ISSN 1027-5495. Functional Materials, 25, No.2 (2018), p. 358-363.
doi:https://doi.org/10.15407/fm25.02.358

Functional materials for medical and biological purposes on the system $CaO–CaF_2–P_2O_5–H_2O$ and additives

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Received April 03, 2018

The system of $CaO–P_2O_5$ has been studied, the polymorphism of $Ca_3(PO_4)_2$ has been verified, the position of binary eutectics and the melting points in them on the $Ca_3(PO_4)_2–Ca_4P_2O_9$ segment have been determined. A diagram of the state of the $CaO–P_2O_5$ system is constructed. The experimental verification of the calculated data by the high-temperature microscopy method *in sity* is performed. The regions of primary crystallization of phases in the system $Ca_3(PO_4)_2–CaCO_3–Ca(OH)_2–H_2O$ are refined. The subsolidus structure of the systems $CaO–CaF_2–P_2O_5–H_2O$ and $CaO–MgO–CaF_2–P_2O_5$ has been studied. The areas promising for the synthesis of materials based on $CaO–P_2O_5–CaF_2–H_2O$ system and additives for the reconstruction of structural defects of the skeleton are established.

Keywords: phase diagram, the $CaO–P_2O_5$ system, polymorphism, high-temperature microscopy, elementary tetrahedras, correction of skeletal disorders.

Исследована система $CaO–P_2O_5$, экспериментально проверен полиморфизм $Ca_3(PO_4)_2$, положение бинарных эвтектик и температур плавления в них на отрезке $Ca_3(PO_4)_2–Ca_4P_2O_9$. Построена диаграмма состояния системы $CaO–P_2O_5$. Выполнена экспериментальная проверка расчетных данных методом высокотемпературной микроскопии *in sity*. Уточнены области первичной кристаллизации фаз в системе $Ca_3(PO_4)_2–CaCO_3–Ca(OH)_2–H_2O$, изучено субсолидусное строение систем $CaO–CaF_2–P_2O_5–H_2O$ и $CaO–MgO–CaF_2–P_2O_5$. Установлены области, перспективные для синтеза материалов на основе четырехкомпонентной системы $CaO–P_2O_5–CaF_2–H_2O$ и добавок для восстановления структурних дефектов скелета.

Функціональні матеріали медико-біологічного призначення на основі системи $CaO–CaF_2–P_2O_5–H_2O$ і домішок. *С.П.Кривільова, В.Ф.Моісєєв.*

Досліджено систему $CaO–P_2O_5$, експериментально перевірено поліморфізм $Ca_3(PO_4)_2$, положення бінарних евтектік і температур плавлення у них на відрізку $Ca_3(PO_4)_2–Ca_4P_2O_9$. Побудовано діаграму системи $CaO–P_2O_5$. Виконано експериментальну перевірку розрахункових даних методом високотемпературної мікроскопії *in sity*. Уточнено області первинної кристалізації фаз у системі $Ca_3(PO_4)_2–CaCO_3–Ca(OH)_2–H_2O$, вивчено субсолідусну будову систем $CaO–CaF_2–P_2O_5–H_2O$ і $CaO–MgO–CaF_2–P_2O_5$. Встановлено області, перспективні для синтезу матеріалів на основі системи $CaO–P_2O_5–CaF_2–H_2O$ і домішок для корекції структурних дефектів скелету.

1. Introduction

The creation of new functional materials for medical and biological purposes is an urgent problem, because for the first time in the history of its development, mankind expects an almost epidemiological increase in the number of elderly people who in the coming decades will massively need help in reconstructive surgery of the osteoarticular system.

Modern biomaterials science offers a wide range of materials — from metals, cermets, oxide glass and bioceramics, to composite materials, gels, designed to repair defects of various genesis, endoprosthetics and targeted delivery of medicaments to problem areas [1–6]. Most of them, are able for a certain time without negative consequences to be in the environment of a living organism and to some extent restore the defects of the skeleton.

But despite numerous and large-scale studies, innovative materials that were no worse than their natural counterparts have not yet been created, as evidenced by the numerous "desperation operations": such as, for example, cardinal joint replacement and the like.

2. Analysis of the literature data and the formulation of the problem

It is known that the composition of bones and teeth on average includes (mass. %): 54,7 CaO, 41.7 P_2O_5, 1.1 MgO, 1.0 NaO, 0.03 K_2O, 1.0 CO_2, and impurities. Therefore, a study of the structure of the CaO–CaF_2–P_2O_5–H_2O system and additives will allow to establish areas promising for the synthesis of materials that, by their properties, can be used to correct defects in the tissues of the skeleton. This will also allow to evaluate the influence of impurities on the operational properties of materials and, thereby, to reduce the number of experimental developments.

One of the most important binary systems for the issues under consideration is the CaO–P_2O_5 system. A large number of studies have been devoted to its study [7, 8]. The presence of a large number of intermediate phases and a number of their phase transitions classify this system as very difficult to construct. This affects the synthesis of calcium phosphates and their combinations. For our purposes, the most interesting area is $Ca_3(PO_4)_2$–$Ca_4P_2O_9$ (C_3P–C_4P), since $Ca_3(PO_4)_2$ is in all respects the most stable phase of this system. On the diagram of the state of the CaO–P_2O_5 system, there is a compound "oxyapatite" $Ca_{10}(PO_4)_6O_2$, the existence of which is not confirmed in practice. For this reason, it is not taken into account by many researchers. Therefore, an attempt was made to synthesize "oxyapatite" ($C_{10}P_3$) in the solid phase from the corresponding oxides, because of the available data on its existence in the temperature range of 853–1050°C and the re-examination of the system. In addition, data on the structure of individual regions and the subsolidus structure of many systems to which it belongs are still practically absent, or there are significant contradictions in domestic and foreign literature. It is also necessary to clarify the areas of primary crystallization of phases in the four-component system of $Ca_3(PO_4)_2$–$CaCO_3$–$Ca(OH)_2$–H_2O, to subdivide into elementary tetrahedra and to study the subsolidus structure of CaO–CaF_2–P_2O_5–H_2O and CaO–MgO–CaF_2–P_2O_5 for the development of simplified technological schemes for the synthesis of bioceramic materials.

3. Purpose and objectives of the study

The purpose of this work is to study the structure of the binary system CaO–P_2O_5 and the subsolidus structure of multicomponent oxide systems that are similar in composition to the bone tissue to determine areas that are promising for the synthesis of new functional materials for medical and biological purposes.

To achieve this goal, it was necessary to solve the following tasks:

Conduct an in-depth study of the structure of the binary system CaO–P_2O_5 in $Ca_3(PO_4)_2$–$Ca_4P_2O_9$ (C_3P–C_4P) segment. To attempt an "oxyapatite" synthesis of $Ca_{10}(PO_4)_6O_2$ ($C_{10}P_3$). Carry out an experimental verification of the polymorphism of $Ca_3(PO_4)_2$ by the method of high-temperature microscopy *in sity*.

Based on the data obtained, we construct a refined phase diagram of the CaO–P_2O_5 system.

On the basis of the data obtained, the regions of primary phase crystallization in the four-component system $Ca_3(PO_4)_2$–$CaCO_3$–$Ca(OH)_2$–H_2O should be clarified.

To study the subsolidus structure, to subdivide into elementary tetrahedrons of four-component systems CaO–CaF_2–P_2O_5–H_2O and CaO–MgO–CaF_2–P_2O_5 for the development of simplified technological schemes for the synthesis of bioceramic materials.

4. Experimental

In the presented study CaO, $Ca(OH)_2$, $CaCO_3$, CaF_2 and H_3PO_4 of high purity were used, the nanopowders $Ca_3(PO_4)_2$, $Ca_{10}(PO_4)_6(OH)$, $Ca_{10}(PO_4)_6F_2$ synthesized with their own hand. $Mg(C_{17}H_{35}COO)_2$ was used as an additive. $Ca_{10}(PO_4)_6(OH)_2$ was obtained from solutions of $Ca(OH)_2$ and

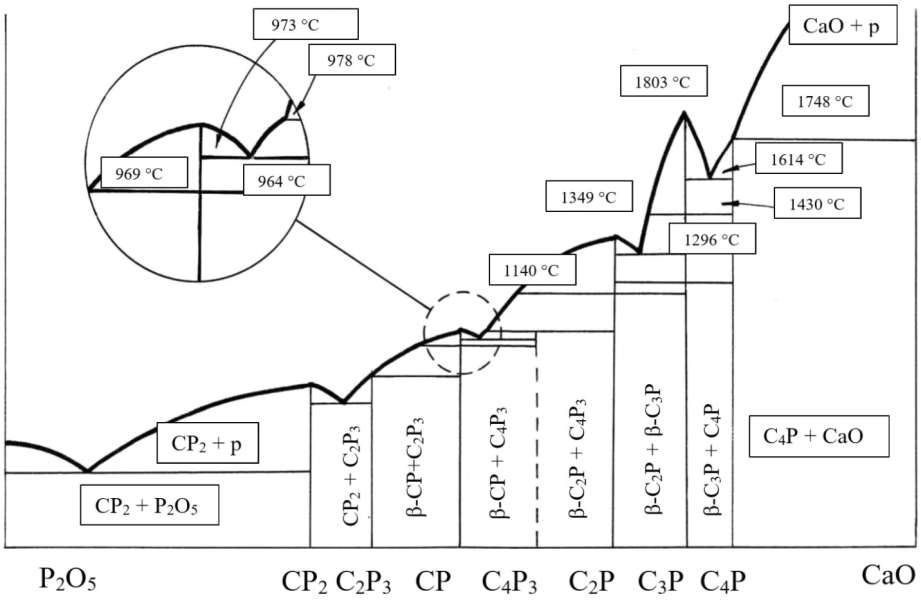

Fig. 1. The phase diagram of the $CaO–P_2O_5$ system.

H_3PO_4 in distilled water by stirring them for 8 h and holding for 170 h at room temperature for aging, ensuring that $n(Ca^{2+})/m(PO_4^{3-}) = 1.67$.

$Ca_3(PO_4)_2$ was synthesized from H_3PO_4 and $Ca(OH)_2$ in the solid phase by triple calcination of the pelletized mixtures at a temperature of 1150–1250°C for 2 hours and intermediate grinding with a multistage temperature rise of 120–150°C in h. Fluorapatite $Ca_{10}(PO_4)_6F_2$ was synthesized from CaF_2 of pre-synthesized $Ca_3(PO_4)_2$ in the solid phase by roasting in the temperature range 1200–1250°C for 3 h, followed by grinding.

A high-temperature chamber furnace with Si–C heaters, with an air atmosphere, as well as an electric furnace with a cryptol resistance and a quartz capsule with periclase padding were used for sintering the samples. Platinum-rhodium thermocouples were used to control the temperatures.

The phase composition of the materials was monitored by X-ray diffraction analysis using a "Drone-3" installation. Petrographic studies were carried out on a polarization microscope MIH-8.

Ca/P ratio in the samples in the synthesis of $Ca_{10}(PO_4)_6(OH)_2$ was monitored by chemical analysis.

The mineralogical composition of the materials was determined using a Scanning Electron Microscope Carl Zeiss, Germany, using a two-stage cellulose-carbon replica and replicas with extraction.

Investigation of binary eutectics and melting points in them was carried out on the preparations of computational compositions by high-temperature microscopy in sity on flat-polished plates 0.3 mm thick, and also on crushed products under direct observation in a microscope with a special attachment — a silicate chamber of the Mikhailov-Shatskii system. Calculations (the position of the binary eutectic, melting temperatures in them) were carried out using known methods and algorithms [9–14].

5. Results and discussion

Experimental verification of the polymorphism of $Ca_3(PO_4)_2$ confirmed the existence of three of its polymorphic varieties: β, α and α′. It was established that the formation of the α–$Ca_3(PO_4)_2$ structure was completed to 1400°C. The limiting factor for this is the size of the β–$Ca_3(PO_4)_2$ grains. It has been established that the conversion of α–$Ca_3(PO_4)_2$ → α′–$Ca_3(PO_4)_2$ occurs rapidly and occurs at a temperature of ~ 1430°C.

It is shown that the optimum component ratio for the synthesis in the solid phase of $Ca_3(PO_4)_2$ and $Ca_{10}(PO_4)_6F_2$ should be determined taking into account the volatility of the phosphorus compounds used as precursors. The results of XRF confirmed that they are nanocrystalline materials of high purity.

The attempt to synthesize $Ca_{10}(PO_4)_6O_2$ oxyapatite in the solid phase from the corresponding oxides (by triple calcination of

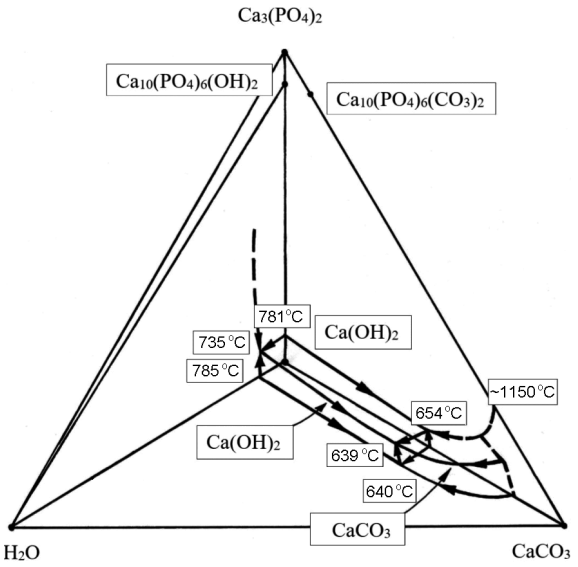

Fig. 2. The regions of primary crystallization of phases in a four-component system $Ca_3(PO_4)_2$–$CaCO_3$–$Ca(OH)_2$–H_2O.

the mixtures pelleted at 50 MPa at 750–1450°C with intermediate grinding) showed no traces in the samples that can be attributed to oxyapatite $Ca_{10}(PO_4)_6O_2$.

Melting temperatures and compositions of binary eutectics were determined using refined thermodynamic constants of substances as initial data [14]. Experimental verification of the calculated data was carried out on the preparations of the calculated compositions. We used the method of high-temperature microscopy (accuracy ±10°C) and the known optical constants of minerals [15]. The carried out check showed good agreement of the experimental and calculated data.

On the basis of the data obtained, a phase diagram of the CaO–P_2O_5 system is constructed, which is shown in the Fig. 1, in which $Ca_{10}(PO_4)_6O_2$ that existed before.

On the basis of the investigations carried out, the regions of primary crystallization of phases in the system $Ca_3(PO_4)_2$–$CaCO_3$–$Ca(OH)_2$–H_2O, which are shown in the Fig. 2. Refined areas of primary crystallization of phases differ significantly from those previously adopted; this opens up additional opportunities for the production of new synthetic nanocrystalline materials of polyvariant composition, purposefully designed to correct structural disturbances of various parts of the skeleton.

The studied subsolidus structure of CaO–CaF_2–P_2O_5–H_2O and CaO–MgO–CaF_2–P_2O_5 systems makes it possible to predict the

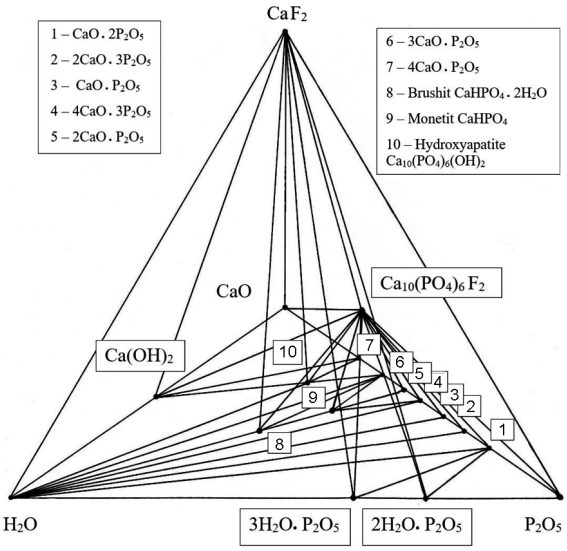

Fig. 3. Splitting the system CaO–CaF_2–P_2O_5–H_2O_5 into elementary tetrahedra.

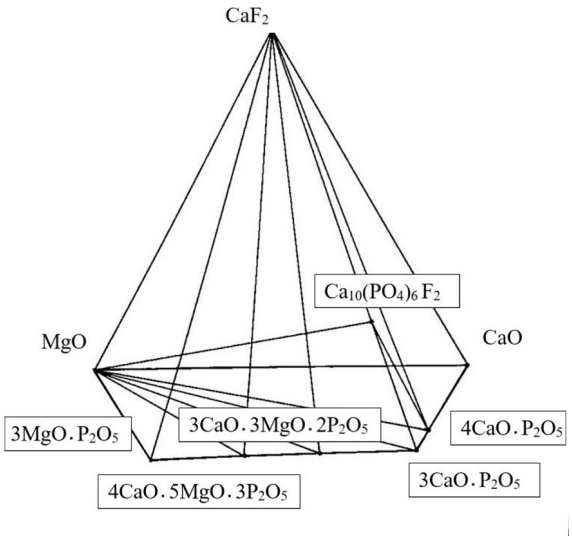

Fig. 4. Splitting the system CaO–MgO–CaF_2–$Ca_3(PO_4)_2$–$Mg_3(PO_4)_2$ into elementary tetrahedra.

phase composition of new materials with a set of specified properties due to the presence of compounds located at the vertices of elementary tetrahedra and taking into account the technological features of their production. The splitting of CaO–CaF_2–P_2O_5–P_2O_5 and CaO–MgO–CaF_2–$Ca_3(PO_4)_2$–$Mg_3(PO_4)_2$ systems into elementary tetrahedra is shown in the Fig. 3 and 4, respectively.

Based on the data obtained, promising compositions for the synthesis of nanocrystalline materials of a polyvariant composition based on the system CaO–P_2O_5–CaF_2–H_2O and additives to correct structural defects of the skeleton have been identified and materials have been developed [16, 17], which, by

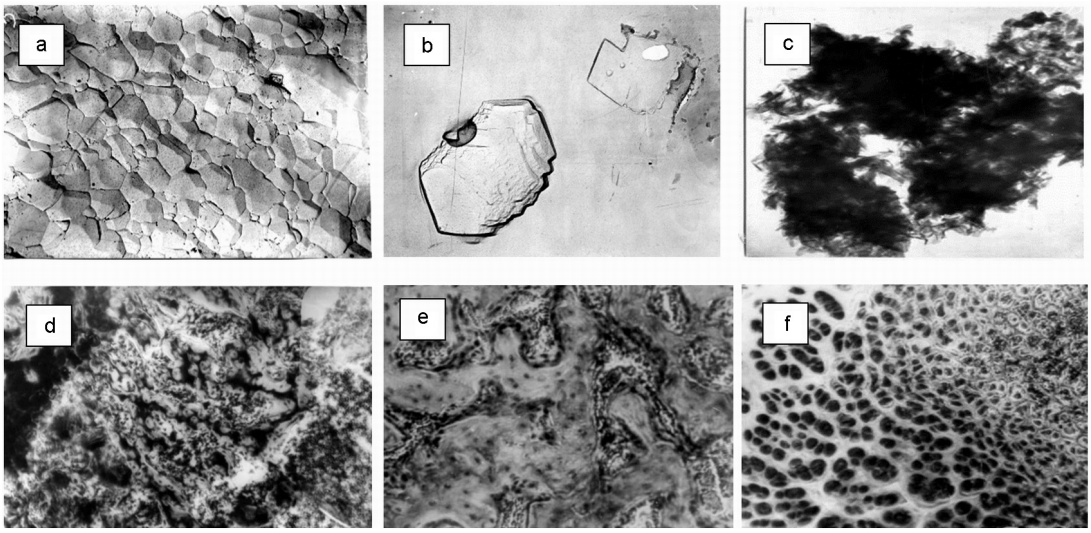

Fig. 5. SEM micrographs of: a — nanocrystalline composite on $Ca_{10}(PO_4)_6(OH)_2$/ $Ca_{10}(PO_4)_6F_2$, ×32000; b — calcium phosphate matrix, self-armored single crystals of periclase, × 32000; c — nanocrystalline powder based on $Ca_3(PO_4)_2$, × 50000; d — formation of bone regenerate using a plastic material based on hydroxylapatite. Regenerate with numerous full-blooded vessels and impregnations of ceramics. 21 day, × 80; e — formation of bone regenerate using a plastic material based on tricalcium phosphate. Filling a cavity defect, filling the medullar space with cellular elements. 21 day, × 80; f — formation of cartilaginous regenerate using a hybrid organo-inorganic composite based on a nanocrystalline powder in a composition with a polymeric binder. Fields of newly formed articular cartilage; cartilaginous cells of different degree of maturity. 14 day. × 80.

their technical and biological properties, can be used to repair defects in the tissues of the skeleton. In the Fig. 5. microstructures are presented: a nanocrystalline composite of the composition $Ca_{10}(PO_4)_6(OH)_2/Ca_{10}(PO_4)_6F_2$ (a), calcium phosphate matrix, self-reinforced single crystal periclase (b), nanocrystalline powder based on $Ca_3(PO_4)_2$ (c).

The developed materials underwent a full complex of toxicological and hygienic tests on warm-blooded animals. It was found that they all have a high biocompatibility with living tissues, are low-toxic, low-risk substances with poorly expressed cumulative properties; they are not inherent in gonadotoxic, embryotoxic, cytotoxic, mutagenic and teratogenic effects, skin-irritating and skin-resorptive properties. Using them to repair defects provides phenomenal results for restoring not only bone tissue, but also blood vessels and bone marrow. When they are used, a complex biomaterials problem of differentiating cartilage tissue cells and restoring the articular cartilage is solved. Features of the formation of bone regenerate using a plastic material based on hydroxylapatite and based on tricalcium phosphate are shown in the Fig. 5 (d) and (e) respectively. In the Fig. 5 (f) shows the formation of a cartilaginous regenerate using a nanocrystalline powder in a composition with a polymeric binder.

6. Conclusions

Experimental verification of the polymorphism of $Ca_3(PO_4)_2$ showed the presence of two structural transitions of this compound, which confirms the existence of three polymorphic varieties of $Ca_3(PO_4)_2$: β, α and α′. It has been established that the conversion of β–$Ca_3(PO_4)_2$ into a high-temperature α-form and the formation of α–$Ca_3(PO_4)_2$ structure is completed only to 1,400°C. The limiting factor for this is the size of the β–$Ca_3(PO_4)_2$ grains. It has been established that the conversion of α–$Ca_3(PO_4)_2 \rightarrow$ α′–$Ca_3(PO_4)_2$ occurs rapidly and occurs at a temperature of ~ 1430°C.

The attempted synthesis of oxyapatite $Ca_{10}(PO_4)_6O_2$ in the 750–1450°C range indicated the absence of any traces in the samples.

The experimental verification of the melting temperatures and compositions of binary eutectics by high-temperature microscopy showed a good agreement between the experimental and calculated data.

On the basis of the obtained data, a diagram of the state of the C $CaO–P_2O_5$ system is constructed, the structure of which is refined in the region of $Ca_3(PO_4)_2–Ca_4P_2O_9$.

On the basis of the investigations carried out, the regions of primary crystallization of phases in the system $Ca_3(PO_4)_2–CaCO_3–Ca(OH)_2–H_2O$ were refined.

The subsolidus structure of $CaO–CaF_2–P_2O_5–H_2O$ and $CaO–MgO–CaF_2–P_2O_5$ systems, their subdivision into elementary tetrahedra, has been studied.

The carried out researches are a base for reception of new functional materials of medico-biological appointment. They allow us to predict the phase composition of new composite materials with a set of specified properties due to the presence of compounds located at the apex of elementary tetrahedra and taking into account the technological features of their production.

All received data are significantly different from those taken earlier.

As a result of the investigations, the composition regions have been optimized and nanocrystalline materials based on the system $CaO–P_2O_5–CaF_2–H_2O$ and additives have been developed, which, depending on their phase composition, are intended to replace various parts of the skeleton. This opens up additional opportunities for obtaining new functional materials of polyvariant composition, purposefully designed to correct structural disturbances of the skeleton.

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