surface when implanted in the body [4, 5]. The same type of apatite formation can be observed on bioactive materials even in a simulated body fluid (denoted as Kokubo solution) with ion concentrations nearly equal to those of human blood plasma [6]. Bioactivity of an artificial material can be therefore evaluated even *in vitro* by examining its apatite-forming ability in Kokubo solution. Moreover, research on reaction of bioactive glasses and glass-ceramics with Kokubo solution reveals that the apatite nucleation is triggered by catalytic effect of Si–OH groups formed on the surface of the material and accelerated by release of Ca^{2+} ion from the material into

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TABLE I Composition of the examined cements

Powder (mass ratio)			Liquid (mass ratio)		
PMMA	Calcium salt	BPO	MMA	Alkoxysilane	NDT
0.776	0.194	0.029	0.794	0.198	0.008

BPO: Benzoyl peroxide; NDT: N,N-dimethyl-*p*-toluidine.

the fluid [7, 8]. The findings led to an idea that a novel bioactive PMMA-based cement could be designed by modification with alkoxysilane that provide Si–OH groups and with calcium salt that release Ca^{2+} ion in the body fluid. In the present study, PMMA bone cement was incorporated with 20 mass % of various kinds of alkoxysilanes and calcium salts, and apatite-forming ability of the modified cements was examined in Kokubo solution.

Materials and Methods

Chemical reagents were used as starting materials. Calcium salts were dried in an oven at 120 °C for more than 12 h to remove excessive water. The other reagents were used without further purification. PMMA powder with molecular weight about 70 000 (Wako Pure Chemical Industries, Ltd., Osaka, Japan) was pulverized to grain size less than 44 μm. The PMMA powder was mixed with a calcium salt among $CaCl_2$, $Ca(CH_3COO)_2$, $Ca(OH)_2$, β-$Ca_3(PO_4)_2$ (β-TCP) and $CaCO_3$, at 20 mass % of the powder. Benzoyl peroxide was then added to the powder as a polymerization initiator. MMA liquid was mixed with an alkoxysilane among 3-methacryloxypropyltrimethoxysilane (MPS), vinyltrimethoxysilane (VTMS), 3-aminopropyltriethoxysilane (APS) and 3-glycidoxypropyltrimethoxyslane (GPS) at 20 mass % of the liquid. N,N-dimethyl-*p*-toluidine was then added to the liquid as a polymerization accelerator. Detailed composition of the prepared cement is given in Table I. The powder was mixed with the liquid at a powder to liquid ratio of 1 g/0.5 g at 23 ± 2 °C. The paste was shaped to a rectangular specimen $10 \times 15 \times 1\,mm^3$ in size. At a half of the setting time of the specimens, they were immersed in 35 mL of a simulated body fluid (Kokubo solution) that has ion concentrations of 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 mol/m^3. The fluid was prepared by dissolving reagents of NaCl, $NaHCO_3$, KCl, $K_2HPO_4 \cdot 3H_2O$, $MgCl_2 \cdot 6H_2O$, $CaCl_2$ and Na_2SO_4 into distilled water, and buffered at pH 7.25 at 36.5 °C with *tris*-hydroxymethylaminomethane ($(CH_2OH)_3CNH_2$) and HCl [9]. After keeping at 36.5 °C for 3, 7, and 14 days, the specimens were removed from the fluid, and were characterized by thin-film X-ray diffraction (TF-XRD; M18XHF^{22}-SRA, MAC Science Co., Ltd., Yokohama, Japan), and scanning electron microscope (SEM; S-3500N, Hitachi Co., Ltd., Tokyo, Japan) observation. In the TF-XRD, incident beam was set at 1° against the specimen. In the SEM observation, the surfaces of the specimens were coated with Au by a sputtering method.

Results

Fig. 1 shows SEM photographs of the surfaces of the cements modified with $CaCl_2$ and various kinds of alkoxysilanes, which were soaked in Kokubo solution for seven days. Assembles of fine particles were observed on

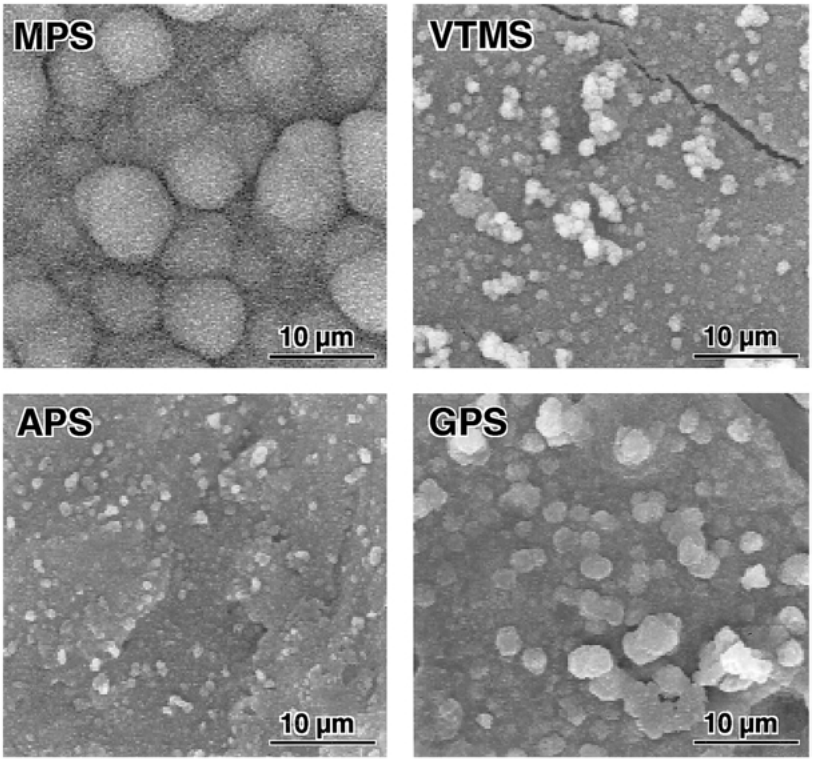

Figure 1 SEM photographs of the surfaces of the cements modified with $CaCl_2$ and various kinds of alkoxysilanes, which were soaked in Kokubo solution for seven days.

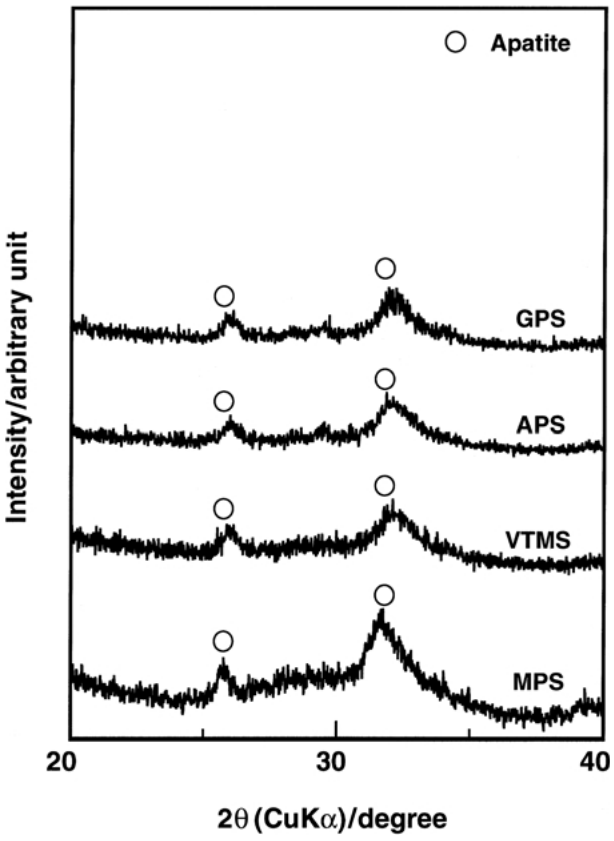

Figure 2 TF-XRD patterns of the surfaces of the cements modified with $CaCl_2$ and various kinds of alkoxysilanes, which were soaked in Kokubo solution for seven days.

all the four types of the modified cements after the soaking. The morphology of the deposited particles on the surface is quite similar to that of hydroxyapatite layer formed on bioactive glasses and glass-ceramics after soaked in Kokubo solution [5, 8, 10]. Fig. 2 shows TF-XRD patterns of the surfaces of the cements with the same modification, after soaking in Kokubo solution for seven days. Peaks assigned to hydroxyapatite with low crystallinity were detected at about 26° and 32° for all the four types of the cement after the soaking. These results indicate that apatite crystals are deposited on the surface of the modified cement, irrespective of kinds of the alkoxysilanes, in Kokubo solution.

Fig. 3 shows SEM photographs of the surfaces of the cements modified with MPS and various kinds of calcium salts, which were soaked in Kokubo solution for seven days. The assembles of the fine particles were also observed on the cements containing $CaCl_2$, $Ca(CH_3COO)_2$ or $Ca(OH)_2$, but not on the cements containing $CaCO_3$ or β-TCP. Fig. 4 shows TF-XRD patterns of the surfaces of the cements with the same modification, after soaking in Kokubo solution for seven days. Peaks ascribed to hydroxyapatite were detected for the cement containing $CaCl_2$, $Ca(CH_3COO)_2$ or $Ca(OH)_2$, whereas they were not detected for the cement containing $CaCO_3$ or β-TCP in the powder.

Ability of the apatite formation on the modified cements in Kokubo solution are summarized in Table II on the basis of the results including estimation for the other soaking periods. The results were determined by SEM that observes the deposition of the fine particles which are ascribed to apatite crystals. The apatite formation in the table implies that the deposited particles covered more than half of the surface area on the specimen. The results indicate that apatite-forming ability was provided to the cement when it is modified with $CaCl_2$, $Ca(CH_3COO)_2$ or $Ca(OH)_2$, in addition to

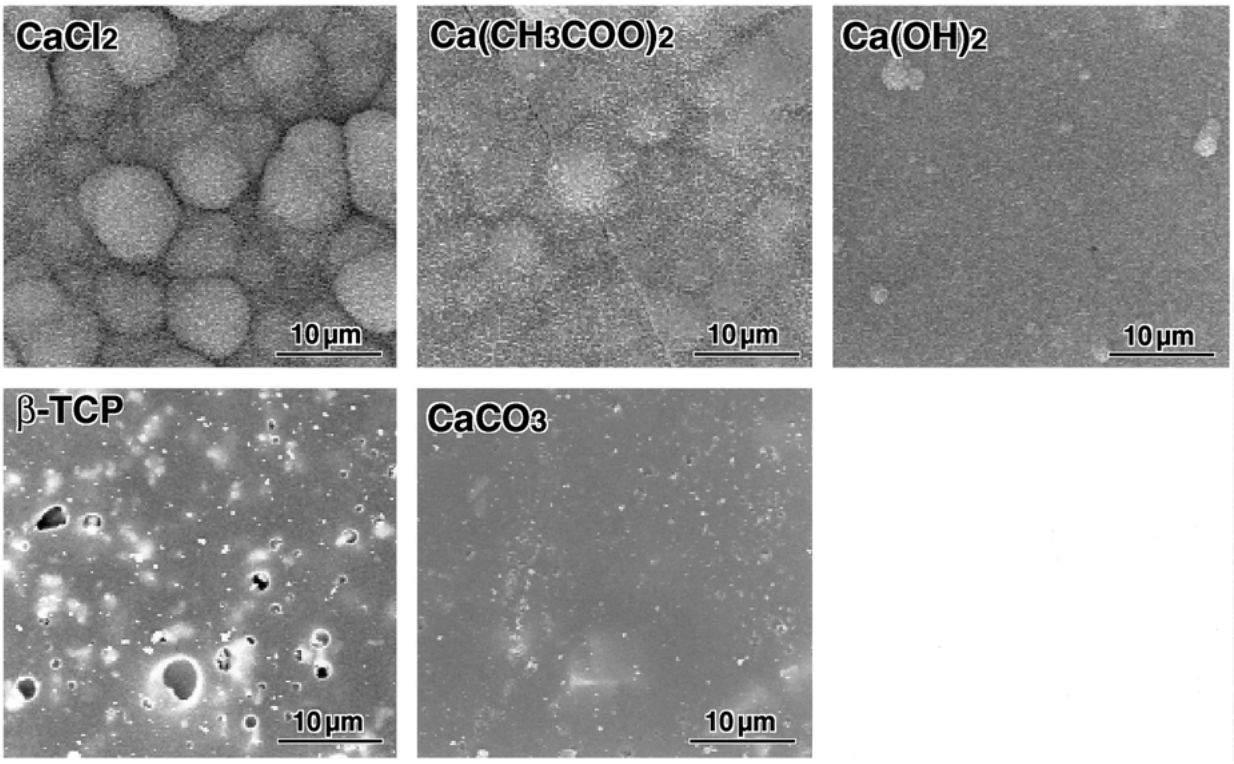

Figure 3 SEM photographs of the surfaces of the cements modified with MPS and various kinds of calcium salts, which were soaked in Kokubo solution for seven days.

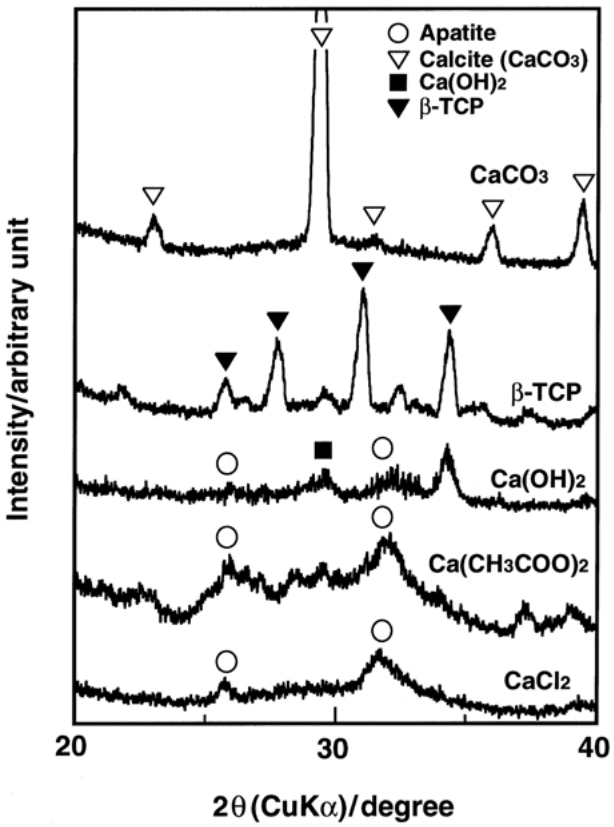

Figure 4 TF-XRD patterns of the surfaces of the cements modified with MPS and various kinds of calcium salts, which were soaked in Kokubo solution for seven days.

the examined alkoxysilanes. Modification with $CaCO_3$ or β-TCP could not provide apatite-forming ability, even when the cement contains the alkoxysilanes.

Discussion

It is apparent from the results described above that modification of PMMA cement by incorporation of $CaCl_2$ and the alkoxysilanes makes the cement capable of apatite formation in body environment. The difference on ability of apatite formation was not observed among the examined alkoxysilanes when 20 mass % of $CaCl_2$ is incorporated. Therefore, these modified cements all have a potential to show bone-bonding, irrespective of the type of alkoxysilanes, when implanted in bony defects. On the other hand, the type of calcium salt added to the cement largely affects the ability for apatite formation. Incorporation of $CaCO_3$ or β-TCP to the cement modified with one of alkoxysilanes, MPS, cannot provide apatite-forming ability, while incorporation of $CaCl_2$, $Ca(CH_3COO)_2$ or $Ca(OH)_2$ can. The difference of the apatite formation is attributed to solubility of the calcium salts. Solubility of the examined calcium salts increases in the order: β-TCP ≈ $CaCO_3$ < $Ca(OH)_2$ < $Ca(CH_3COO)_2$ < $CaCl_2$. Higher solubility of calcium salt results in easier increase in degree of supersaturation of the surrounding fluid with respect to hydroxyapatite, hence the apatite deposition can be accelerated on the surface. In such a mechanism, phosphate is not an essential component to provide the cement with bioactivity because phosphate ions required to form apatite crystals can be supplied from surrounding body fluid.

Conclusions

Modification with alkoxysilanes and calcium salts can provide PMMA bone cement with apatite-forming ability, and hence the modified cements are expected to tightly bond to living bone when implanted in the body. Incorporation of the calcium salt with higher solubility is effective for providing PMMA bone cements with the apatite-forming ability in the body environment. This type of modified cement is expected to be a novel bone-repairing material with bioactivity as well as mechanical properties close to conventional PMMA bone cement.

Acknowledgments

This study was supported by Grant-in-Aid for Scientific Research ((B)13450272), Japan Society for the Promotion of Science.

TABLE II Apatite formation on PMMA-based cements modified with various kinds of alkoxysilanes and calcium salts in Kokubo solution, which was determined by SEM observation

Effect of alkoxysilane					
Calcium salt	Alkoxysilane				
	MPS	VTMS	APS	GPS	
$CaCl_2$	++	++	++	++	
Effect of calcium salt					
Alkoxysilane	Calcium salt				
	$CaCl_2$	$Ca(CH_3COO)_2$	$Ca(OH)_2$	β-TCP	$CaCO_3$
MPS	++	++	+	–	–

– Apatite was not formed after 14 days.
\+ Apatite was formed within 7 days.
++ Apatite was formed within 3 days.

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Received 14 May
and accepted 21 May 2001