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Synthesis of Stoichiometric and Substituted β -Tricalciumphosphate Using Mechanochemistry

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Abstract

A solid-phase method was developed for the synthesis of β -tricalciumphosphate (β -TCP) with the stoichiometric composition and with partial substitution of calcium ions for copper, zinc and silver ions. The method involves preliminary preparation of precursors by means of mechanical activation of reaction mixtures. The start of β -TCP formation was detected directly during the activation of reaction mixtures in the mill. The optimal conditions for activation, the temperature and the duration of annealing were determined.

Keywords: β -tricalciumphosphate, synthesis, mechanical activation, precursor

INTRODUCTION

β -Tricalcium phosphate (β -TCP) $\text{Ca}_3(\text{PO}_4)_2$ is biocompatible, exhibits active bioresorbability and is widely used in traumatology, orthopedics, craniofacial surgery and dentistry as a material for filling bone defects, as coating for implants and as medical ceramics [1]. Stoichiometric β -TCP gets resorbed in the fluids of an organism with a higher rate than hydroxyapatite (HAP) and is used in the cases when active degradation of implanted material is necessary for the reconstruction of the host bone tissue. An essential problem is connected with post-surgical complications after implantation. One of the methods to solve this problem is to include bactericidal ions into the structure of β -TCP [2].

An extensive amount of publications dealing with the methods of synthesis of various ion substituted varieties of β -TCP pay major attention to bactericidal substituent ions such as Cu^{2+} , Zn^{2+} and Ag^+ [3–8]. As a rule, the goal of investigations is connected with the choice of the simplest method and the development of optimal condi-

tions for the synthesis of a product with the required composition. A widespread method is the precipitation of calcium-deficient hydroxyapatite (CDHAP) from the soluble salts of calcium and phosphates (or the solutions of phosphoric acid) with the ratio of Ca/P ~ 1.5, followed by filtration, drying of the precipitate, and annealing for many hours at a temperature of 800–1200 °C [3, 4, 6, 7].

In some works, the synthesis of substituted β -TCP is carried out using the solid-phase method, by means of preliminary grinding of initial components – phosphorus and calcium containing salts with dopants as bactericidal elements, among which the most frequently used ones are the compounds of copper, zinc and silver [4, 8]. In particular, β -TCP samples with the required composition were synthesized [8]: $\text{Ca}_{3-x}\text{Zn}_x(\text{PO}_4)_2$, where $x = 0.001, 0.03, 0.05, 0.01$, from a mixture of CaHPO_4 , CaCO_3 and ZnO through preliminary comminution of the mixture, followed by its annealing at 1000 °C for 6 h. The fine structure of the synthesized samples was investigated using a number of experimental and calculation methods. On this basis, the models for

the position of zinc in the structure of substituted β -TCP were proposed.

In [9] the synthesis of β -TCP was carried out using three different methods: 1) precipitation from the solutions of salts $\text{Ca}(\text{NO}_3)_2 \cdot 4\text{H}_2\text{O}$ and $(\text{NH}_4)_2\text{HPO}_4$; 2) sol-gel method from the same salts; 3) by means of burning the solutions, so that the exothermal reaction supplies the heat which is necessary to maintain combustion between the oxidizer and the organic fuel in the aqueous solution. Synthesis methods affect the size of particles and crystallites, behaviour during consolidation and shrinkage of the product when the powder is used to make ceramics.

The samples of β -TCP with calcium substitution by metal ions [4]: Cu^{2+} , Zn^{2+} and Ag^+ , either by only one of them – Ag-TCP, Cu-TCP, Zn-TCP, or with double substitution – (Ag, Cu)-TCP, (Ag, Zn)-TCP were synthesized. The synthesis was carried out using the solid-phase method from the mixtures of $\text{CaHPO}_4 \cdot 2\text{H}_2\text{O}$, CaCO_3 and CaO with dopants AgNO_3 , CuO and ZnO through preliminary grinding followed by annealing at 1000 °C for 24 h, with the repeating of this procedure. The concentrations of dopants Cu^{2+} and Zn^{2+} were varied within the range 0–15 mol. % with the ratio $(\text{Ca} + \text{dopant})/\text{P} = 1.5$. The concentration of Ag^+ ion was constant (9.09 mol. %). The synthesized samples were single-phase systems up to the dopant concentration 9.09 mol. %. It was established that the lattice parameters of the phase of doped β -TCP decrease with an increase in the concentrations of zinc and copper ions up to 9.09 mol. % and then remain constant independently of an increase in dopant concentration. A decrease in the lattice parameters with the introduction of dopants may be explained by the smaller ion radii compared with calcium: the radii of Zn^{2+} , Cu^{2+} , Ca^{2+} are equal to 0.074, 0.073 and 0.100 nm, respectively.

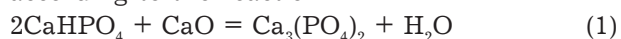
A brief review of the literature on the synthesis of β -TCP provides evidence of high labour intensity and great time consumption for the synthesis of the final product.

Stoichiometric β -TCP is used in clinical practice for more than ten years [1], while β -TCP with substitutions is still at the stage of trial for its bactericidal and cytotoxic properties [3, 4, 6]. The cations of copper, zinc and silver exhibit bactericidal properties but these ions become toxic in definite concentrations. It was discovered [3] that 1 mass % Zn concentration in β -TCP starts to suppress the development of cells, therefore, this concentration is considered to be toxic. Silver ions are not cytotoxic but in high concentrations they may cause argyrosis with grey-blue pigmentation of the skin cover. In [3, 4, 6], dopant concentrations were 0.01–0.1 mole per 1 mole of β -TCP.

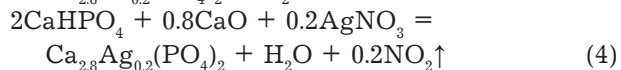
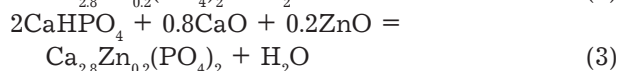
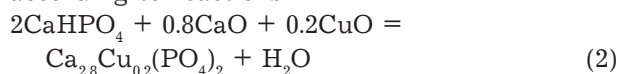
The goal of the present work is to study the effect of preliminary mechanical activation of the reaction mixture on the acceleration of diffusion during high-temperature synthesis of stoichiometric and cation-substituted β -TCP.

EXPERIMENTAL

Initial components for the synthesis of precursors were monetite CaHPO_4 (Ch. grade, Vekton) and freshly calcined CaO (Ch. D. A. reagent grade, Vekton), ZnO (Ch. grade, GOST 10262–73, REAKHIM), CuO (Os. Ch. grade, TU-6-09-3098–77, REAKHIM); AgNO_3 (Kh. Ch. reagent grade, GOST 1277–75, PZTsM-VTORChM). The components ratio for the synthesis of stoichiometric β -TCP was taken according to the reaction



and for the synthesis of substituted β -TCP – according to reactions



Mechanical activation (MA) of the reaction mixtures of precursors was carried out in AGO-2 planetary mill (Russia) in water-cooled steel jars with steel balls at the frequency of rotation equal to 1800 r.p.m. The ratio of the portion of the reaction mixture under treatment and the mass of balls was 1 : 20. To avoid product contamination with iron abrasion from milling balls and the walls of mill jars, the preliminary lining of the working zone in the mill was carried out using the reaction mixture of the same composition. Samples were annealed in the PVK 1.4-8 electric furnace (Russia) at a temperature of 700 and 800 °C for 1 and 2 h with the heating rate of 10 °C/min.

The samples were investigated by means of X-ray structural analysis and IR spectroscopy. Diffraction patterns were recorded with a powder diffractometer D8 Advance (Bruker, Germany) in Bragg-Brentano geometry with CuK_α -radiation, nickel K_β -filter and superfast position-sensitive one-dimensional detector Lynx-Eye. X-ray phase analysis of the compounds was carried out using the powder diffraction database ICDD PDF-4 (2011). Refinement of the unit cell parameters, crystallite size and calculation of phase concentrations were carried out according to the Rietveld method using Topas

4.2 software (Bruker, Germany). IR spectra were recorded with an Infracum-801 spectrometer (Russia), the tablets of samples were prepared using a standard procedure by pressing with KBr.

RESULTS AND DISCUSSION

Synthesis of stoichiometric β -TCP

To develop an energy-saving and rapid method of β -TCP synthesis, it was necessary to accelerate the diffusion of the components of the reaction

mixture during its annealing. The classical solid-phase synthesis of β -TCP involves twofold annealing of the reaction mixture for many hours, with sample grinding between two annealing cycles to obtain a single-phase product as described in [4].

To accelerate the synthesis during annealing, we used MA of the mixture of reagents to obtain precursors. It was necessary to choose the optimal activation time, temperature and duration of annealing.

We chose monetite CaHPO_4 , as initial calcium phosphate because the use of other calcium

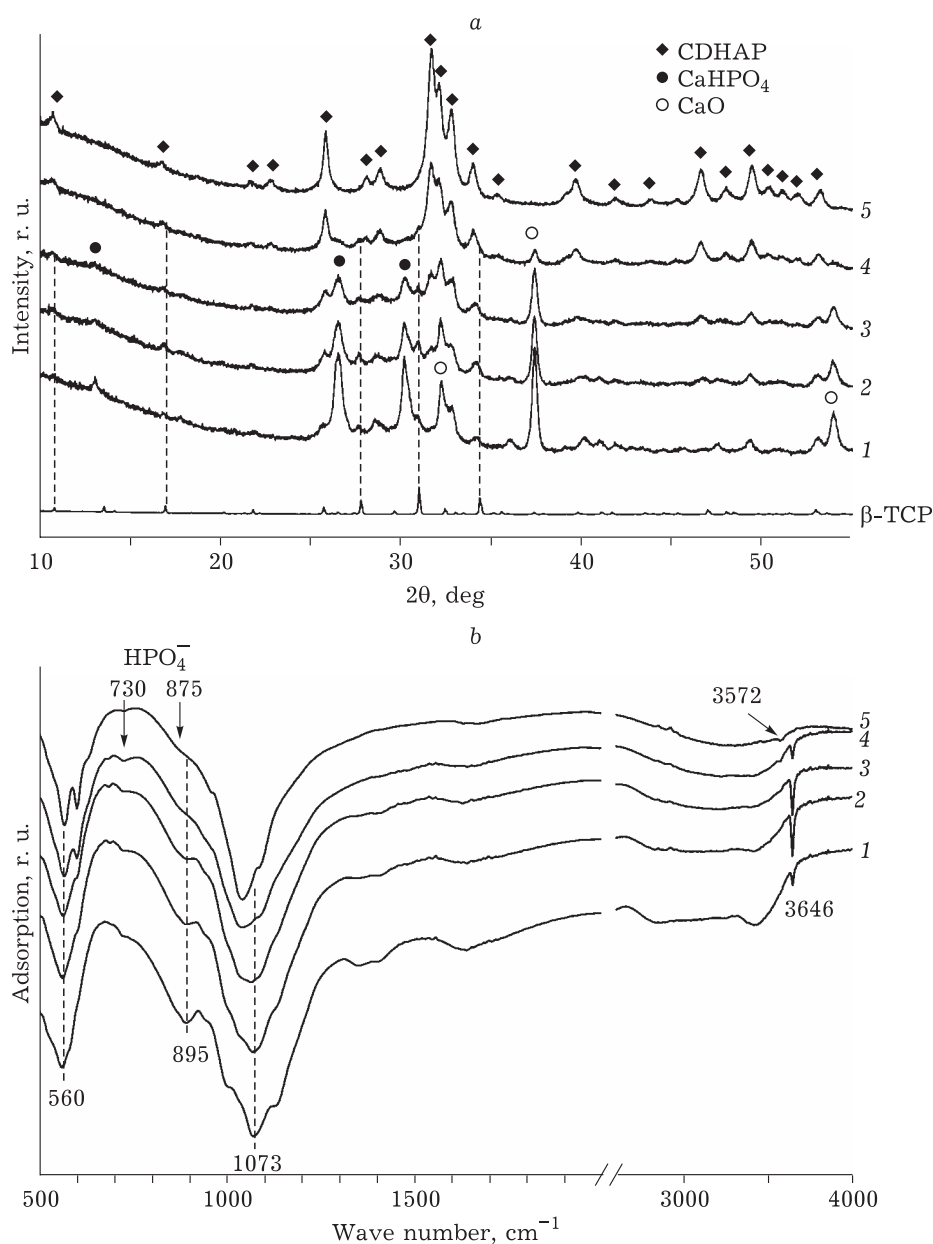


Fig. 1. Diffraction patterns (a) and IR spectra (b) of the samples of reaction mixture ($2\text{CaHPO}_4 + \text{CaO}$) depending on the time of mechanical activation, min: 3 (1), 5 (2), 7 (3), 10 (4), 25 (5).

phosphates, such as $\text{Ca}(\text{H}_2\text{PO}_4)_2 \cdot \text{H}_2\text{O}$ and $\text{Ca}_2\text{P}_2\text{O}_7$, is accompanied by mixture cementing and sticking on balls and the walls of mill cylinders during activation.

The diffraction patterns of precursors in the reaction mixture with the composition ($2\text{CaHPO}_4 + \text{CaO}$) activated for 3 to 25 min are shown in Fig. 1, *a*. It should be noted that reflections at $2\theta = 27.77$ and 31.01° (marked with dash lines in Fig. 1, *a*) characteristic of β -TCP appear in the diffraction patterns after MA for 3 min but disappear after MA for 25 min. It is known that β -TCP is usually formed after sample annealing at a temperature of 600–1000 °C [10]. It was demonstrated in [11] that activation of powders in AGO-2 mill may involve local temperature rise to 600 °C. The presence of the reflections of β -TCP in the diffraction patterns of activated samples allows us to suppose that the level of mechanical energy input during activation in powerful planetary mills is equivalent to the level of energy consumed for sample annealing at 600 °C. According to the prescribed components ratio for reaction (1), activation should have left to the formation of 100 % β -TCP, however, we observe it as an intermediate product disappearing after MA for 25 min. Only the reflections of CDHAP

corresponding to the formula $\text{Ca}_9\text{HPO}_4(\text{PO}_2)_5(\text{OH})$ are observed in the diffraction pattern of the sample activated for 25 min. The data of IR spectroscopy (see Fig. 1, *b*) confirm the presence of absorption bands related to acid HPO_4^{2-} -groups (730 and 875 cm^{-1}). The formation of CDHAP is explained by the fact that the formation of apatite lattice is more profitable from the viewpoint of energy than for β -TCP (Gibbs energy of the formation $\Delta G^{\text{CDHAP}} = -11\,980\text{ kJ/mol}$, $\Delta G^{\text{TCP}} = -3889\text{ kJ/mol}$).

To determine the optimal conditions for the synthesis of β -TCP, the samples activated for different time intervals were annealed at a temperature of 700 and 800 °C. It was established that after annealing at 700 °C the samples contain an admixture of CDHAP (Fig. 2). With an increase in annealing temperature to 800 °C, CDHAP admixture is observed only in the samples activated for less than 10 min. Incomplete transformation of the precursor into β -TCP may be connected with the fact that after activation for a short time the samples still contain residues of unreacted initial compounds (see Fig. 1, *a*).

The optimal conditions for the synthesis of single-phase stoichiometric β -TCP were determined as a result of the investigation: MA of

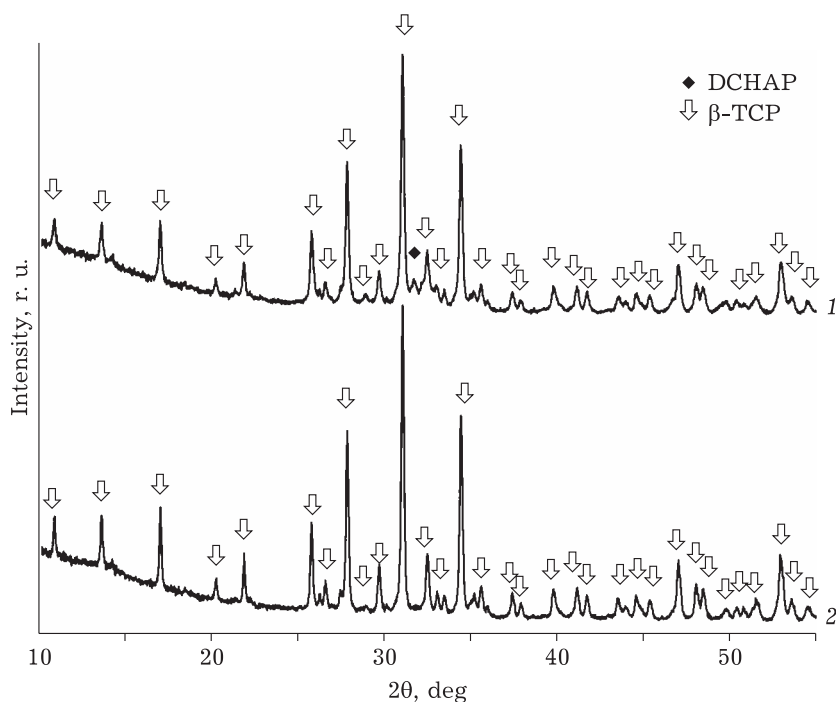


Fig. 2. Diffraction patterns of β -TCP samples from the precursor ($2\text{CaHPO}_4 + \text{CaO}$), activated for 10 min and then annealed at a temperature of 700 (1) and 800 °C (2) for 2 h.

the initial mixture for 10 min and subsequent annealing at a temperature of 800 °C for 2 h.

Synthesis of cation-substituted β -TCP

The reflections of β -TCP are present in the diffraction patterns of precursors activated for 10 min and doped with copper and zinc cations

(Fig. 3). Reflections of β -TCP are absent from the diffraction patterns of the precursor doped with silver ions, though intense reflections of unreacted silver nitrate are present (see Fig. 3). It is probable that the interaction of acid phosphate and nitrate proceeds *via* another mechanism different from that involved in the interaction between the acid

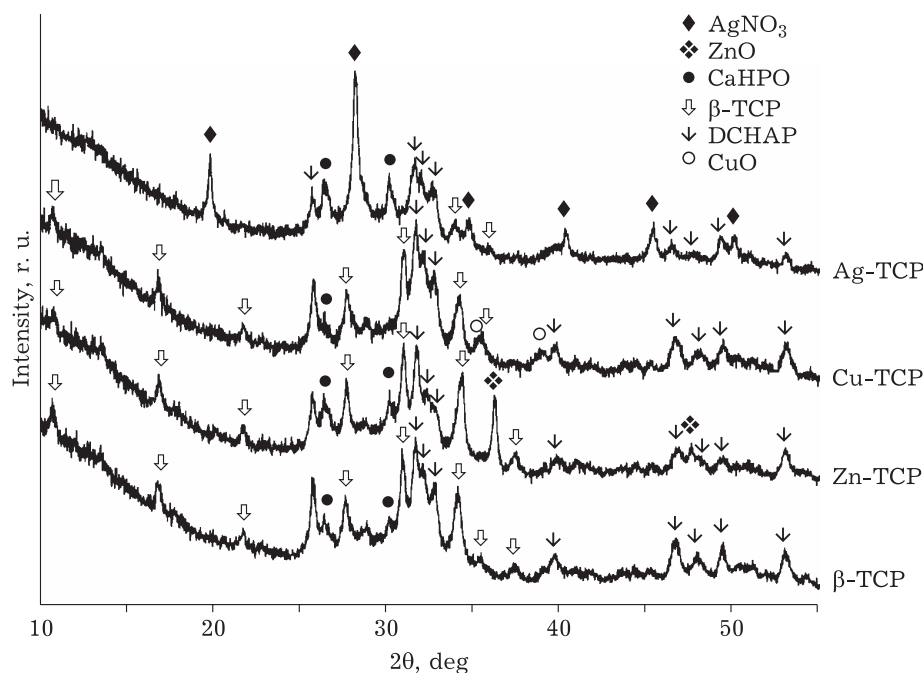


Fig. 3. Diffraction patterns of the precursors of cation-substituted samples of mixtures after activation for 10 min.

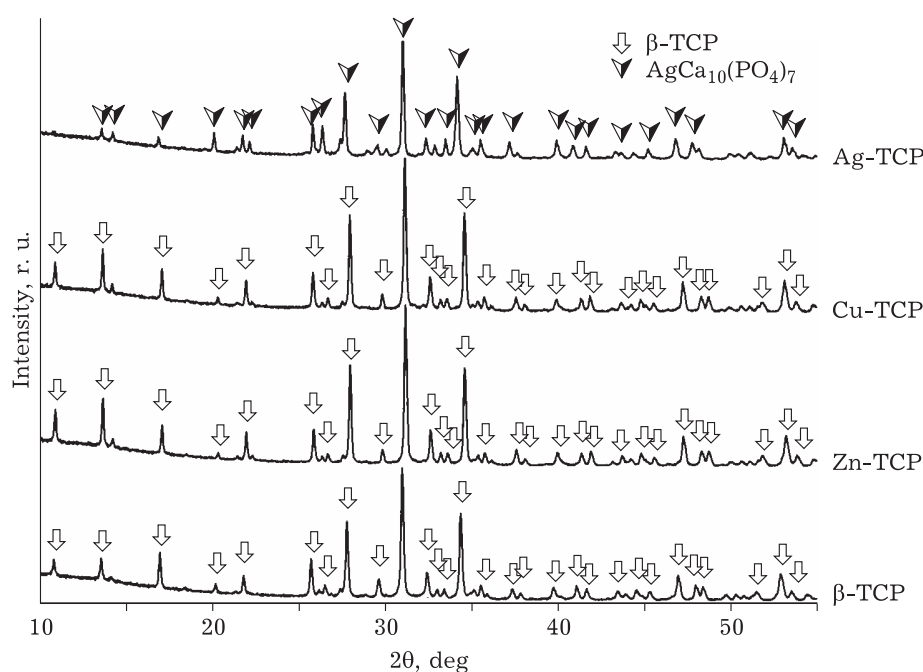


Fig. 4. Diffraction patterns of cation-substituted β -TCP samples after activation for 10 min and annealing at 800 °C for 2 h.

TABLE 1
TCP lattice parameters in annealed samples

Sample	Lattice parameters, Å		Coherent length, nm
	<i>a</i>	<i>c</i>	
TCP	10.427(1)	37.456(4)	87(3)
Zn-TCP	10.368(1)	37.338(4)	101(4)
Cu-TCP	10.364(1)	37.272(4)	97(4)
Ag-TCP	10.4990(4)	37.295(2)	98(3)

phosphate and the oxide, as a result of which only CDHAP crystallites are formed.

The samples doped with copper and zinc ions are single-phase after annealing, which is confirmed by the data of X-ray phase analysis, and have the structure of β -TCP (Fig. 4). Lattice parameters *a* and *c* for these samples are substantially smaller than those for the stoichiometric β -TCP (Table 1), which may be explained by smaller ion radii of the dopants (Cu – 0.073 nm, Zn – 0.074 nm) in comparison with the radius of calcium ion (0.100 nm). Change in lattice parameters and the absence of additional reflections from the diffraction patterns of these samples are evidence of the formation of the single-phase product and complete inclusion of substituents into the β -TCP structure, with the formation of the product of required composition.

The diffraction pattern of the annealed sample doped with silver ions contains reflections characteristic of the double salt, silver – calcium phosphate $\text{AgCa}_{10}(\text{PO}_4)_7$ with the structure similar to that of β -TCP [12]. Lattice parameter *a* for the Ag-TCP sample is much larger than that for the stoichiometric β -TCP (see Table 1), which may be explained by the larger radius of silver ion (0.113 nm) than the ion radius of calcium.

CONCLUSION

The samples of β -TCP with the stoichiometric composition $\text{Ca}_3(\text{PO}_4)_2$ and copper-, zinc-substituted varieties are synthesized. To accelerate the diffusion of the components during sample annealing, precursors were synthesized preliminarily by means of mechanical activation of reaction mixtures for 3–25 min. It was revealed that β -TCP particles, an intermediate product before the formation of CDHAP structure, are formed during activation directly in the mill. After mechanical activation of the mixture for 25 min, no β -TCP reflections are observed in the diffraction pattern of the sample. Optimal conditions for the

synthesis of β -TCP were revealed: mechanical activation for 10 min and annealing at a temperature of 800 °C for 2 h.

Single-phase Cu-TCP and Zn-TCP samples are synthesized in the case of sample doping by introducing copper and zinc oxides in the amount of 0.2 moles per 1 mole of β -TCP under the conditions described above. In the case of sample doping with silver ions, unreacted AgNO_3 was detected in the precursor activated for 10 min. After annealing of the samples, the reflections of double salt $\text{AgCa}_{10}(\text{PO}_4)_7$ with the β -TCP structure were detected in the diffraction patterns.

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REFERENCES

- 1 Barinov S. M., Komlev V. S., *Bioceramics Based on Calcium phosphates*, 2nd ed., Moscow: Nauka, 2014. 201 p.
- 2 Skalniy A. V., Rudakov I. A., *Bioelements in Medicine*, Moscow: Mir, 2004. 272 p.
- 3 Tas A. C., Bhaduri S. B., Jalota S., Preparation of Zn-doped β -tricalcium phosphate (β - $\text{Ca}_3(\text{PO}_4)_2$) bioceramics, *Mater. Sci. Engin. C*, 2007, Vol. 27, No. 3, P. 394–401.
- 4 Matsumoto N., Sato K., Yoshida K., Hashimoto K., Toda Y., Preparation and characterization of β -tricalcium phosphate co-doped with monovalent and divalent antibacterial metal ions, *Acta Biomater.*, 2009, Vol. 5, No. 8, P. 3157–3164.
- 5 Sanosh K. P., Chu M. C., Balakrishnan A., Kim T. N., Cho S. J., Sol-gel synthesis of pure nano sized β -tricalcium phosphate crystalline powders, *Curr. Appl. Phys.*, 2010, Vol. 10, No. 1, P. 68–71. DOI: 10.7868/S0869565216360123
- 6 Fadeeva I. V., Gafurov M. R., Filippov Ya. Yu., Davydova G. A., Savintseva I. V., Petrakova N. V., Antonova O. S., Akhmetov L. I., Gabbasov B. F., Izotov V. V., Orliinskiy S. B., Barinov S. M., Copper-substituted tricalcium phosphates, *Dokl. AN*, 2016, Vol. 471, No. 6, P. 1–4.
- 7 Chaair H., Labjar H., Britel O., Synthesis of β -tricalcium phosphate, *Morphologie*, 2017, Vol. 101, No. 334, P. 120–124.
- 8 Kawabata K., Yamamoto T., Kitada A., Substitution mechanism of Zn ions in β -tricalcium phosphate, *Phys. B: Cond. Matter*, 2011, Vol. 406, No. 4, P. 890–894.
- 9 Ghosh R., Sarkar R., Synthesis and characterization of sintered beta-tricalcium phosphate: A comparative study on the effect of preparation route, *Mater. Sci. Eng. C*, 2016, Vol. 67, P. 345–352.
- 10 Elliott J. C., *Structure and Chemistry of Apatite and Other Calcium Orthophosphates*, Amsterdam: Elsevier, 1994. 389 p.
- 11 Kwon Y.-S., Gerasimov K. B., Yoon S.-K., Ball temperatures during mechanical alloying in planetary mills, *J. Alloys Compd.*, 2002, Vol. 346, P. 276–281.
- 12 Strutynska N. Yu., Zatovsky I. V., Ogorodnyk I. V., Slobodyanik N. S., Rietveld refinement of $\text{AgCa}_{10}(\text{PO}_4)_7$ from X-ray powder data, *Acta Cryst. Sect. E*, 2013, Vol. E69, No. 5, P. i23. DOI: 10.1107/S1600536813007848