ISSN 0020-1685, Inorganic Materials, 2017, Vol. 53, No. 3, pp. 292–299. © Pleiades Publishing, Ltd., 2017.
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Microstructure and Properties of α-Tricalcium Phosphate-Based Bone Cement

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Received September 22, 2016

Abstract—This paper examines the physicochemical properties and microstructure of brushite calcium phosphate cements possessing strength acceptable for application in surgery (15–20 MPa) and ensuring an optimal acidity (pH 6.5–7.5) of solutions in contact with them. Holding in a physiological saline produces significant changes in the microstructure of the cement relative to that before immersion in the solution: it causes a transformation of the most soluble components into platelike hydroxyapatite crystals.

Keywords: brushite calcium phosphate cements, behavior in model media, microstructure, compressive strength

DOI: 10.1134/S0020168517030049

INTRODUCTION

Surgical treatment in oncology, traumatology, and orthopedics often leads to the formation of extensive bone defects. They are treated using calcium phosphate materials that offer biocompatibility and osteoconductivity. Calcium phosphate ceramics have been applied in medicine for several decades now [1], but their main drawbacks are that they have a low bioresorption rate in comparison with the rate of new bone tissue formation and are incapable of filling complex-shaped defects.

Calcium phosphate cements (CPCs) are free from the inherent drawbacks of the ceramic materials, they are easy to use in the case of surgical intervention, are capable of filling defects of any configuration, and are osteoconductive materials, that is, are capable of supporting bone tissue cell ingrowth into a material. An important advantage of the CPCs is that their setting is not accompanied by any heat release, which otherwise might cause a burn and necrosis of the surrounding tissue, like in the case of polyacrylate-based polymer cements. Cements in which the major phase is brushite, or dicalcium phosphate dihydrate (DCPD), $CaHPO_4 \cdot 2H_2O$, are referred to as brushite CPCs and have obvious advantages over other synthetic biomaterials for bone regeneration: the rate of their bioresorption is comparable to the rate of new bone tissue formation [2]. However, the increased acidity due to the incompleteness of brushite formation reaction and the presence of the residual acid component of the starting mixture in the CPC implant location, which influences their cyto- and biocompatibility, and their low mechanical strength prevent wide clinical use of brushite CPCs.

There is some interest in choosing α-$Ca_3(PO_4)_2$ (α-TCP) as a starting solid component [2], which is due to two causes.

1. When present in excess relative to the stoichiometry of the main reaction that takes place in a cement mixture and leads to the formation of DCPD, unreacted α-TCP remains in the cement stone. Since α-TCP is rather readily soluble, its dissolution during the cement resorption process, is accompanied by orthophosphate anion hydrolysis: $PO_4^{3-} + H_2O \leftrightarrow HPO_4^{2-} + OH^-$. This compensates for the reduction in pH accompanying the resorption of single-phase brushite CPC.

2. The presence of unreacted α-TCP particles in cement stone may prove to be useful for strengthening the material. Mechanisms that inhibit crack formation may include reorientation and branching of a crack, bridging of its faces by a foreign particle, which is characteristic of precipitation hardening, and dissipation of the energy of a growing crack through microcracking in a limited zone. The last mechanism is of interest

because α-TCP particles initially contain a large number of microcracks.

The acidic pH of a brushite CPC can be compensated for by producing a composite cement containing particles of a calcium phosphate more alkaline than brushite, with Ca/P > 1.5, for example, hydroxyapatite (HA), $Ca_{10}(PO_4)_6(OH)_2$. For the same purpose (raising pH and inhibiting crack growth), it appears promising to introduce ceramic granules of carbonate hydroxyapatite (CHA)—whose composition is identical to that of bone mineral and whose resorbability is well documented—into the composition of cement stone.

The purpose of this work is to develop physicochemical principles for designing the composition and microstructure of brushite CPCs with a strength suitable for application in surgery (15–20 MPa) and optimal acidity (pH 6.5–7.5) of solutions in contact with them. Our main task can be formulated as analysis of the effect of the composition and microstructure of CPC on its strength characteristics and behavior in solutions.

EXPERIMENTAL

α-TCP was prepared as described by Kolmas et al. [3], by firing a stoichiometric mixture of calcium carbonate and calcium pyrophosphate according to the reaction scheme

$$CaCO_3 + Ca_2P_2O_7 \rightarrow Ca_3(PO_4)_2 + CO_2 + H_2O. \quad (1)$$

Eventually, SiO_2 (no more than 0.1 wt %) was added to the starting mixture to stabilize the high-temperature phase α-TCP.

The reaction product was sintered in a compartment furnace at 1400°C for 2 h. The resultant material was ground in butanol in a planetary mill with corundum balls at a powder-to-ball weight ratio of 1 : 10. After drying, the powder was run through nylon sieves with aperture sizes of 400 and 200 μm.

Since α-TCP solubility is rather high (especially in acid solutions), the setting time of brushite CPCs based on such a phosphate does not exceed 2 min, which is unsatisfactory for practical applications. Plokhikh et al. [4] proposed sodium hexametaphosphate as a modifier of cement paste, retarding its setting, which allowed the setting of a β-TCP-based brushite CPC to be retarded to 30 min. In this study, sodium hexametaphosphate was also used as a set retarder for the CPC. It should be taken into account, however, that, depending on cooling conditions, commercially available sodium hexametaphosphate, prepared by melting sodium dihydrogen phosphate, can be qualified as Graham's salt (glassy mass resulting from rapid cooling) or Kurrol's salt (fibrous mass resulting from slow cooling). In any case, sodium hexametaphosphate is a mixture of long-chain polyphosphates, containing three- and four-membered ring metaphosphates as impurities [5]. In this study, the sodium hexametaphosphate preparation conditions corresponded to Kurrol's salt with a large percentage of long-chain polyphosphates: sodium dihydrogen phosphate was dehydrated in a muffle furnace at 600°C for 2 h and then furnace-cooled, which can be formally represented by the scheme

$$6NaH_2PO_4 \rightarrow (NaPO_3)_6 + 6H_2O. \quad (2)$$

CHA was synthesized as described by Komlev et al. [9]. Ceramics were obtained by sintering precompacted mixtures [7] in a muffle furnace at a temperature of 900°C. Ceramic CHA granules containing 6 wt % carbonate groups were produced by crushing the densely sintered CHA ceramics, followed by separation of 400- to 600-μm size fractions.

Cement powder was prepared by mixing α-TCP powder (10 g), sodium hexametaphosphate (1 g), and CHA granules (1 g) with corundum balls in butanol at a powder-to-ball weight ratio of 1 : 4. As a gauging liquid, we used a 30% aqueous magnesium dihydrogen phosphate solution. Cement was prepared by mixing the cement powder, gauging liquid, and glycerol. The experimentally determined cement powder : gauging liquid weight ratio was 4 : 3. It was adjusted so that the cement paste could be conveniently cast in a mold, with allowance for strength test results [2]. To improve the plasticity and moldability of the cement paste, up to 5 wt % glycerol was added during cement mixing. Cement samples were shaped into cylinders 8 mm in diameter and 16 mm in height in a Teflon die. The pH value was monitored with an Ekspert-001 pH meter (Russia). The setting time was determined using a Vicat apparatus in conformity with the ISO 1566 standard.

The phase composition of the cement samples was determined by X-ray diffraction on a Rigaku D/Max-2500 rotating anode diffractometer (Japan). Intensity data were collected in reflection geometry with CuK_α radiation 2 h after cement mixing.

The microstructure of the set cement were examined by scanning electron microscopy (SEM) on a Tescan Vega II (Czechia) at an accelerating voltage of 20 kV, using secondary electron imaging. The specimens used were precoated with gold. The microstructure of the starting TCP powders was examined by field emission scanning electron microscopy on a LEO Supra 50 VP (Carl Zeiss, Germany). Images were obtained in low vacuum at an accelerating voltage of 20 kV (VPSE secondary electron detector) or at voltages in the range 3–20 kV (SE2 detector).

As a model medium in studies of cement solubility, we used an aqueous 0.9% sodium chloride solution

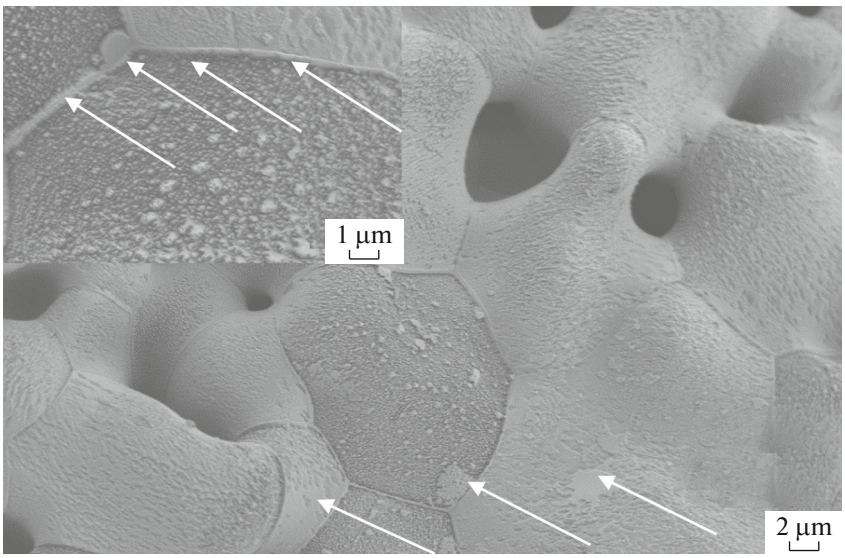

Fig. 1. Micrograph of sintered α-TCP powder after a partial transformation into β-TCP during slow cooling from 1400°C; etching with boiling water. The arrows mark a poorly soluble β-TCP layer on the surface of α-TCP grains.

containing tris(hydroxymethyl)aminomethane. The cement solubility was assessed from changes in the concentration of calcium ions in solution, which was determined using an ion-selective electrode (Elit-041 Ekoniks ekspress) for determining calcium ions.

The compressive strength of the cement samples was determined at a crosshead speed of 1 mm/min on a P-05 electromechanical testing machine equipped with a Spider multichannel measuring system. To obtain statistically significant results, five tests were carried out for each type of specimen.

Ionic equilibria in solutions whose ionic composition corresponded to that of the CPC under investigation were modeled with Medusa/Hydra software [8] at 25°C.

RESULTS AND DISCUSSION

β-TCP impurities reduce the strength of cement powders [9], so it is important to obtain α-TCP with no β-TCP impurities. Analysis of the phase composition of the powder showed that, for complete transformation into α-TCP, the holding time of β-TCP at a given temperature (above 1200°C) was of great importance: at least 0.5 h at 1400°C. Also important was the rate of cooling from the α-TCP synthesis temperature. The adequate cooling rate was estimated at 5°C/min as a result of isothermal experiments with X-ray diffraction analysis of the products and using dilatometry at a variable temperature to follow the α–β transformation of TCP. We found conditions for the preparation of a phase-pure α-TCP powder for obtaining a solid cement phase. The $\beta \rightarrow \alpha$ transformation begins on grain boundaries and can readily be detected because the α- and β-TCP phases differ in solubility (in water and acid etchants) (Fig. 1). Thus, surface β-TCP impurities inhibit phosphate dissolution in the gauging liquid and reduce the hydraulic activity of the cement.

To stabilize the α-TCP phase, a small amount of silicate ions (no more than 0.1 wt %) was added during synthesis [10]. As a result of the doping and cooling at a sufficient rate, we obtained α-TCP powder free of β-TCP impurities.

The mixing of the α-TCP-containing solid cement phase with a $Mg(H_2PO_4)_2$ solution initiates the main reaction, which leads to the formation of the DCPD phase. The reaction can be represented by the scheme

$$\begin{aligned} &Ca_3(PO_4)_2 + Mg(H_2PO_4)_2 + 9H_2O \\ &\rightarrow 3CaHPO_4 \cdot 2H_2O + MgHPO_4 \cdot 3H_2O, \end{aligned} \quad (3)$$

under the assumption that magnesium dihydrogen phosphate converts into newberyite, $MgHPO_4 \cdot 3H_2O$, a thermodynamically stable phase nonisomorphic with brushite (DCPD). Since newberyite crystallizes slowly, through the formation of intermediate crystalline hydrates differing in water content from newberyite, for example, monoclinic phosphorrosslerite, $MgHPO_4 \cdot 7H_2O$ (PDF-2 no. 46-1267), which is structurally similar to DCPD, the main reaction can be represented by a scheme in which the only reaction is a brushite solid solution:

$$\begin{aligned} &Ca_3(PO_4)_2 + Mg(H_2PO_4)_2 + 8H_2O \\ &\rightarrow 4(Ca_{0.75}Mg_{0.25}HPO_4) \cdot 2H_2O. \end{aligned} \quad (4)$$

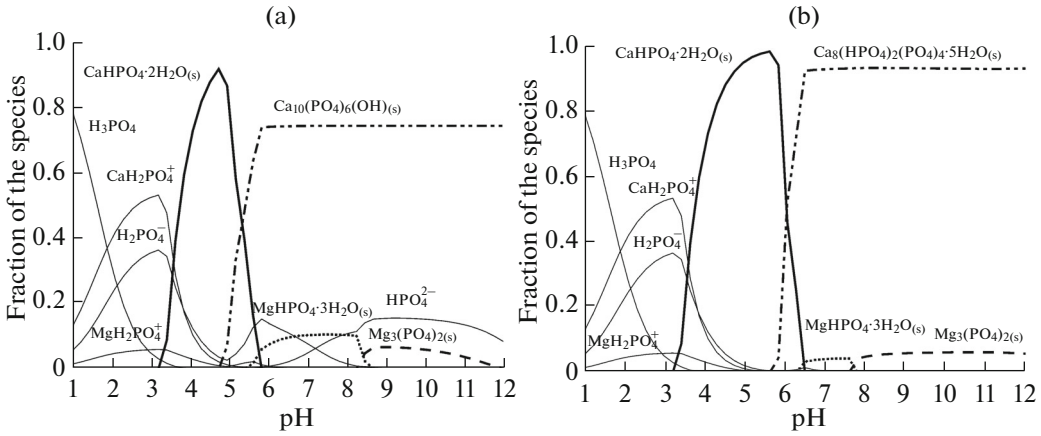

Fig. 2. Effect of pH on the fractions of some soluble complexes and solid phases in the $Ca_3(PO_4)_2$–$Mg(H_2PO_4)_2$–H_2O system at 25°C, with $[Ca^{2+}] = 0.1$ M, $[PO_4^{3-}] = 0.08$ M, and $[Mg^{2+}] = 0.01$ M: (a) thermodynamic control, HA ($Ca_5(PO_4)_3OH$) precipitation is permitted; (b) kinetic control, $Ca_4H(PO_4)_3$ precipitation is permitted, whereas HA is excluded from analysis.

Reactions (3) and (4) involve equimolar amounts of TCP and magnesium dihydrogen phosphate, whereas the α-$Ca_3(PO_4)_2$: $Mg(H_2PO_4)_2$ molar ratio in the cement paste is 3 : 1. Given that some of the magnesium dihydrogen phosphate reacts with the CHA granules,

$$\begin{aligned} &Ca_{10}(PO_4)_6(OH)_{1.8}(CO_3)_{0.1} \\ &+ 4Mg(H_2PO_4)_2 + 26.1H_2O \\ &\rightarrow 14(Ca_{0.71}Mg_{0.29})HPO_4 \cdot 2H_2O + 0.1CO_2, \end{aligned} \quad (5)$$

the amount of unreacted α-TCP in the cement paste is at least two-thirds of its initial amount. Its subsequent evolution depends on pH. In weakly acidic solutions ($6 < pH < 7$), the formation of octacalcium phosphate is possible:

$$\begin{aligned} &2Ca_3(PO_4)_2 + 2CaHPO_4 \cdot 2H_2O \\ &+ H_2O \rightarrow Ca_8(HPO_4)_2(PO_4)_4 \cdot 5H_2O. \end{aligned} \quad (6)$$

In alkaline solutions ($pH > 7$), nonstoichiometric HA will be formed, for example, one with Ca/P = 1.5:

$$3Ca_3(PO_4)_2 + H_2O \rightarrow Ca_9(HPO_4)(PO_4)_5(OH). \quad (7)$$

To understand processes that take place in the $Ca_3(PO_4)_2$–$Mg(H_2PO_4)_2$–H_2O system at different pH values, we carried out thermodynamic modeling of ionic equilibria in solutions with $[Ca^{2+}] = 0.1$ M, $[PO_4^{3-}] = 0.08$ M, and $[Mg^{2+}] = 0.01$ M, that is, in proportions corresponding to the cement paste. We considered two situations: (a) precipitation of all the possible solid phases, including HA, was permitted, that is, complete thermodynamic control was assumed, and (b) HA was excluded from analysis of ionic equilibria, which corresponded to kinetic control, at least in the pH range 5.5–7, where, as a rule, octacalcium phosphate is experimentally observed to be the first to precipitate, even though HA is thermodynamically stable under these conditions (Fig. 2).

Our calculations predict that, at pH above 6, the heterogeneous system under consideration will contain a solid phase more basic than DCPD (octacalcium phosphate or, in a thermodynamic limit, HA) owing to the reaction of the DCPD with the solution. Clearly, in a real cement paste with a low water content, all of the recrystallization processes under consideration will be rather slow. It is worth noting that the precipitation of a magnesium-containing solid phase requires nearly neutral or weakly alkaline pH values. The variation in pH during the mixing process

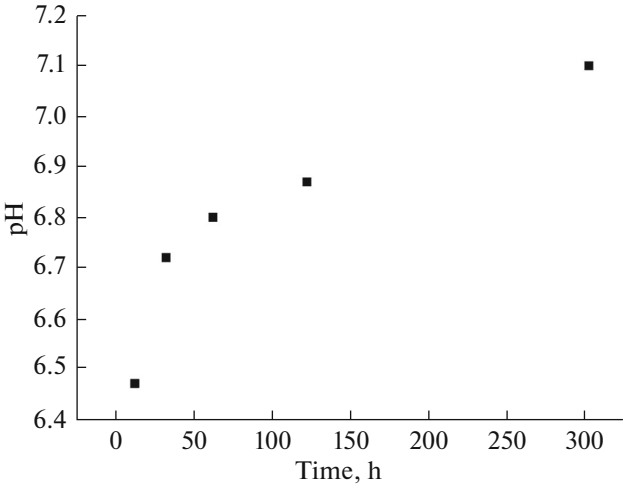

Fig. 3. Variation in the acidity of the cement during the mixing process.

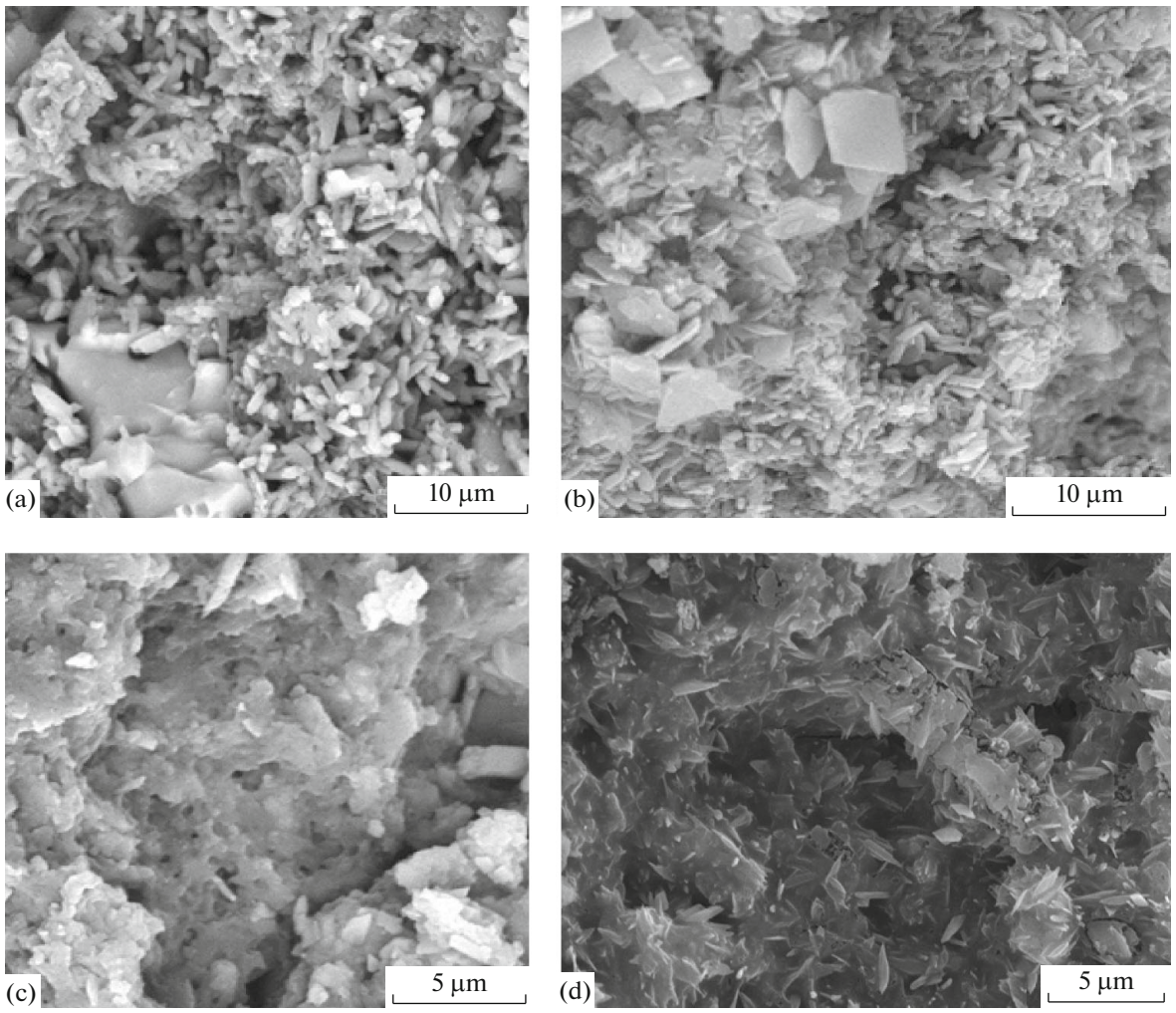

Fig. 4. Microstructure of the cement samples (a) 24 h, (b) 3 days, (c) 7 days, and (d) 14 days after cement mixing.

is illustrated in Fig. 3. It is seen that pH rapidly rises to 6.7–6.8 because magnesium dihydrogen phosphate, an acid salt, participates in the main reaction (3) and (4) and CHA dissolution (6). The subsequent slow growth of pH to neutral and weakly alkaline values is possibly due to the formation of phosphates more basic that DCPD: octacalcium phosphate or HA. Thus, the cements under development are neutral (pH near 7), which is extremely important for their potential application in medicine. Another important aspect of controlling the acidity of the cement was that 10 wt % ceramic CHA granules were added to the cement paste and reacted with the acid solution according to scheme (5).

At 20°C, the setting time of the CPC prepared from pure α-TCP is shorter than 1 min, which is unacceptable in medical applications. Raising the temperature of the cement mixture in the cement mixing process to 40°C further reduces the setting time, because the main reaction is exothermic. To retard cement setting, 5 wt % sodium polyphosphate was added to the cement powder. The mechanism underlying its effect seems to be related to the blocking of the surface of the phosphates through polyanion adsorption, which inhibits both α-TCP dissolution and DCPD crystal growth [4, 11]. To optimize the CPC acidity, dense ceramic CHA granules were added to the cement powder. The addition of ceramic CHA granules reduces the setting time, probably, as a result of local pH changes near the granules, which have carbonate ions on their surface. Without CHA granules, the addition of 5 wt % sodium polyphosphate increases the setting time of the cement to 10 min. The optimal amount of CHA granules added to the cement was experimentally determined to be 10 wt % [12, 13]. The setting time of the cement containing CHA granules is 6–7 min, and its pH 5 min after mixing is 6.9–7.0.

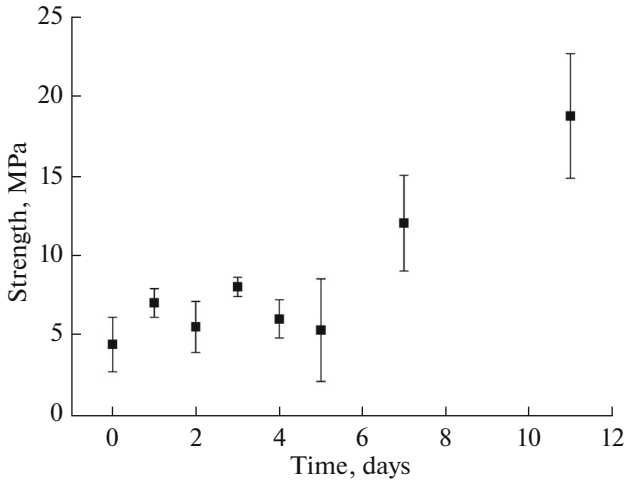

Fig. 5. Compressive strength as a function of the time after cement mixing.

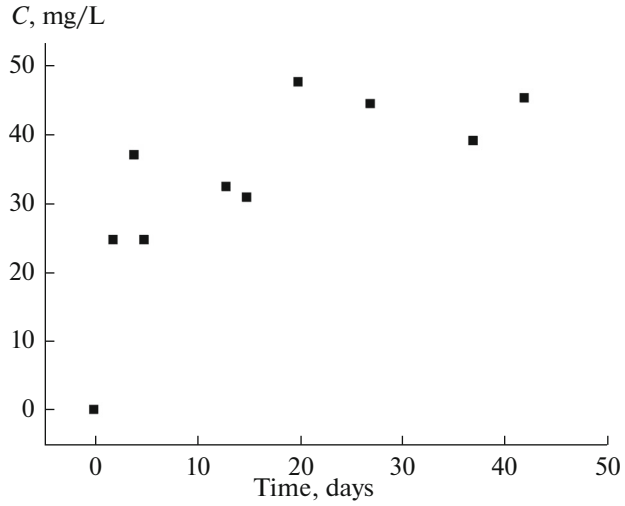

Fig. 6. Calcium concentration in solution as a function of the residence time of the cement in a physiological saline.

The phases identified by X-ray diffraction in the hardened cement are α-TCP and a phase isostructural with HA. The latter phase may originate from the remains of the CHA granules and, in addition, HA may form in the cement stone as a result of the reaction between DCPD and the residual mixing solution at pH > 6 (Fig. 3a) or the hydrolysis of the unreacted α-TCP. Irregularly shaped ceramic particles 5–10 μm in size, probably consisting of α-TCP, were detected by microstructural analysis of the cement (Fig. 4a). Despite the relatively high magnesium content of the cement (about 10–12 wt %), no magnesium-containing phases were detected by X-ray diffraction in our samples. This suggests that scheme (4) represents the main chemical reaction in the cement paste. The HA-containing phase can be attributed to the continuous, poorly crystallized mass detected in the microstructure of the samples having a setting time of one week or longer (Figs. 4c, 4d). During the hardening process, the structure of the samples changes from inhomogeneous, with inclusions of different components, in the first few hours after cement mixing (Fig. 4a) to more homogeneous, with inclusions of ceramic granules, after 24 h (Fig. 4b). The shape of the crystals is typical of DCPD: the crystals have the form of irregularly shaped plates 2 μm in length and 0.5 μm in width. As the time after cement mixing increases, their structure becomes more uniform. After three days, we observe characteristic small DCPD crystals. After 7 days, their size is markedly larger, and there are monolithic regions, with a poorly crystallized component in between (Figs. 4c, 4d).

During the first five days, the strength of the cement ranges from 5 to 8 MPa, typical of the brushite CPC (Fig. 5). As shown earlier [14], the strength of brushite cements typically does not exceed 10 MPa. The low strength of the brushite CPCs is commonly attributed to the small number of phase contacts between the rather large platelike DCPD particles. Moreover, from the purely crystallographic point of view, the chemical bonding energy at a contact between two low-symmetry DCPD crystals is rather low (compared, for example, to the HA/HA contact energy) [4]. Further cement hardening is due to the formation of denser, poorly crystallized regions in the cement stone (Figs. 4b, 4c). It is reasonable to assume that the formation of such regions is due to the further increase in pH and, hence, the formation of HA nanocrystals through the crystallization of amorphous calcium phosphate (it should be noted that the presence of Mg^{2+} ions slows down this process and reduces the HA crystal size). The nanocrystals form a denser microstructure, with stronger HA/HA phase contacts (Fig. 4c).

Thus, the high compressive strength (17–20 MPa) reached in this study is due to the following factors: (1) The ceramic α-TCP particles present in the cement act as reinforcing agents. Moreover, because of the presence of radial cracks in such particles, reaching an α-TCP particle the main crack causes its microcracking, which is accompanied by crack energy dissipation, preventing further crack propagation. (2) Partial DCPD conversion into HA with increasing pH during the CPC hardening process yields a dense nanocrystalline material containing many strong phase contacts, such as HA/HA.

The solubility of the cements was studied in a physiological saline at pH 7.4. The solubility criterion was a change in the concentration of calcium ions in solution. Interaction of the cement with solution involves

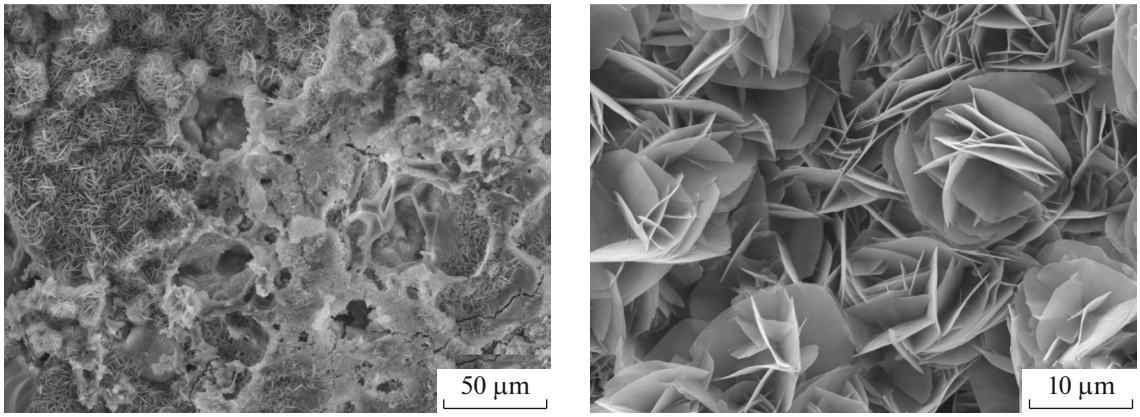

Fig. 7. Microstructure of the cement after holding in a physiological saline for 30 days (different magnifications).

two processes: physical dissolution of the DCPD and residual α-TCP, which leads to an increase in $[Ca^{2+}]$, and chemical reaction, which results in the formation of octacalcium phosphate and/or HA and is accompanied by a decrease in $[Ca^{2+}]$. The time needed for dynamic equilibrium to be reached in the physiological saline at pH 7.4 is at least 40 days (Fig. 6). This strongly suggests that, in the time interval under consideration, dissolution processes prevail over HA (octacalcium phosphate) precipitation, which provides conclusive evidence that the proposed CPC has good resorption properties.

Holding in the physiological saline produces significant changes in the microstructure of the cement relative to that before immersion in the solution: it causes a transformation of the most soluble components, including DCPD and the poorly crystallized material, into platelike HA crystals (Fig. 7).

CONCLUSIONS

The proposed alpha tricalcium phosphate-based brushite cement has a sufficiently high compressive strength (up to 20 MPa) and high pH values of solutions in contact with it (at least 7). This allows us to recommend this cement for medical and biological testing. The cement is a three-phase composite: DCPD/ α-TCP/HA. The presence of α-TCP and HA in the composition of the brushite cement makes it possible to improve the strength characteristics of the cement stone and shift the pH of solutions in equilibrium with it to neutral or weakly alkaline values. Such an approach is potentially attractive for producing high-strength brushite CPCs with acid properties that have a negative effect on the biological microenvironment during the setting process.

ACKNOWLEDGMENTS

This study was supported by the Russian Foundation for Basic Research, grant no. 15-29-04871-ofi_m. The work on tricalcium phosphate synthesis was supported in part by grant no. 15-03-09387-a from the Russian Foundation for Basic Research.

In this study, we used equipment purchased through the Development of the Moscow State University Program.

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Translated by O. Tsarev