Doped calcium carbonate-phosphate used for bone tissue technology

Lyubov Fedorovna Koroleva*, Maria Nikolaevna Dobrinskaya† and Ivan Sergeevich Kamantsev‡

1Institute of Engineering Science, Ural Branch of the Russian Academy of Sciences, 34 Komsomolskaya st., Ekaterinburg, Russian Federation
2Ural State Medical University, 3 Repina st., Ekaterinburg, Russian Federation

Abstract

Doped with K+, Mg2+, Fe2+, Zn2+, Mn2+, Li+, Au3+, SiO2 nanocrystalline calcium carbonate-phosphate extends significantly the functionality for drug delivery: it can be used to speed up the processes of bone repair and bone tissue strengthening. The advantage over other calcium phosphate biomaterials is strengthening of bone and tooth tissues of a human being of any age, the substances being transported through skin to restore broken bones in a critically short period of time regardless of age. The mechanical fracture strength of bone tissue increases almost in 5 times. These studies suggest doped calcium carbonate-phosphate is the most appropriate material, because reduce of the cholesterol rate in the blood in 2-2.5 time. The best results have been observed with concentrations of 5-10% doped calcium carbonate-phosphate in the implant used the polycaprolactone. Young’s modulus is maximal for specimens with 5% doped calcium carbonate-phosphate.

Introduction

Tissue engineering is intensively researching solutions that have the potential to reduce the complications related to current treatment methods. Tissue engineering can be defined as an interdisciplinary field that applies the principles of engineering and life sciences to develop biological substitutes that restore, maintain or improve tissue function. This concept involves three main strategies: the use of isolated cells or cell substitutes to replace limited functions of the tissue; utilization of tissue-inducing substances such as growth factors; and scaffolds to direct tissue development. Calcium phosphate has been the subject of many studies in the last decade because of it biocompatibility, ability to fill bone cavities and properties which are desirable for surgical applications. The synthesis of nanocrystalline calcium hydroxapatites for the fabrication of composite materials as bone graft substitutes is a critical issue in bioceramic research [1-11].

There is considerable interest in the study of the interaction of the surface of hydroxyapatite crystals and their coatings with amine- and carboxy-groups of proteins in relation to the resorption of biomaterials and osteogenesis in living organisms [12]. Such processes of bone regeneration were takes from four to six months [13,14]. Hydroxyapatite is known to be very similar in composition to the inorganic component of bone tissue: the dry residue of bone tissue contains 70% hydroxyapatite and 30% organic component of collagen. In addition to Ca2+ and PO4 3−, calcium hydroxapatite in bone tissue contains Na+, K+, Mg2+, Fe2+, Si4+, Cl− и CO3 2− possibly Zn2+, and the less desirable ions Sr2+, Al3+, Pb2 [15-18].

It is necessary to create a material based on inorganic calcium phosphates, which are easily assimilated, and not only through the gastrointestinal tract. Doped nanocrystalline calcium carbonate-phosphate is a biocompatible material that has an active effect on osteogenesis, including activity through the skin, on the strengthening of bone and dental tissues [19-22].

The morphology, stability, degree of crystalline and mechanical properties of calcium hydroxapatite depend on isomorphous substitution of calcium on such cations as Na+, K+, Mg2+, Fe2+, Zn2+. They play an important role in the biological process of the osteogenesis [23-26].

It is also known elements such as platinum, gold in the colloid form previously used as a treatment for rheumatoid arthritis in humans and tumors, but used doses were accompanied with side effect [27-29]. In case of a possible transfer of cations Au and Pt on molecules doped nanocrystalline carbonate-calcium phosphates dose can be significantly reduced, that would nullify the adverse effects to a minimum, at the same time, will reach the therapeutic effect. In the synthesis of alloyed gold and platinum carbonate-calcium phosphates concentrations of these elements make up the thousandths parts mole.

The bioactivity of calcium phosphates can be enhanced by partial substitution of carbonate groups for phosphate groups, leading to the formation of calcium deficient hydroxyapatites, containing cation vacancies, which ensures the incorporation of doping micromolecules into the crystal structure of the material. The processes for the preparation of calcium hydroxyapatite are well documented in the literature. They can be divided into high temperature (pyrolysis) and low temperature (precipitation and hydrolysis) processes.

Previously the mechanism of the synthesis of nanocrystalline doped calcium carbonate-phosphate was considered and proposed a model to describe the kinetics of oscillating system as brusselator of simple cubic nonlinearity. The mechanism of obtaining this biomaterial is quite...
difficult, and this process can be considered as oscillating reactions in living organism [30].

The simplest classic example of the existence of autooscillations in the system of chemical reactions is the trimolecular model ("brusselator") offered by I.R. Prigogine and R. Lefever [31]. The main purpose for the study of this model was to determine the qualitative types of behavior, which are compatible with the fundamental laws of chemical and biological kinetics. In this context, the brusselator plays the role of a basic model, like a harmonic oscillator in physics. A classic brusselator model describes the hypothetical scheme of chemical reactions: \( A \rightarrow X; B + X \rightarrow Y + C; 2X \rightarrow Y + 3X; X \rightarrow R; A + B \rightarrow R + C \). The key is the stage of transformation of two \( X \) molecules and one \( Y \) molecule into \( X \) (the so-called trimolecular reaction). The nonlinearity of this reaction, coupled with processes of diffusion of the substance, guarantees the possibility of space-time regimes as well as the formation spatial structures in an initially homogeneous system of morphogenesis. Although the trimolecular reaction occurs in chemical kinetics is not as common as bimolecular processes, expressions for the speed of some chemical reactions in some definite cases can be called cubic-type.

The properties of time dependent wave function are determined by the views of potential energy surface and initial state \( \Psi (x, 0) \). The physical significance of wave function is according to the Copenhagen interpretation of quantum mechanics, the probability density of finding a particle at a given point of space at this point in time is deemed to be equal to the square of the absolute value of the wave function of this condition in the coordinate representation [32,33].

A wide variety of chemical transformations can occur in areas where the potential surfaces of different electron states intersect. These areas in quantum dynamics called conical intersections. Reaching conical intersections, a wave packet is split: one part continues to move in the same State, and the second goes to a different State, which could in the future lead to different processes: dissociation, isomerization or radiation less transitions, in which the excitation energy is dissipated to other degrees of freedom. Splitting of wave packet was modeled by parallel reactions. The rate constants are determined of the electronic transition probability \( p \) [34]:

\[
\begin{align*}
\begin{array}{c}
\text{k} \quad n \rightarrow s \quad \psi^2 \quad \text{pk} \quad r \rightarrow \ldots \\
(\psi^2) \quad \text{s} \quad \text{p}
\end{array}
\end{align*}
\]  

(4)

The probability of electronic transition in the field of conical intersection depends on the type of potential surfaces and the wave packet speed. Knowing the dependence of wave packet from time, \( \Psi (x, t) \), you can determine the probability of the individual channels of the chemical reaction, that is the output of products, as well as time of reaction. For the first time kinetic model was built for the reactions of straight dissociation of small molecules. These reactions are ones of the most simple (and therefore, most studied), since the dynamics bring to rupture of the one chemical bond [34].

The infinite movement of wave packet on this surface is described by a set of consecutive first- order reactions that you can observe in case of synthesis of doped calcium carbonate phosphates. Space time regimes, predicted in oscillation–diffusion type models, can be observed in chemical reactions. Biochemical oscillations have been studied from complementary experimental and theoretical perspectives for many years. Well known instances are circadian rhythms and the oscillation of ATP and ADP concentrations during phosphorylation of fructose-6-phosphate in glycolysis [35,36].

Reaction of the synthesis of doped calcium carbonate-phosphate, which were described in [19-21], include several initial compounds as a calcium carbonate of three polymorphic crystal forms (calcite, aragonite, and vaterite), ortho–phosphoric acid, ammonium chloride, ammonium hydroxide, and microelements of the living organism (K\(^{+}\), Mg\(^{2+}\), Fe\(^{2+}\), Zn\(^{2+}\), Mn\(^{2+}\), Li\(^{+}\), Au\(^{3+}\), SiO\(_2\)).

This work deals with the effect of nanocrystalline calcium carbonate-phosphate doped with cations of iron, magnesium, potassium, zinc, lithium, manganese, copper, gold, silicon, which is intended for bone repair by drug delivery; it is also studies the strengthening of bone tissue and the strength of ceramics to be used for implants.

**Materials and methods**

Calcium carbonate-phosphate samples doped by microelements were prepared using three CaCO\(_3\), polymorphous phases: calcite (rhombohedra structure), vaterite (hexagonal), and aragonite (orthorhombic). The last two phases are known to be metastable.

Calcium carbonate phosphates were precipitated by orthophosphoric acid, which was added to a calcium carbonate suspension in a solution of ammonium bicarbonate and ammonium chloride (2 M) at 45–55°C. The \( \text{pH} \) of the solution was 5.2 to 6.5, depending on the Ca/P molar ratio (1.55–1.67). Doping cations were added during calcium carbonate precipitation: Fe\(^{3+}\) and Mg\(^{2+}\), 0.01–0.06; Zn\(^{2+}\), 0.00015–0.002; K\(^{+}\), 0.05–0.3; SiO\(_2\), 0.0002–0.006; and Mn\(^{2+}\), Au\(^{3+}\) – 2 × 10\(^{-7}\) to 1 × 10\(^{-7}\) mol %.

The samples thus obtained were characterized by X-ray diffraction (XRD) (CuKa radiation; STADI-P diffractometer, software for diffraction peak identification using JCPS–ICDD PDF2 data), IR spectroscopy (Shimadzu JR-475 spectrophotometer, KBr disk method). Particle-size analysis was performed with the Shimadzu SA-CP2 centrifugal analyzer (viscosity of the dispersion medium, 0.0093 P\(_\text{v}\); density of the liquid phase, 1.0 g/cm\(^3\)). Elemental composition was determined by X-ray fluorescence analysis (EDX-900HS energy dispersive spectrometer).

The poly(b-caprolactone) composites can be to be used as bone analogous materials in applications such as bone fracture fixation devices or, in the case of a porous structure, scaffolds for bone tissue engineering [6].

For the education of the implant used the poly(b-caprolactone): \([-\text{CH}_2\text{-COOH-}]_n\).

For research receive the following mixture of the poly(b-caprolactone) with doped calcium carbonate-phosphate: 5%, 10% and 15%. Polycaprolactone previously heated in water to the softening temperature (70-80°C). Poly(b-caprolactone) is often used as resorptive material thermal implant prolonged action (filler), has both the ability to stimulate the growth of fibrous tissue. Poly(b-caprolactone) is a biodegradable polymer with a low melting point and a glass transition temperature of about 60°C.

A test on stretch and compression ware performed on a Zwick/Roell Z2.5 universal testing machine. The samples were used in the form of a parallelepiped with a height of 8.8 mm and a cross-section of 30.5 mm.

The animals (50Wistar male rats) were assigned to the following five test groups: group I (placebo, distilled water); the animals of II...
-V group were with the 50% doped calcium carbonate-phosphate suspension in 1 mL of the vehicle, once daily, for a period of 40 days. Throughout the treatment, blood was collected from the heart cavity for clinical pathology assessment, which included analysis of various hematological parameters and biochemical parameters. II group was accepted on the 10th day, III– on the 20th, IV – 30th, V – the 40th day accordingly. A Testmetric M500-100AT universal testing machine (100 KN maximum load, embedded computer) was used in the experiment.

**Results experimental and discussion**

The synthesis of nanocrystalline calcium carbonate-phosphate doped with microelements and having a transdermal effect was performed by the development of ammonium calcium hydroxy-carbonate containing different doping cations of microelements which are specific for living tissue and which enter the calcium channels of the crystal structure. The biomaterial based on doped nanocrystalline calcium carbonate-phosphates has a high degree of resorption; it is used to activate osteogenesis in a human organism of any age in order to both restore and strengthen bone tissues, as well as to strengthen tooth tissue.

The formation of complex compounds of \( M_n M'_x (OH)_2 [(CO_3)_{n-1} \cdot x \cdot (OH)] \) is typical for transition elements. For example, in the medium of ammonium hydroxide, three polymorphic forms of \( CaCO_3 \) can form metastable ammonium hydroxy-carbonate complexes on the following reaction:

\[
CaCO_3 + NH_4 OH \rightleftharpoons NH_4 CaCO_3 OH
\]  

According to the law of mass speed reactions (1) characterizes the equation

\[
\frac{dx_1}{dt} = k_1[NH_4][OH];
\]

The formation of three types of crystal structures of calcium carbonate (in the medium of ammonium hydroxide and ammonium chloride) is typical for the reaction (1): calcite, vaterite, and aragonite, which was proven by the data of XRD.

In Figure 1 shows a crystal of calcite, aragonite, and vaterite. Calcium carbonate has the following crystalline system: calcite is rhombohedral, space group R-3c; hexagonal structure with space group R63/mmc vaterite; aragonite is orthorhombic with space group Pmcn.

Under the action of ortho-phosphoric acid in the presence of magnesium cations and silicon dioxide, carbonate is replaced in the phosphate group with the formation of CaHPO₄ (brushite) according to the reaction

\[
NH_4 CaCO_3 OH + H_3 PO_4 = CaHPO_4 + NH_4 + CO_2 + 2H_2 O
\]  

The doping of cations \( Mg^{2+}, Fe^{3+}, Zn^{2+}, Mn^{2+} \) leads to the basic crystal phase of phosphate hydrogen \( Ca_9 H_2 (PO_4)_6 \cdot 5H_2 O \), for example, by equation (3):

\[
10NH_4 CaCO_3 OH + 6H_3 PO_4 = Ca_9 H_2 (PO_4)_6 + 2CaCO_3 + 8CO_2 + 10NH_4 OH + 8H_2 O
\]  

The reaction rate (2, 3) is a direct response

\[
\frac{dx_23}{dt} = k_{23}[NH_4]^+[O^H^-][H_2 PO_4^-]^m
\]

The next stage in the presence of such doping microelements as \( K^+, Mg^{2+}, Fe^{3+}, Zn^{2+}, Mn^{2+}, \) \( Au^{3+}, Si^{4+} \) microelements is the formation of hydroxychlorapatites.

The general schema will be the next:

\[
3CaHPO_4 + 2CaCO_3 + 8NH_4 Cl + 6H_2 O + CO_2 \rightleftharpoons Ca_{10}(PO_4)_6(OH)_2 + 3NH_4 HCO_3 + 3NH_4 Cl + CO_2 + 6H_2 O
\]

The reaction rate (4,5) is characterizing the equation:

\[
\frac{dx_45}{dt} = k_{45}[NH_4]^+[CO_3]^-
\]

In addition CaHPO_4 transforms into CaCO_3:

\[
CaHPO_4 \rightleftharpoons CaCO_3
\]

Thereby in the presence of such doping as \( K^+, Mg^{2+}, Fe^{3+}, Zn^{2+}, Mn^{2+}, Au^{3+}, Si^{4+} \) microelements is the formation of hydroxychlorapatites. The samples compositions inferred from chemical analysis, X-Ray diffraction (XRD Figure 2, Table 1), and IR spectroscopy data agree well. In Fig. 2 presented diffraction pattern of doped cations magnesium, zinc, iron (a) and doped magnesium, zinc, iron, gold (b) calcium carbonate-phosphate.

In connection (samples gold calcium carbonate-phosphate include: brushit-36.6%; calcite-13.5% %; hydroxyapatite \( Ca_5(PO_4)_3 OH \). SEM micrographs of synthetic calcium carbonate: calcite, vaterite, and aragonite and doped Fe 0.004; Mg 0.007; Zn 0.002; Mn 0.00002 mol. % calcium carbonate-phosphate shown in Figure 3.

The IR spectra of the samples doped calcium carbonate-phosphates show absorption bands due valence vibrations of the group at \( \delta_1 = 525, 560, \) and 600 cm⁻¹; symmetric vibrations at \( \nu_1 = 525, 560 \) and 600 cm⁻¹ and asymmetric vibrations at \( \nu_2 = 1038, 1078, 1100-1118 \) cm⁻¹ and also an absorption band corresponding the deformation vibrations of the group at \( \nu_3 = 420 \) cm⁻¹. The absorption band 1630 cm⁻¹ corresponds to deformation vibrations OH-water groups. Absorption band 3800 cm⁻¹ corresponds to valence vibrations molecule \( H_2 O \) and are features crystallization water. The values for the triplet valence fluctuation of the phosphate- group \( \delta_2 \) agrees to known [37].

The particle-size analysis has shown that the composition of calcium carbonate-phosphate samples is polydisperse. The basic fraction of particles ranges from 5 to 20 microns for samples doped with cations. In addition the ultra-dispersed fraction with the size of particles up to 10 nm in amounts of 4.5% is observed.

When conducting biomedical research it was found that owing transit to doped calcium carbonate-phosphate through the epithelium and through the skin is increase of the bone strength in living organism, it restores the trauma bone tissue and tooth tissue [38,39].
Figure 2. XRD pattern of doped calcium carbonate-phosphates: doped magnesium, zinc, iron (a) and doped magnesium, zinc, iron, gold (b).

Table 1. Elemental and phase compositions of doped calcium carbonate phosphates.

<table>
<thead>
<tr>
<th>Mole percent</th>
<th>Phase composition, wt. %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fe 0.001, Mg 0.02, Zn -</td>
<td>CaH$_2$(PO$_4$)$_6$·5H$_2$O 76%</td>
</tr>
<tr>
<td>Mn, Au - -</td>
<td>Ca$_9$P$<em>6$O$</em>{23}$·Cl$<em>2$·(OH)$</em>{2.01}$ 18%</td>
</tr>
<tr>
<td>SiO$_2$ -</td>
<td></td>
</tr>
<tr>
<td>Fe 0.001, Mg 0.005, Zn 0.002, Mn 0.001</td>
<td>CaH$_2$(PO$_4$)$_6$·2H$_2$O 72%</td>
</tr>
<tr>
<td>Mn, Au - -</td>
<td>Ca$_9$P$<em>6$O$</em>{23}$·Cl$<em>2$·(OH)$</em>{2.01}$ 13%</td>
</tr>
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<td></td>
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</tr>
<tr>
<td>SiO$_2$ -</td>
<td></td>
</tr>
<tr>
<td>Fe 0.002, Mg 0.06, Zn 0.002</td>
<td>CaH$_2$(PO$_4$)$_6$·2H$_2$O 70%</td>
</tr>
<tr>
<td>Mn, Au - -</td>
<td>Ca$_9$P$<em>6$O$</em>{23}$·Cl$<em>2$·(OH)$</em>{2.01}$ 18%</td>
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</tr>
<tr>
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<td></td>
</tr>
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<td>CaH$_2$(PO$_4$)$_6$·2H$_2$O 80%</td>
</tr>
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<td>Mn, Au - -</td>
<td>Ca$_9$P$<em>6$O$</em>{23}$·Cl$<em>2$·(OH)$</em>{2.01}$ 18%</td>
</tr>
<tr>
<td>SiO$_2$ -</td>
<td></td>
</tr>
<tr>
<td>Fe - 0.002, Mg 0.06, Zn 0.001</td>
<td>CaH$_2$(PO$_4$)$_6$·2H$_2$O 85%</td>
</tr>
<tr>
<td>Mn, Au - -</td>
<td>Ca$_9$P$<em>6$O$</em>{23}$·Cl$<em>2$·(OH)$</em>{2.01}$ 7%</td>
</tr>
<tr>
<td>SiO$_2$ -</td>
<td>Ca$_9$H$_2$(PO$_4$)$_6$·H$_2$O·K$_2$CO$_3$·H$_2$O 6%</td>
</tr>
<tr>
<td>Fe - 0.003, Mg 0.01, Zn 0.001</td>
<td>CaHPO$_4$·2H$_2$O 60%</td>
</tr>
<tr>
<td>Mn, Au - -</td>
<td>Ca$_9$H$_2$(PO$_4$)$_6$·5H$_2$O 16%</td>
</tr>
<tr>
<td>SiO$_2$ -</td>
<td></td>
</tr>
<tr>
<td>Fe - 0.004, Mg 0.035, Zn 0.002</td>
<td>CaHPO$_4$·2H$_2$O 80%</td>
</tr>
<tr>
<td>Mn, Au - -</td>
<td>Ca$_9$H$_2$(PO$_4$)$_6$·5H$_2$O 86%</td>
</tr>
<tr>
<td>SiO$_2$ -</td>
<td></td>
</tr>
<tr>
<td>Fe - 0.002, Mg 0.02, Zn 0.001</td>
<td>CaHPO$_4$·2H$_2$O 10%</td>
</tr>
<tr>
<td>Mn, Au - -</td>
<td>Ca$_9$H$_2$(PO$_4$)$_6$·5H$_2$O 50%</td>
</tr>
<tr>
<td>SiO$_2$ -</td>
<td></td>
</tr>
</tbody>
</table>

Evidence is the participation in the osteogenesis doped calcium carbonate-phosphate in the process of rebuilding bone with bone fractures and its reinforcement. In addition, when realize the subcutaneous implantation the powder form after 26-30 days doped calcium carbonate-phosphate fully absorbed in tissues of animals without any inflammatory reactions. There has been an increase in the concentration of calcium and mechanical fracture strength of the bone tissue [39].

It was established that the level of cholesterol in the blood plasma, including low-density lipoprotein decreases 2-2.5 times, which is particularly positive (Figure 4).

The level of cholesterol significantly decreases that may be a positive sign of doped calcium carbonate-phosphate influence [40].

The influence of doped calcium carbonate-phosphate on the structure of newly formed bone tissue in the area of the fracture has research using histomorphological analysis. The samples of bone calluses in animals investigated receiving treatment in the form of doped calcium carbonate-phosphate.

Sampling carried out on 60 day after surgical intervention after humane euthanasia. At 60 days of histologically observed the existence of hotbeds of cartilage tissue samples of bone calluses animals (Figure 5a), whereas prototypes receiving treatment with doped calcium carbonate-phosphate is defined fully formed bone (Figure 5b).

Figure 6 presents a diagram of tensile strength for the destruction of bone tissue depending on the samples of doped calcium carbonate-phosphates used for introduction into the animals.

The mechanical fracture strength of bone tissue increases almost 5 times.

For the education of the implant used the poly(β-caprolactone). For research was generating of the following mixture of the

<table>
<thead>
<tr>
<th>Chemical elements, sample 1</th>
<th>Chemical elements, sample 2</th>
<th>Chemical elements, sample 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ca, wt.%</td>
<td>P, wt.%</td>
<td>Mg, mol.%</td>
</tr>
<tr>
<td>33-35</td>
<td>16-17</td>
<td>0.005</td>
</tr>
<tr>
<td>Fe, mol.%</td>
<td>0.001</td>
<td>K, mol.%</td>
</tr>
<tr>
<td>0.002-0.003</td>
<td>0.003</td>
<td>Li, mol.%</td>
</tr>
<tr>
<td>Mg, mol.%</td>
<td>Fe, mol.%</td>
<td>K, mol.%</td>
</tr>
<tr>
<td>0.005</td>
<td>0.002</td>
<td>Zn, mol.%</td>
</tr>
<tr>
<td>0.002-0.03</td>
<td>0.02</td>
<td>SiO₂</td>
</tr>
<tr>
<td>Ca, wt.%</td>
<td>P, wt.%</td>
<td>Fe</td>
</tr>
<tr>
<td>33-35</td>
<td>16-17</td>
<td>0.004</td>
</tr>
<tr>
<td>Mg</td>
<td>Fe</td>
<td>SiO₂</td>
</tr>
<tr>
<td>0.001</td>
<td>0.001</td>
<td>0.002</td>
</tr>
</tbody>
</table>

Figure 6. Mechanical fracture strength of bone tissue depending on the samples of doped calcium carbonate-phosphates used for the introduction into animals: point 1 on the x-axis is placebo, point 2 - sample 1, point 3 - sample 2, point 4 - sample 3 (Table 2).
polycaprolactone with doped calcium carbonate-phosphate: 5%, 10% and 15%.

Figure 7 presents a diagram of tensile strength for the destruction of the samples implants depending on the content of doped calcium carbonate-phosphate used for introduction into the poly(β-
caprolactone).

In Table 3 shows of uniaxial tensile test results, carry out when testing polycaprolactone composite with doped calcium carbonate-phosphate. The experimental results have been processed by methods of mathematical statistics. The best results have been observed with concentrations of 5-10% doped calcium carbonate-phosphate. Young’s modulus is maximal for specimens with 5% doped calcium carbonate-phosphate.

Thus, the possibility of application of doped calcium carbonate-phosphate has for implants by bone defects. These studies suggest doped calcium carbonate-phosphate is the most appropriate material, because reduce of the cholesterol rate in the blood.

Conclusion
The synthesis of nanocrystalline doped calcium carbonate phosphate with a transdermal effect was fulfilled by the creation through ammonium calcium hydroxy-carbonate complexes with entering doping cations of microelements which are specific for living tissue. Doped nanocrystalline calcium carbonate phosphate extends significantly the functionality for drug delivery: it can be used to acceleration up the processes of bone repair and bone tissue strengthening. The advantage over other calcium phosphate biomaterials is strengthening of bone and tooth tissues of a human being of any age, the substances being transported through skin to restore broken bones in a critically short period of time regardless of age. The mechanical fracture strength of bone tissue increases almost in 5 times. The level of cholesterol significantly decreases; this is a positive role of doped calcium carbonate-phosphate. The possibility of application of doped calcium carbonate-phosphate has for implants by bone defects.

The biomaterial based on nanocrystalline calcium carbonate-phosphates doped with K⁺, Mg²⁺, Fe²⁺, Zn²⁺, Mn²⁺, Au³⁺, SiO₂ can be considered a new-generation medicinal substance by drug delivery.

Acknowledgement
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References
13. Dorozhkin SV (2011) Biocomposites and hybrid biomaterials based on calcium orthophosphates. Biomater 1: 3-56. [Crossref]

Table 3. Test of uniaxial tensile results.

<table>
<thead>
<tr>
<th>№</th>
<th>δ, Elongation %</th>
<th>E, Young’s modulus, GPa</th>
<th>σ, Strength, MPa</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (0%)</td>
<td>215</td>
<td>0,331</td>
<td>12,3</td>
<td>homogeneous</td>
</tr>
<tr>
<td>2 (5%)</td>
<td>535</td>
<td>0,426</td>
<td>19,9</td>
<td>homogeneous</td>
</tr>
<tr>
<td>3 (10%)</td>
<td>566</td>
<td>0,392</td>
<td>17,0</td>
<td>homogeneous</td>
</tr>
<tr>
<td>4 (15%)</td>
<td>409</td>
<td>0,286</td>
<td>10,1</td>
<td>The structure of the sample is not homogeneous</td>
</tr>
</tbody>
</table>


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