Volume 6, Issue 6, 2016, 1879 - 1882 ISSN 2069-5837

Biointerface Research in Applied Chemistry

www.BiointerfaceResearch.com

Original Research Article **Open Access Journal**

Received: 30.08.2016 / Revised: 28.11.2016 / Accepted: 12.12.2016 / Published on-line: 15.12.2016

Oscillating reactions in the synthesis of doped nanocrystalline calcium carbonate phosphates of transdermal ability

Lyubov Fedorovna Koroleva [1]

[1] Institute of Engineering Science of the Russian Academy of Sciences, Ural Branch, 34 Komsomolskaya St., Ekaterinburg, 620049, Russia

*corresponding author e-mail address: ***lq@imach.uran.ru***

ABSTRACT

Doped calcium carbonate-phosphate is a biocompatible material that influence actively on the osteogenesis, bone regenerate, strengthening of bone and dental tissues including through the transdermal absorption. A mechanism of the synthesis reactions of doped nanocrystalline calcium carbonate -phosphate an oscillating type of model for these reactions is proposed. The results indicate that the synthesis involves the formation of hydroxycarbonate complexes from the three calcium carbonate polymorphs (calcite, vaterite, and aragonite) in a solution of ammonium chloride and ammonium carbonate, followed by reaction with orthophosphoric acid. This ensures the preparation of a bioactive material based on octacalcium hydrogen phosphate, and calcium chloride hydroxide phosphates containing cation vacancies. The biomaterials have transdermal ability.

Keywords: *Doped, Calcium carbonate-phosphate; Phosphate chloride; Synthesis; Oscillating type; biocompatible materials; Osteogenesis.*

1. INTRODUCTION

The synthesis of nanocrystalline doped calcium hydroapatites in order to obtain composite materials and use them in orthopedics to substitute bone tissue is one of the most topical directions of bioceramics all over the world [1–8].

However, the problems of modern medicine and bioceramics include not only the creation of implants for substituting bone tissue and organs, but the synthesis of biologically active materials supporting the more complete restoration of tissues and maintaining the necessary functions of the organism. Calcium is a construction material for the inorganic part of the bone tissue. Seventy percent of the solid residue of bone tissue consists of calcium hydroxyapatite $Ca_{10}(PO_4)_6(OH)_2$; 30% consists of the organic component (collagen protein). Osseous tissue should be characterized as an organic matrix impregnated by amorphous calcium phosphate $Ca_3(PO_4)_2$ and by crystals of calcium hydroxyapatite $Ca_{10}(PO_4)_6(OH)_2$, which is synthesized by the cells of osseous tissue called osteoblast. Except for Ca^{2+}, the structure of calcium hydroxyapatite of osseous tissue contains the following cations and anions: Na^+, K^+, Mg^{2+}, Fe^{2+}, Si^{4+}, Cl^-, and ; possibly Zn^{2+}; and, less desirable, Sr^{2+}, Al^{3+}, and Pb^{2+}. The content of anions of CO_3^{2-} in calcium hydroxyapatite of osseous tissue may reach 8 wt %; they replace hydroxyl and phosphate groups [9, 10].

After the age of 55, most people suffer from different joint diseases; a decrease of bone tissue strength, osteochondrosis, osteoporosis and, oftentimes, bone fractures, which is why it becomes necessary to create a light digestible material on the basis of inorganic calcium phosphate. It is very important that it is well delivered via skin while entering the bloodstream directly through capillaries and blood vessels.

The synthesis of nanocrystalline doped microelements of calcium carbonate phosphates with a transdermal effect was fulfilled by the creation of ammonium hydroxy-carbonate complexes of calcium entering different doping cations of microelements which are specific for living tissue and which enter the calcium channels of the crystal structure according to [11, 12]. The mechanism of obtaining this biomaterial is quite difficult, and this process can be considered oscillating reactions in a living organism [13].

Previously was considered the mechanism of the synthesis of nanocrystalline doped calcium carbonate-phosphates and proposed a model to describe the kinetics of oscillating system as brusselator of simple cubic nonlinearity [14].

The simplest classic example of the existence of autooscillations in the system of chemical reactions is the trimolecular model (“brusselator”) offered by I.R. Prigozhine and R. Lefebre [15]. 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:

$$\begin{gathered} A \rightarrow X \\ B + X \rightarrow Y + C \\ 2X + Y \rightarrow 3X \\ X \rightarrow R \quad (1) \end{gathered}$$

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 stage in chemical kinetics is not as common as in biomolecular processes, expressions for the speed of some chemical reactions in some definite cases can be called cubic-type.

2. RESULTS SECTION

From the aspect of quantum dynamics system state in the process of a chemical reaction is described by a wave function Ψ (x, t) depending on the coordinates of the nuclei of atoms x and time t. This function satisfies the Schrödinger equation temporarily and its square modulus |Ψ(x, t)|2 sets the distribution function of the coordinates of the nuclei:

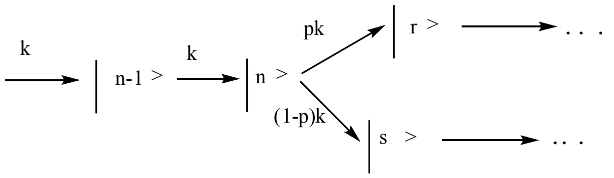
$$\frac{d^2\psi}{dx^2}+\frac{2m}{\hbar^2}\left[E-U(x)\right]\psi=0. \qquad (2)$$

The properties of time dependent wave function are determined by the views of potential energy surface and initial state Ψ (x, 0). The physical significance of wave function is that 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 func-tion of this condition in the coordinate representation. For the wave functions just the superposition principle, namely, that if the system can be in conditions that are waves/and/, then it can be and able, described the wave function:

$$\Psi_\Sigma = c_1\Psi_1 + c_2\Psi_2 \qquad (3)$$

In any complex C1 and C2.

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 modeled parallel reactions with rate constants are determined by the electronic transition probability p [16]:



(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, Ψ (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 one of the most simple (and therefore, most studied); all the dynamic leading to rupture the only connection is a potential energy surface, pure repulsion by nature.

The infinite movement of wave packet on this surface is described by a set of consecutive first- order reactions that you can watch in case of synthesis of doped calcium carbonate phosphates.

Calcium flows in and out of a cell through the plasmatic membrane considered there. Space time regimes, predicted in oscillating reaction–diffusion type models, can be observed in chemical reactions as well [17].

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, a key step in glycolysis [18, 19].

Reaction of the synthesis of doped calcium carbonate phosphates, which were described in [11, 20, 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^+, SiO_2).

The formation of complex compounds of $M_{g\text{-}x}M_x(OH)_2[(CO_3)_x\text{-}2H_2O]$ 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 scheme:

$$CaCO_3 + NH_4OH \rightleftarrows NH_4CaCO_3OH \qquad (5)$$

Or, in general form:

$$A \rightleftarrows X$$

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 (3): calcite, vaterite, and aragonite, which was proven by the data of XRD. 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

$$NH_4CaCO_3OH + H_3PO_4 = CaHPO_4 + NH_3 + CO_2 + 2H_2O \qquad (6)$$

The doping of cations $Mg^{2+,}$ Fe^{2+}, Zn^{2+}, Mn^{2+} leads to the basic crystal phase of phosphate hydrogen $Ca_8H_2(PO_4)_65H_2O$, for example, by equation (7)

$$10NH_4CaCO_3OH + 6H_3PO_4 = Ca_8H_2(PO_4)_6 + 2CaCO_3 + 8CO_2 + 10NH_4OH + 8H_2O \qquad (7)$$

Or, in the general form:

$$B + X \rightarrow Y + C$$

The next stage in the presence of such doping microelements as K^+, Mg^{2+}, Fe^{2+}, Zn^{2+}, Mn^{2+} and Si^{4+} is the formation of hydroxychlorapatites according to the following:

$$3CaHPO_4 + 2\,CaCO_3 + 2\,NH_4Cl + 2\,NH_3 + 3\,H_2O + CO_2 \rightleftarrows Ca_5(PO_4)_2(OH)_2Cl_2 + 3\,NH_4HCO_3 + NH_4H_2PO_4$$

$$Ca_8H_2(PO_4)_6 + 2CaCO_3 + NH_4Cl + NH_3 \rightleftarrows Ca_{10}(PO_4)_6OHCl + 2NH_4HCO_3 \qquad (8)$$

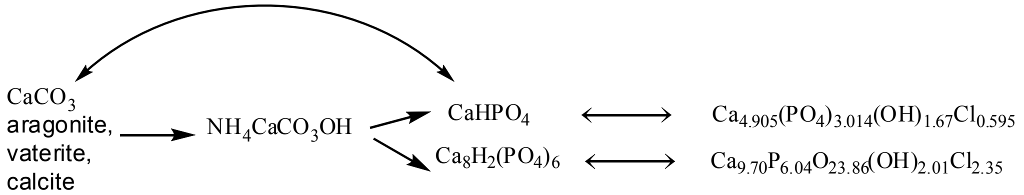
In addition $CaHPO_4$ transforms into $CaCO_3$:

$$CaHPO_4 \rightleftarrows CaCO_3 \qquad (9)$$

Description in the general form:

$$C \rightleftarrows A$$

Thereby in the presence of such doping as K+, Mg2+, Fe^{2+}, Zn^{2+}, Mn^{2+}, Si^{4+} microelements is the formation of hydroxychlorapatites. The schema will be the next:



According to the law of mass speed reactions (5) characterizes the equation

$$\frac{dx_5}{dt} = k_5[NH_4OH];$$

The reaction rate (7) is a direct response

$$\frac{dx_7}{dt} = k_7[NH_4^+]^{10}[H_2PO_4^-]^6$$

The reaction rate (8) is characterizing the equation:

$$\frac{dx_8}{dt} = k_8[NH_4^+][Cl^-][NH_3]$$

In Figure 1 shows the kinetic dependence of products receipt reaction in synthesis of doped calcium carbonate-phosphates, as in Figure 2 present data on the change of concentration of chloride ion (1), magnesium cations (2) and hydroxychlorapatites. (3). Sequence of education: brushite, hydroxychlorapatite, and calcite.

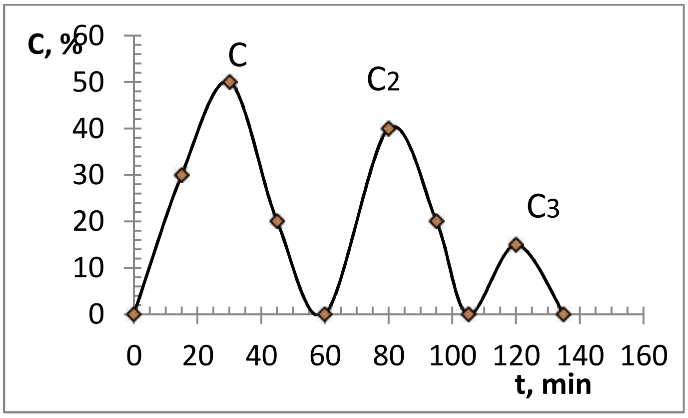


Figure 1. Kinetic changes of concentrations in the synthesis of doped calcium carbonate- phosphates: brushite (C1), hydroxychlorapatite (C2), calcite (C3).

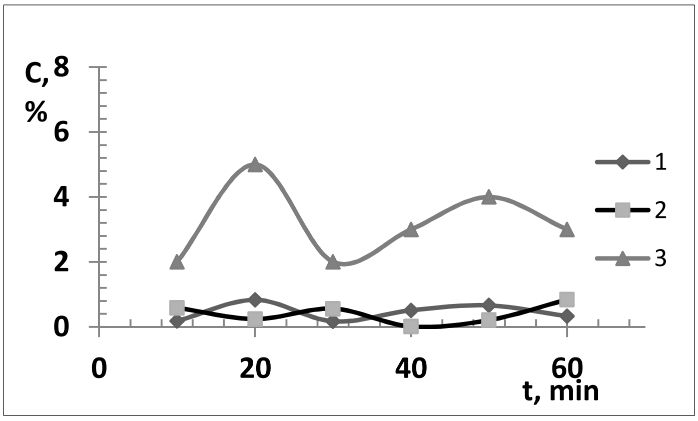


Figure 2. Kinetic concentration dependency: a) chloride ion (1), magnesium cations (2) and hydroxychlorapatite (3) synthesis of doped elements (Mg, Fe, Zn, Mn)-carbonate phosphate.

Thus, the mechanism of the reactions of synthesis of doped calcium carbonate – phosphate has a wave nature and can be represented by a model oscillating in nature. Data are confirmed by X-ray fluorescence analysis (EDX -900HS energy dispersive spectrometer), X-ray diffraction (XRD) STADI-P diffractometer, CuKα radiation, software for diffraction peak identification using JCPDS–ICDD PDF2 data X-ray analysis (11).

From the point of view of quantum chemistry does not contradict the basic wave equation, describing the State of the system.

It is shown that nanocrystalline doped calcium carbonate-phosphates are biocompatible, actively influencing the osteogenesis of bone fractures and their hardening with the delivery of medications. Introduction of doped nanocrystalline calcium carbonate-phosphates animals increases the mechanical strength of the bone tissue at fracture in 5 times. Duration of receipt of the calluses has 26 days. Our results demonstrate the possibility of obtaining bioceramics based doped nanocrystalline calcium carbonate- phosphates [22, 23].

Delivery of doped calcium carbonate- phosphates, cations and anions through the skin, makes it the promising biomaterial as a medicinal substance for bone fracture repair and hardening of bony dental tissue in the any age of human [24].

As one of the possible mechanisms for transporting the doped calcium carbonate- phosphates it can be assumed that in the process of transport occurs trans-membrane pH gradient. Within the existing structure of the ammonium cation doped calcium carbonate-phosphates education dissociate and be generated proton-containing phosphate on the surface of the membrane as a result of the ammonium cation:

$$NH_4^+ + Ca_{4.905}(PO_4)_{3.014}Cl_{0.595}(OH)_{1.67} \curvearrowright NH_3 + Ca_{4.905}(PO_4)_{3.014}Cl_{0.595}(OH)_{1.67}{*}H^+$$

Schema migration mechanism of doped calcium carbonate - phosphates molecules through the membrane is represented in Figure 3.

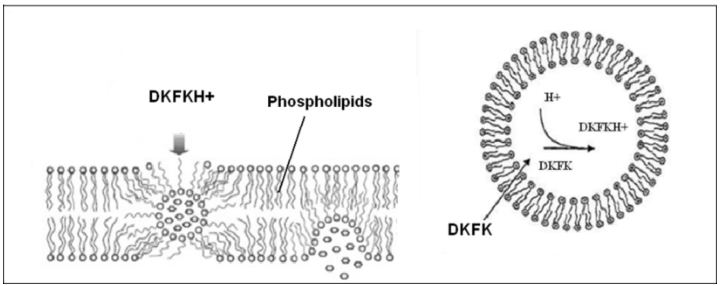


Figure 3. Scheme of the transport through the membrane doped calcium carbonate-phosphates (DKFK).

A similar scheme to transport drugs through the liposome by ammonium cation dissociation and hydrolysis with the formation of a proton is discussed in [25, 26]. In our case, the ammonium cation dissociation also can be found in the structure of the doped calcium carbonate- phosphates with the formation of a proton on the membrane surface.

3. CONCLUSIONS

Advantage over other biomaterials has to hardening of bone and tooth tissue at any age person with transportation of substances through the skin and restoring bone fracture in a critically short time period. Transdermal biomaterial based on doped nanocrystalline Fe^{2+}, Mg^{2}, Zn^{2+}, K^{+}, Si^{4+}, Mn^{2+} calcium carbonate-phosphates can be considered the medicinal substances of new generation.

4. REFERENCES

[1] Bouyer E., Gitzhofer F., Boulos M. I., Morphological study of hydroxyapatite nanocristal suspension, *J. of Materials Science: Materials in Medicin*e, 11, 523-531, **2000.**

[2] Jaroslav C., Klara C., Direct Synthesis of Nanocrystalline Hydroxyapatite by Hydrothermal Hydrolysis of Alkylphosphates. Monatshefte für Chemie, *Chemical Mont*hly, 133, 6, 761-771, **2002.**

[3] Samar J. K., Abhilasha B., Himesh A. B., Nanocrystalline calcium phosphate ceramics in biomedical engineering, *Materials Science and Engineering: C*, 27, 3, 441-449, **2007.**

[4] Mohammadi M. S, Ahmed I., Muja N., Almeida S., Rudd C. D., Bureau M. N., Nazhat S.N., Effect of Si and Fe doping on calcium phosphate glass fibre reinforced polycaprolactone bone analogous composites, *Acta Biomater*, 8, 4, 1616-1626, **2012.**

[5] Brigitte W. T., Jill D. P., A mineralogical perspective on the apatite in bone, *Materials Science and Engineering: C*, 25 131–143, **2005.**

[6] Changsheng L., Yue H., Wei S., Jinghua C., Kinetics of hydroxyapatite precipitation at pH 10 to 11, *Biomaterials*, 22, 301-306, **2001.**

[7] Sherina P., Zhimei D., Nora henriette de Leeuw., A computer modeling study of uptake, structure and distribution of carbonate defects in hydroxyl-apatite, *Biomaterials*, 27, 9, 2156-2161, **2006.**

[8] Li M., Xiao X., Liu R., Chen C., Huang L., Structural characterization of zinc-substituted hydroxyapatite prepared by hydrothermal method, *J. Mater Sci: Mater Med*., 19, 2, 797-803, **2008.**

[9]Hughes M. N., The Inorganic Chemistry of Biological Processes. Moscow: Mir, 348-358, **1983.**

[10]Yuri D. T., Development of inorganic chemistry as a fundamental for the design of new generations of functional materials, *Russian Chemical Reviews*, 73, 831-846, **2004.**

[11] Koroleva L. F., Doped Nanocrystalline Calcium Carbonate Phosphates, *Inorganic Mate*r, 46, 4, 405–411, **2010.**

[12] Koroleva L. F., Larionov L. P., Gorbunova N. P., Biomaterial based on doped calcium carbonate-phosphate for Active Osteogenesis, *J. of Biomaterials and Nanobiotechnology*, 3, 226-237, **2012.**

[13] Dupont G., Goldbetter A., Protein phosphorylation driven by intracellular calcium oscillations: a kinetic analysis, *Biophys. Chem*, 42, 257–270, **1992.**

[14] Koroleva L. F., An oscillating mechanism in the synthesis of doped nanocrystalline calcium carbonate phosphates, Nanotechnologies in Russia, 5, 9–10, 635–640, **2010.**

[15] Prigozhine I. R., Lefebre R., Simmetry breaking instabilities indissipative systems, *J. Chem. Phys*., 48, 1665-1700, **1968.**

[16] Eremin V.V., Pakhomova Yu.Yu., Kuz'menko N.E. Kinetic modeling of femtosecond dinamics of nuclei in systhems with avoided crossing of electronic terms. Russian Journal of Physical Chemistry A. 2004; 78(5): 735-740.

[17] Feleke E., Douglas F. R., Spike Frequency Decoding and Autonomous Activation of Ca2+– Calmodulin-Dependent Protein Kinase II in Dorsal Root Ganglion Neurons, *The Journal of Neuroscience*, 1, 21, 17, 6694–6705, **2001.**

[18] Dupont G., Goldbetter A., Oscillations and Waves of Cytosolic Calcium: Insights from Theoretical Models, *BioEssay*s, 14, 485–493 **1992.**

[19] McAinsh M. R., Brownlee C., Hetherington A. M., Visualizing changes in cytosolic-free Ca2+ during the response of stomatal guard cells to abscisic acid, Plant Cell, 4, 1113–1122, **1992.**

[20] Koroleva L. F., Larionov L. P., Gorbunova N. P., Doped Calcium Carbonate-Phosphate- Based Biomaterial for Active Osteogenesis. Osteogenesis. Edited by: Yunfeng Lin, *Publisher: InTech*, 5, 117-134 **2012.**

[21] Koroleva L. F., Doped Calcium Phosphates—A Promising Biomaterial, *Perspekt. Mate*r., 4, 30– 36, **2007.**

[22] Koroleva L. F., Dobrinskaya M. N., Kamantsev I. S., Doped nanocrystalline calcium carbonate-phosphate – a biomaterial for bone repair and strengthening by drug delivery, *Diagnostics, Resource and Mechanics of materials and structure*, 5, 147-157, **2015.**

[23] Dobrinskaya M. N., Larionov L. P., Koroleva L. F. Acute and subchronic toxicity investigation of new doped nanocrystallized materials. Proceedings of IRF International Conference, 28 February 2016, Goa, India, **2016.**

[24] Koroleva L. F., Nanocrystalline doped calcium carbonate-phosphates as a bio-material for osteogenesis, *Research Journal of Pharmaceutical*, Biological and Chemical Sciences. 5, 6, 704-710, **2014**.

[25] Eunkyoung J., Seung-Hoon C., Nam K. L., Sang-Kee K., Yun-Jaie C., Jae-Min S., Kihang C., Dong H. J., Machine learning study for the prediction of transdermal peptide, *J. Comput. Aided Mol Des*, 2, 339–347, **2011**.

[26] Tazina E. V., Kostin K. V., Oborotova N. A., Specific features of drug encapsulation in liposomes (A review), *Pharmaceutical Chemistry Journal*, 45, 8, 481-490, **2011**.

5. ACKNOWLEDGEMENTS

This research was funded by the Russian Basic Research Fund – Urals, project no. 07-03-96076-a**.**