Bioactive PMMA bone cement modified with combinations of phosphate group-containing monomers and calcium acetate

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Abstract

Bone cement prepared from polymethylmethacrylate (PMMA) powder and methylmethacrylate (MMA) liquid has been successfully demonstrated as one kind of artificial material to anchor joint replacements in bone. However, the cement itself lacks the capability to bond directly to living bone, so long-term implantation leads to an increased risk of loosening. It has been found that bioactive materials show better performance in fixation to bone, and the chemical bonding depends on bone-like apatite formation. This is triggered by surface reactions of biomaterials and body fluid. For these reactions, superficial functional groups like silanol (Si-OH) are ideal sites to induce apatite nucleation and the release of Ca^{2+} ions accelerates the apatite growth. Therefore, incorporation of materials containing these key components may provide the cement with apatite-forming ability. In this study, phosphoric acid 2-hydroxyethyl methacrylate ester (Pa2hme) or bis[2-(methacryloyloxy)ethyl] phosphate (BisP) supplying a phosphate group (PO_4H_2) was added into MMA liquid, while calcium acetate as a source of Ca^{2+} ions was mixed into PMMA powder. The possibility of developing a bioactive PMMA bone cement using combinations of various amounts of calcium acetate and phosphate group-containing monomers was examined. The influences of the combinations on the setting time and compressive strength were also investigated. An apatite layer was observed on the cements modified with 30 mass% of P2ahme or BisP. The induction period was shortened with increased amounts of $Ca(CH_3COO)_2$. The setting time could be controlled by the $Ca(CH_3COO)_2$/monomer mass ratio. Faster setting was achieved at a ratio close to the mixing ratio of the powder/liquid (2:1), and both increases and decreases in the amount of $Ca(CH_3COO)_2$ prolonged the setting time based on this ratio. The highest compressive strength was 88.8±2.6 MPa, which exceeded the lower limit of ISO 5833 but was lower than that of the SBF-soaked reference. The increase of additives caused the

decline in compressive strength. In view of balancing apatite formation and clinical standard ISO 5833, BisP is more suitable as an additive for bioactive PMMA bone cement, and the optimal modification is a combination of 30 mass% of BisP and 20 mass% of $Ca(CH_3COO)_2$.

Introduction

As one kind of clinical material used for anchoring artificial hip joints to contiguous bone, polymethylmethacrylate (PMMA) bone cement has been paid much attention in the orthopedic field because of its better performance at the early recovery stage [1]. However, one significant problem is that PMMA cement lacks chemical bonding ability to bone. Intrinsic mechanical interlocking [2] is insufficient to sustain long-term stable implantation, so loosening between the cement and the implant is liable to occur.

It is essential to develop a biocompatible and adhesive PMMA bone cement for implantation without loosening. Some bioactive materials such as bioglass 45S5 [3, 4] and glass-ceramic A-W [5, 6] can generate a physiologically active bone-like apatite that creates a tight contact with living bone when implanted into the body environment. Incorporating such fillers into PMMA cement by mechanical mixing has also achieved the purpose of improved bone bonding [7], but this method still faces challenges in its details. For example, the formation of apatite was restricted to spots where the bioactive particles could be exposed to body fluid, and acquiring a better performance for affinity and osteoconductivity required an increase in the content of glass bead filler to 70 wt% [8]. The addition of massive amounts of bioactive powder may limit the physical properties of PMMA cement. Therefore, an alternative design for the fabrication of bioactive PMMA bone cement needs to be developed.

It has been revealed that simulated body fluid (SBF), whose composition is nearly equal to that of human blood plasma [9], has a similar ability to body fluid for the production of bone mineral apatite [10]. Therefore, studies [11] related to the reaction mechanism between bioactive materials and SBF could be viewed as evidence to understand the formation process of apatite, and some functional groups such as Si-OH [12], -COOH [13], or PO_4H_2 [14] played an

important role in attracting apatite nucleation while Ca^{2+} ions released into SBF accelerated the growth of apatite. These findings suggest that utilization of combinations of Si-OH groups and Ca^{2+} ions can possibly equip PMMA bone cement with apatite-forming ability. A previous study recommended calcium acetate as the ideal choice of calcium source, because of its appropriate solubility, satisfactory performance on setting time, and compressive strength among all calcium salts [15]. Tanahashi and Matsuda [14] discovered that the potentials of functional groups differed from one another in the aspect of inducing apatite nucleation. Because the nucleation rate decreased in the order of $PO_4H_2 >$ -COOH $>>$ -$CONH_2 \approx$ -OH $>$ -NH_2, a phosphate group (PO_4H_2) was considered to be the optimal option [14]. It was reported that addition of phosphorylated hydroxyethylmethacrylate (HEMA-P) to the powder phase of PMMA cement promoted calcium phosphate mineralization in cell culture media, although improvement of SaOs-2 cell differentiation was not observed [16]. It is expected that addition of monomers with a phosphate group to the liquid phase would produce a cement with higher homogeneity.

In the present study, two phosphate group-containing monomers, phosphoric acid 2-hydroxyethyl methacrylate ester (Pa2hme) and Bis [2-(methacryloyloxy)ethyl] phosphate (BisP), were employed to supply a phosphate group (PO_4H_2), and their chemical structures were shown in **Figure 1(a)** and **Figure 1(b),** respectively. The primary aim was to develop a bioactive PMMA bone cement by modification with combinations of various amounts of calcium acetate and phosphate group-containing monomers, and the effects of these additives on the properties of the prepared cements were also investigated. Bioactivity was estimated by the apatite-forming ability in an SBF environment, and setting time and compressive strength were examined as workability and mechanical properties, respectively. The contents of calcium acetate and monomers were also optimized for practical application in clinical settings.

Materials and Methods

All chemical regents used for the preparation and analyses in our study were of reagent grade without further purification. PMMA powders with a molecular weight about 70,000 and an average grain size of 4 μm were supplied by Sekisui Plastics Industries (Tokyo, Japan). Calcium acetate was produced by sintering calcium acetate monohydrate ($Ca(CH_3COO)_2 \cdot H_2O$; Wako Chemical Industries, Osaka, Japan) at 220°C for 2 h and sieving to a particle size of <44 μm, followed by storage at 120°C before cement preparation.

Cement preparation

The sources for PMMA cement preparation were divided into two parts: powder source and liquid source. For the powder source, PMMA powders were mixed with pretreated $Ca(CH_3COO)_2$ powders combined with the polymerization initiator benzoyl peroxide (BPO; Wako Chemical Industries). For the liquid source, a mixture consisting of methylmethacrylate (MMA) liquid (Wako Chemical Industries), Pa2hme or BisP monomer (Aldrich, Tokyo, Japan), and N,N-dimethyl-p-toluidine (DmpT; Wako Chemical Industries) as a polymerization accelerator was used. The contents of the additives and the detailed compositions of the powder and liquid are shown in **Table 1**. The sample prepared with P00 and L00 (viewed as the reference) had the same composition as commercially available PMMA bone cement CMW® 1 (DePuy International Ltd., Leeds, England). The mixing ratio of powder/liquid was 1:0.5 (g/g), and the whole preparation process was maintained at 23±2°C with a relative humidity of 50±10%.

Setting time tests

A mixed paste of 5 g of cement was used for determination of the setting time. For this, a thermocouple probe (plamic 100 Ω) connected to a thermo recorder (TR-81; T&D Corp., Matsumoto, Japan) was installed into the center of the paste to test the curing temperature per second, until the temperature started to drop. The setting time was defined as the time corresponding to $(T_{max}+T_{start.})/2$ (T_{max}: maximum temperature; T_{start}: temperature at start of setting) on the temperature/time curve according to ISO 5833 [17]. The tests were repeated four times for each combination. All of the setting times are presented as means ± SD.

Bioactivity evaluation in SBF

Bioactivity was evaluated by the formation of apatite on the cement surface in a simulated body environment. SBF (in mol m^{-3}: 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, SO$_4^{2-}$ 0.5) was prepared by dissolving the initial reagents (NaCl, NaHCO$_3$, KCl, K$_2$HPO$_4$·3H$_2$O, MgCl$_2$·6H$_2$O, CaCl$_2$, Na$_2$SO$_4$) in ultrapure water and buffering to pH 7.40 with (CH$_2$OH)$_3$CNH$_2$ and an appropriate amount of 1 M HCl solution. Further details of the SBF preparation were described in a previous report [10]. The cements were polished with #1000 SiC paper, cut into rectangular pieces with dimensions of 10×15×1 mm^3, and stored in plastic containers filled with 35 mL of SBF at 37°C. After soaking for designated periods (1, 3, 7, and 14 days), the cements were removed, rinsed, and dried at room temperature. A thin-film X-ray diffractometer (TF-XRD) (MXP3V; MAC Science Ltd., Yokohama, Japan) and scanning electron microscope (SEM) (S-3500N; Hitachi High-Technologies, Tokyo, Japan) were employed to investigate the surface changes in the structure and morphology of the SBF-soaked cements. The TF-XRD patterns were obtained using a step scanning mode at 0.02° steps per second with CuKα radiation. Before SEM observation, a thin film of carbon was sputter-coated on all specimens. A pH meter (F-23IIC; Horiba Ltd., Kyoto, Japan) was introduced to detect the

pH values of the SBF used for bioactivity examinations after the designated periods. The concentrations of calcium (Ca) in SBF after the same periods were measured by inductively coupled plasma-optical emission spectrometry (ICP-OES) (Optima 4300 DV; PerkinElmer Inc., Waltham, MA).

Mechanical measurement

Cylindrical samples of 6 mm in diameter and 12 mm in height were utilized for compressive strength measurement. Samples of all specimens before complete hardening were immersed in SBF at 37°C for 7 days, and then subjected to a compressive load with a crosshead speed of 20 mm/min controlled by a Universal Testing Machine (Autograph AG-1; Shimadzu Co., Kyoto, Japan) until fracture occurred. The compressive strength was calculated by the fracture load and the sample's cross-sectional area. The means and SDs were collected from ten specimens for each combination.

RESULTS

It was noted that P2ahme only dissolved well in the MMA liquid phase without separation beyond 30 mass%. In addition, the cements prepared with P2ahme50# and CA20% remained in a dough state after standing for 2 h. Therefore, these preparations were only subjected to bioactivity examination.

Setting behavior

Table 2 lists the setting times of all cements prepared with the combinations of calcium acetate and P2ahme or BisP under various contents. The combinations of $Ca(CH_3COO)_2$ and monomers led to accelerated setting compared with the reference sample. Comparisons among all the modified cements revealed that the P2ahme-based cements had longer setting times than

the BisP-based cements when modified with the same content of $Ca(CH_3COO)_2$. Under the same content of both monomers, the samples with $Ca(CH_3COO)_2$/monomers mass ratios close to the powder/liquid mixing ratio (2:1) showed a tendency to exhibit a shorter setting time. Both increases and decreases in the amount of $Ca(CH_3COO)_2$ prolonged the setting time.

Characterization of apatite formation

Figure 2 shows SEM photographs of the surface morphologies of cements modified with the combinations of various contents of $Ca(CH_3COO)_2$ and monomers after soaking in SBF for 14 days. Only scratches were observed on the surface of the reference sample. The other photographs shown in Figure 1(b), and (h) to (m) retained similar surface features to the reference sample, meaning that no precipitates were deposited on these cements. Meanwhile, the surfaces of the remaining samples were covered with a layer composed of homogeneous precipitated particles, and the individual particles were spherical.

Figure 3 shows the TF-XRD patterns of the reference sample and the cements covered with a precipitated layer after soaking in SBF for various periods. The peaks with low crystallinity appearing at about 26°, 32°, and 34° in 2θ were assigned to the diffractions of apatite on the basis of JCPDS Card No. 09-0432. Therefore, the spherical deposits observed under the SEM were identified as low-crystallized apatite by comparison with the results for the reference sample.

The apatite-forming ability of the cements with various contents of $Ca(CH_3COO)_2$ and monomers in SBF was judged by the TF-XRD results, and the evaluations are summarized in Table 3. The induction period varied from 1 to 14 days depending on the combinations of $Ca(CH_3COO)_2$ and monomers. The BisP-based cements exhibited better performances than the

P2ahme-based cements. An increase in $Ca(CH_3COO)_2$ accelerated the formation rate of apatite, while increases in the monomers rather delayed the formation rate.

Variation in compressive strength

The compressive strength of the cements as a function of the contents of additives after 7 days of soaking in SBF are summarized in **Figure 4**. The highest compressive strength was 88.8±2.6 MPa, and still lower than that of the SBF-soaked reference (96.9±7.2 MPa). The cements prepared with Bis30# and CA20%, Bis30# and CA35%, and Bis50# and CA20% as well as P2ahme30# and CA20% exceeded the lower limit of ISO 5833 [17]. It was clearly seen that the compressive strength decreased with increases in the additives, and that P2ahme produced greater deterioration than BisP under the same $Ca(CH_3COO)_2$ content.

Figure 5 shows the changes in the concentration of Ca^{2+} ions in SBF (Figure 5(a)) and the corresponding pH values of SBF measured at 37°C (Figure 5(b)) after various periods of cement immersion. The rapid release of Ca^{2+} ions was completed within 3 days of soaking for most of the specimens. As more $Ca(CH_3COO)_2$ was added to the cements, more Ca^{2+} ions were released irrespective of the formation of apatite. The contents of both monomers had no significant influence on the Ca^{2+} ion release. Generally, hydrolysis of acetate ions (CH_3COO^-) provides OH^- to increase the pH. Therefore, it is assumed that the decrease in pH was induced by the release of acidic monomers or consumption of OH^- during the apatite precipitation.

Discussion

The acceleration of cement setting observed in our study is consistent with the results for modification of PMMA cement with HEMA-P [16]. Considering the corresponding relationship between the shortest time and the mass ratio of $Ca(CH_3COO)_2$/monomer, it is assumed that the

ionic phosphate-containing monomers and Ca^{2+} counteracted each other in the condition close to the powder/liquid mixing ratio. However, no regular variation could be found in the relationship of the setting time and the contents of both monomers, because a high content (50#) of monomers did not just prolong the setting, but damaged the radical polymerization reaction (as seen the specimen prepared with P2ahme50# and CA20%).

Incorporation of $Ca(CH_3COO)_2$ and phosphate group-containing monomers provided the traditional PMMA bone cement with bioactivity in terms of apatite formation. In addition, the generation of a bioactive surface consisting of spherical apatite particles under SEM observation indicates that this concept successfully overcame the remaining drawback in the bioactivity modification by adopting bioactive glass bead fillers. Compared with combinations of calcium chloride ($CaCl_2$) and methacryloxypropyltrimethoxysilane (MPS), the phosphate (PO_4H_2) in the structure of P2ahme or BisP shares the same role as the silane (Si-OH) [18]. Specifically, these sufficient functional groups are uniformly distributed on the cement surface and initiate heterogeneous nucleation of apatite, while continuous release of Ca^{2+} ions boosts its concentration in the surrounding environment, leading to an increasing supersaturation degree with respect to apatite, and thereby increasing the amount of $Ca(CH_3COO)_2$ to shorten the apatite-forming period of the modified cements. However, the increase in $Ca(CH_3COO)_2$ in the cement modified with 50 mass% of the monomers did not enhance the apatite-forming ability. A possible reason is that the condition produced by the pH of SBF combined with the ions (Ca^{2+} or PO_4^{3-}) on the surface was not suitable for apatite precipitation (as seen in Figure 5 (a, b)). On the other hand, incorporation of $Ca(CH_3COO)_2$ and P2ahme or BisP was incapable of making up the loss of compressive strength from the replaced parts of the cements, and thus more additives led to greater deterioration in the mechanical strengths, while the continuous release of Ca^{2+} ions

(seen in Figure 5. (a)) left pores in the modified cements, which caused further loss of strength after exposure to SBF [19]. Even if the pores in bioactive PMMA cements could be filled by apatite, tiny amounts of apatite were unable to sustain the strength of the cements.

Consequently, BisP was more suitable than P2ahme as a modifier for PMMA bone cement, and the optimized modification to satisfy practical standard ISO 5833 was obtained by addition of 30 mass% of BisP and 20 mass% of $Ca(CH_3COO)_2$, when the bioactivity and mechanical properties in this study were taken into consideration. Although the setting time of this optimal modified cement just passed the lower limit of ISO 5833, the monomer BisP is unlike P2ahme, and still has the potential for lowering of its content in the liquid phase, which means that not only the setting time, but also the mechanical strength in a balance with the bioactivity can be further improved by choosing appropriate combinations of both additives. Deeper optimization related to the contents of $Ca(CH_3COO)_2$ and BisP should be investigated in a future study.

CONCLUSIONS

Modification with $Ca(CH_3COO)_2$ and a phosphate group-containing monomer (P2ahme or BisP) can equip PMMA bone cement with apatite-forming ability in simulated body environment, which is expected to bring a higher potential of bone bonding once implanted into body. The monomer BisP showed better performance than Pa2hme on the apatite-forming ability and mechanical strength of the cement. Increasing the content of $Ca(CH_3COO)_2$ significantly shortened the formation period of the bioactive layer, while high ratios of all additives in modified cements resulted in deterioration of the compressive strength. Incorporation of 30 mass% of BisP and 20 mass% of $Ca(CH_3COO)_2$ was identified as the optimized modification with a

view to a balance of bioactivity and practical standard ISO 5833. The combinations of $Ca(CH_3COO)_2$ and phosphate group-containing monomers expand the feasibility for the design of bioactive bone cements for orthopedic use.

Acknowledgments

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Table 1. Detailed constituents of the powder and liquid phases

CA	$\dfrac{CA}{PMMA + CA}$	powder (mass ratio)			XX	$\dfrac{XX}{MMA + XX}$	liquid (mass ratio)		
		PMMA	CA	BPO			MMA	XX	DmpT
P00	0.00	0.971	0	0.029	L00	0.00	0.496	0	0.004
20%	0.20	0.777	0.194	0.029					
35%	0.35	0.631	0.340	0.029	30#	0.30	0.347	0.149	0.004
50%	0.50	0.486	0.485	0.029	50#	0.50	0.248	0.248	0.004

CA: heat-treated $Ca(CH_3COO)_2$. XX: phosphate group-containing monomer (Pa2hme or BisP).

Table 2. Setting times for the cements containing various contents of $Ca(CH_3COO)_2$ and monomers

Cement composition	Setting time (s)		
	CA20%	CA35%	CA50%
Pa2hme30#	215 ± 18	183 ± 16	200 ± 7
Bis30#	185 ± 8	159 ± 3	168 ± 8
Pa2hme50#	∞	247 ± 6	192 ± 17
Bis50#	210 ± 10	135 ± 7	120 ± 10

Reference: 361±25 s.
∞: No heat release was detected; viewed as an unset cement.

Table 3. Apatite-forming ability of PMMA cements modified with combinations of various amounts of $Ca(CH_3COO)_2$ and monomers (P2ahme or BisP) in the SBF environment, based on the TF-XRD results[#] of designated soaking periods

Cement composition	apatite-forming period (d)		
	CA20%	CA35%	CA50%
Pa2hme30#	–	+	++
BisP30#	+	++	+++
Pa2hme50#	–	–	–
BisP50#	–	–	–

[#]–: No apatite found after 14 days; +: apatite formed within 14 days; ++: apatite formed within 3 days; +++: apatite formed within 1 day.
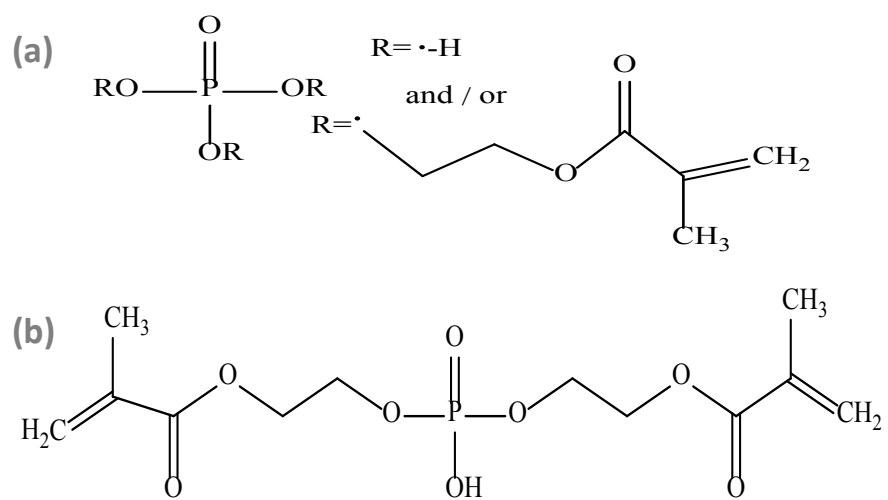
Figure 1. (a, b) Chemical structures of phosphoric acid 2-hydroxyethyl methacrylate ester (a) and Bis [2-(methacryloyloxy)ethyl] phosphate (b)
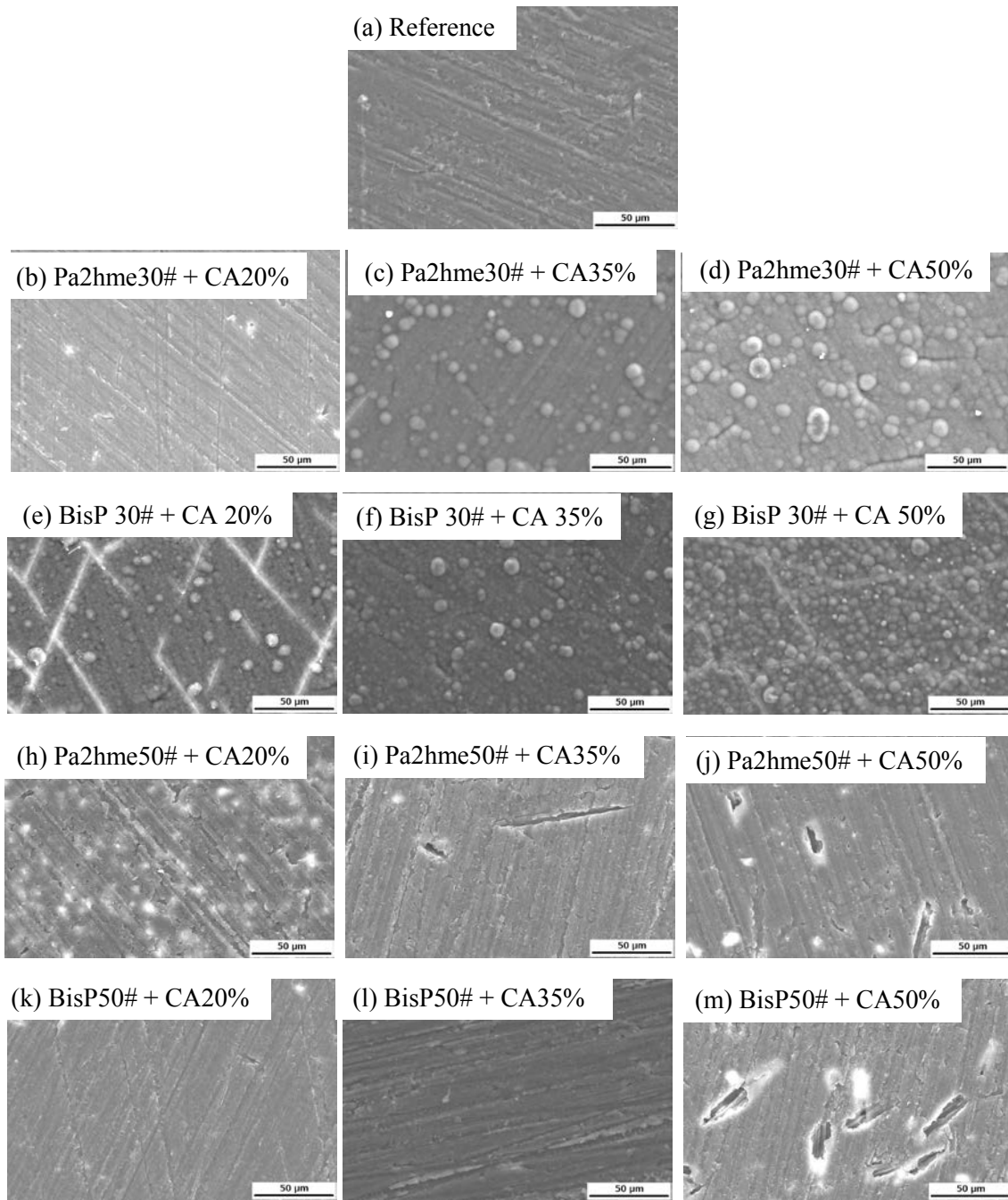
(a) Reference

(b) Pa2hme30# + CA20%

(c) Pa2hme30# + CA35%

(d) Pa2hme30# + CA50%

(e) BisP 30# + CA 20%

(f) BisP 30# + CA 35%

(g) BisP 30# + CA 50%

(h) Pa2hme50# + CA20%

(i) Pa2hme50# + CA35%

(j) Pa2hme50# + CA50%

(k) BisP50# + CA20%

(l) BisP50# + CA35%

(m) BisP50# + CA50%

Figure 2. SEM photographs of the surfaces of cements modified with the combinations of various amounts of $Ca(CH_3COO)_2$ and P2ahme or BisP after soaking in SBF for 14 days.
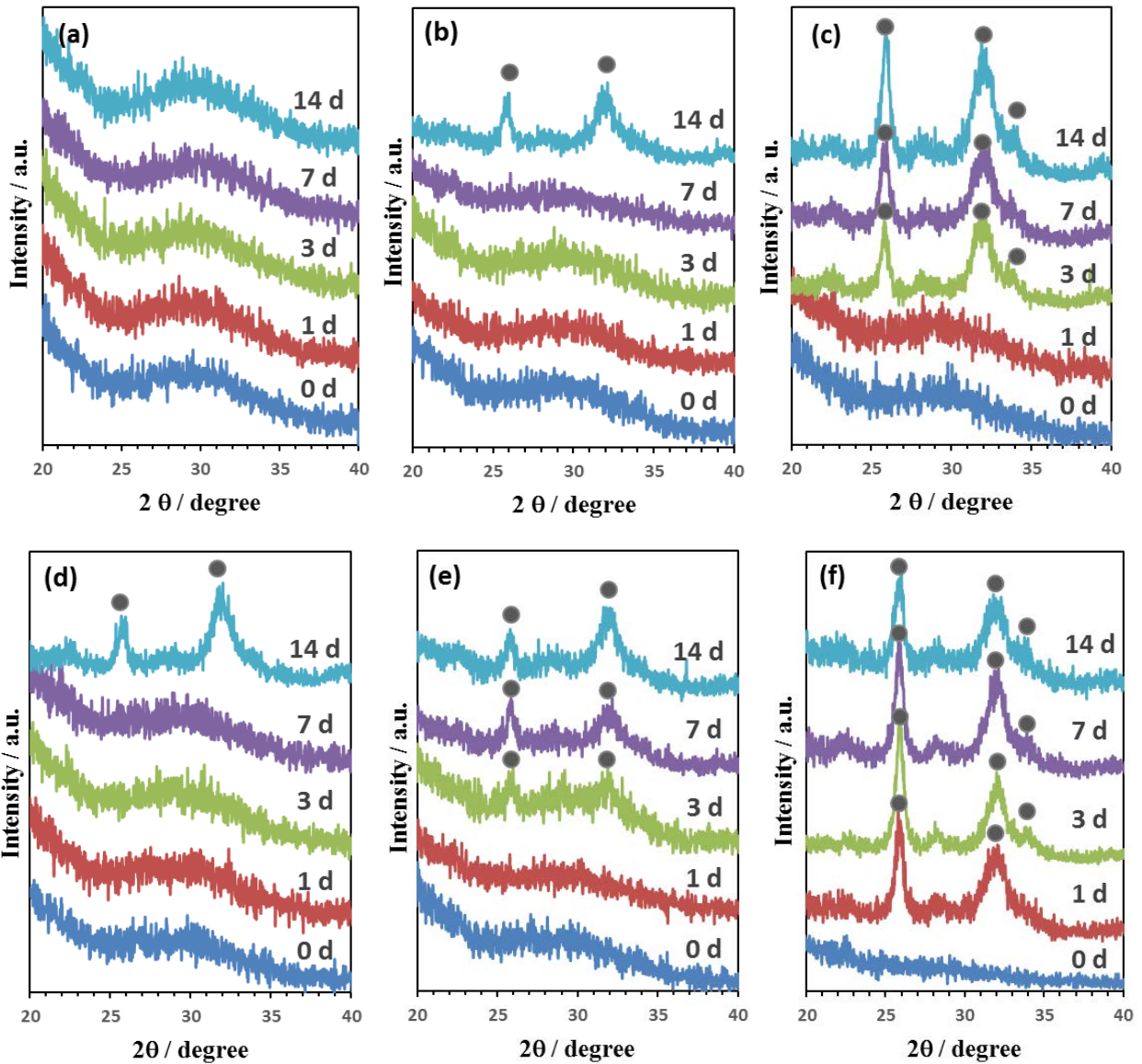
Figure 3. TF-XRD patterns of the surfaces of the cements prepared with (a) P00 and L00, (b) Pa2hme30# and CA35%, (c) Pa2hme30# and CA50%, (d) BisP30# and CA20%, (e) BisP30# and+ CA35%, and (f) BisP30# and CA50% before (0 d) and after soaking in SBF for the designated periods. Black circles (⬤): apatite.
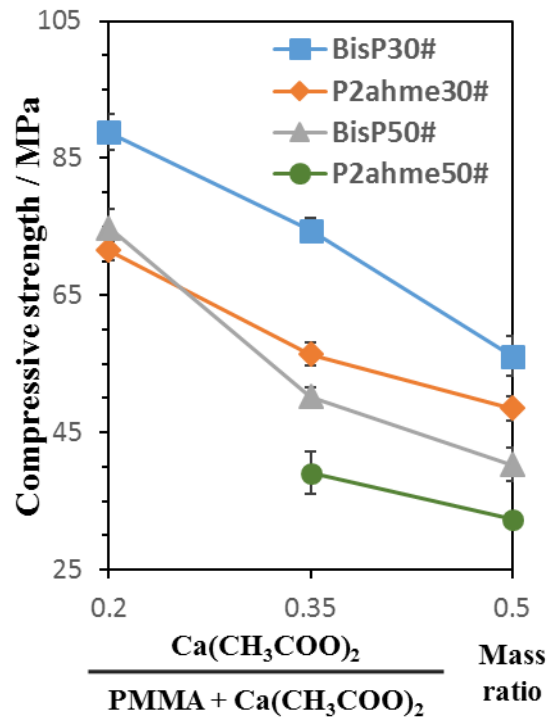
Figure 4. Variations in compressive strength of the cements as a function of the contents of $Ca(CH_3COO)_2$ and monomers after soaking in SBF for 7 days.
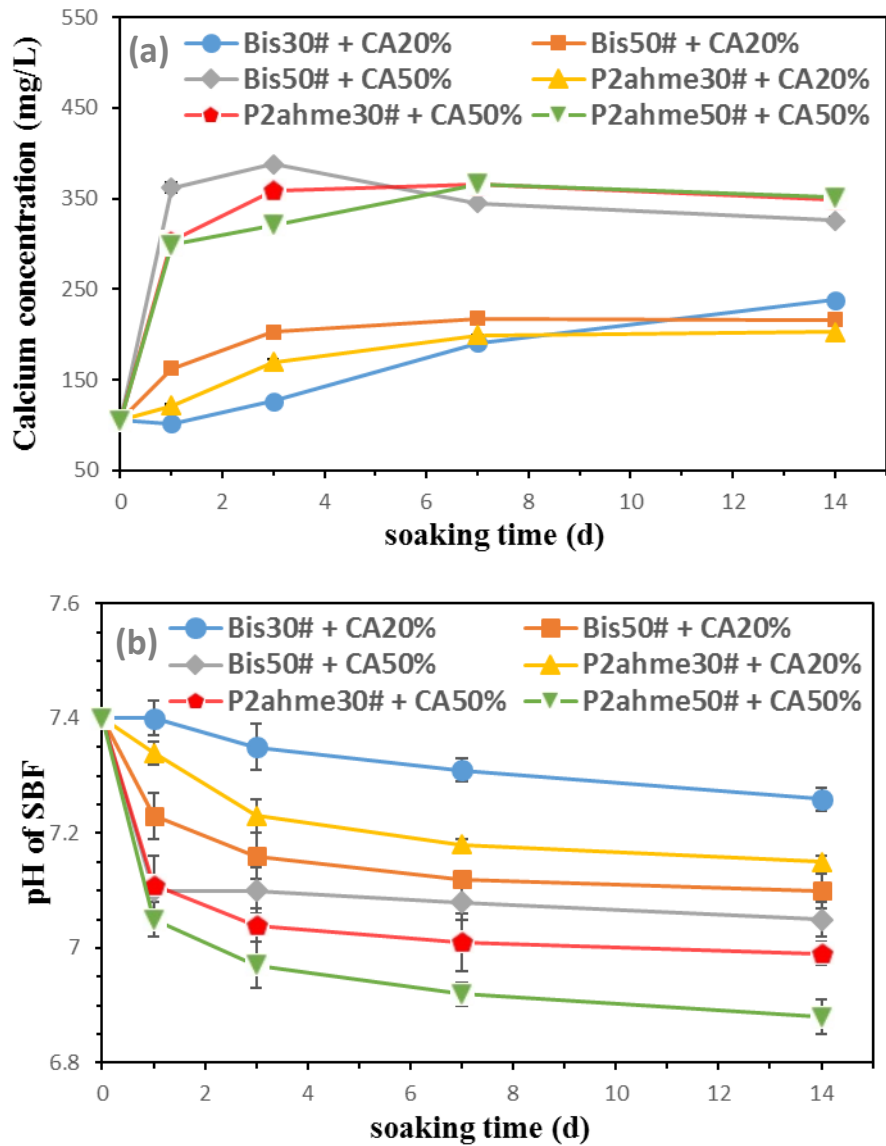
Figure 5. (a, b) Concentrations of Ca^{2+} ions in SBF (a) and pH values of SBF measured at 37°C (b) after soaking the modified cements for the designated periods.