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### **Kinetic characteristics of crystallization in prototypes of human blood plasma**

This paper presents the results of studies on the kinetics of nucleation and growth process of crystals in solutions simulating the composition of human blood plasma. By using optical density, conductivity and pH ranges of the identified properties of the system that simulates the blood plasma, depending on the supersaturation: 3–15, 15–30, 30–90. The order and the constant nucleation ( $n = 1.6$ ;  $k = 88.61$ ) calcium phosphate forming in model solution of blood plasma. A comparison of model types crystallization solutions for plasma systems with different initial supersaturation. And the presence of octocalciumphosphate calcium-deficient hydroxyapatite in the composition of the sediment was found. It was found that when the supersaturation changes the composition of the precipitate — calcium octophosphate in converted into hydroxyapatite. The influence of some inorganic (magnesium ions) and organic (alanine and glucose) additives on the crystallization kinetics of human plasma prototype was shown.

*Keywords:* kinetics of nucleation and crystal growth, solution of blood plasma, order and constant reaction, inorganic and organic additions, supersaturation, calcium phosphate.

#### *Introduction*

Crystallization processes of slightly soluble compounds have always attracted the attention of researchers [1, 2]. Interest in the study of these compounds due to the fact that they are part of the pathogenic and minerals are human diseases such as arteriosclerosis that is disease associated with the deposition of calcium salts in the blood vessels. This disease is the second of the prevalence of all sclerotic lesions of blood vessels after atherosclerosis. That's why researches of the Pathological Cardiovascular Deposits (PCD) possess high priority nowadays. Structure and chemical composition of PCD themselves have been already reported in a considerable amount of papers. It is common knowledge now that PCD consist of mineral and organic components [3–5]. Main mineral of the PCD is carbonated hydroxyapatite [5–11], but other minerals like Mg-containing whitlockite ( $\beta$ -TCMP) or calcite can also be presented [12]. PCD apatites as other biological apatites are non-stoichiometric, with high amount of  $\text{Na}^+$ ,  $\text{Mg}^{2+}$  and vacancies at Ca sites, carbonate- and hydrophosphate ions at  $\text{PO}_4^{3-}$  sites and with water at  $\text{OH}^-$  sites [4]. Their crystallite size are about 20–60 nm [5, 12].

Furthermore, the study of these compounds is of interest for the synthesis of the promising biomaterials [13]. Information about the crystallization of pathogenic and necessary for human body slightly soluble compounds from biological fluids is very few in number [14]. The main difficulty of the study of such systems is their composition. Biological fluids consist of inorganic and organic compounds [15].

For example, blood plasma is the link between all located outside the blood vessels fluids, that is why it was chosen as a model environment. Blood is liquid tissue in the body carries out transportation of chemicals. In addition, blood performs a protective, regulatory, and other thermoregulatory function.

The plasma occupies 55–60 % of blood volume. Plasma contains 90–91 % water and 9–10 % of dry substance. Low molar mass organic compounds (urea, uric acid, amino acids and so on) are very large and

complex structure of protein molecules, partially ionized inorganic salts is among the substances dissolved in the plasma [15].

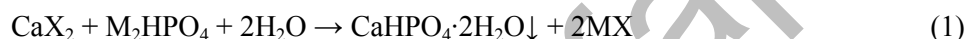
Percentage of pathogenic mineral formation in the blood vessels and heart valves increased in recent years. This is due to several factors as exogenous and endogenous nature [1, 16]. Therefore, the study of the processes of crystallization of poorly soluble compounds formed in the human body for the purpose of prevention and disease prevention is a promising area of research.

The purpose of the research is to study the kinetics of crystallization from simulated solutions of human blood plasma under near physiological conditions.

#### Materials and methods

The solutions containing ions, which joint presence does not yield in slightly soluble compounds, were used to study the crystallization of a solution simulating the composition of human blood plasma [15].

The choice of the initial reagents and their ratio in the solution was determined so that the concentration of ions and the ionic strength of the solution were as close as possible to the given parameters of the simulation system. Supersaturation was obtained due to the chemical reaction (1), which was realized through mixing the solutions of slightly soluble compounds of calcium chloride and hydrophosphates of ammonium and potassium in a crystallizer.



The initial reagents were salts of analytical and reagent grades and distilled water. For each series of the experiments, the solutions containing cations and anions, which joint presence does not form slightly soluble compounds under these conditions, were prepared. In each series of the experiments, the pH values were corrected to physiological pH (from 7.0 to  $8.0 \pm 0.01$ ) by adding a 20 % solution of NaOH (KOH) or HCl (concentrated). After mixing equivalent volumes of solution, the following parameters were determined: induction periods, optical density, electrical conduction and calcium concentration in solution. Following supersaturation: 5, 10, 20, 30, 40 were selected for kinetic studies. This is based on data obtained by determining the induction period. The pH was varied from 7.0 to 8.0 in increments of 0.1 during the subsequent experiments.

To study the influence of inorganic and organic compounds the following components were added to the simulation system (Table 1) in physiological concentrations and exceeding their pH.

Table 1

Concentrations of variation of the studied additions

Substance	Concentration, mmol/l		
	$C_{\text{phys}}$	$C_{\text{phys}} * 50$	$C_{\text{phys}} * 100$
Lactic acid	1.15	57.5	115
Glucose	4.55	227.5	455
Citric acid	0.125	6.25	12.5
Magnesium ions	$C_{\text{phys}} * 2$	$C_{\text{phys}} * 4$	$C_{\text{phys}} * 6$
	1.9	3,8	5.7
Substance	Concentration, mol/l		
	$C_{\text{phys}}$	$C_{\text{phys}} * 50$	$C_{\text{phys}} * 100$
Alanine	0.495	24.75	49.5
Glycine	0.250	12.5	25

The visual method to measure the induction periods was used to determine the parameters of nucleation. The regulation of the nucleation process was carried out by observing the uniformity of conditions of mixing. The time of the turbidity of solutions was determined with a stopwatch, 4–5 parallel measurements were performed for each concentration. The obtained data were processed using equation [17]. The dependence of the induction period on supersaturation enables to experimentally determine the free surface energy of the forming nucleus. The value  $\sigma$  was found by equation [17].

The crystallization rate was assessed by different methods (turbidimetric, potentiometric). The measurements were carried out with KFK-2, and distilled water was used as a blank reagent. The measurements of the optical density of solutions were made at a wavelength  $\lambda = 670$  nm in Baly tubes with light path  $l = 2.007$  cm. Three parallel measurements were made for each experiment. The error did not exceed 5 %.

The potentiometric method (ionomer «I-150-MI») was used to study partial dependencies of the kinetics of crystallization by deposit-forming ions (calcium ions). The calcium ions concentration in the crystallization process was determined by the direct potentiometry method using an ion-selective electrode. The crystallization was conducted in a temperature-controlled solution at  $25 \pm 0.5$  °C. The potential in the sample solution was measured after certain time periods, and the concentration of  $\text{Ca}^{2+}$  ions was determined using the calibration curve. This experiment was repeated three times. The measurement error was 5–10 %.

In solid phase the end of the experiment filtered, dried and analyzed by X-ray diffraction analysis (XRD) qualitative and quantitative phase analysis. XRD was conducted with the Bruker D8 Advance X-ray diffractometer (Germany) in monochromate  $\text{Cu-K}\alpha$  radiation. The qualitative analysis of the phase composition of the sample was carried out by comparing the experimental values of the interplanar spaces and relative intensities of the diffraction peaks with a set of corresponding values for each of the proposed phases in the international database obtained by powder diffractometry PDF-2. IR spectra of the precipitates were recorded on a spectrophotometer FSM-2202. The scanning range was  $400\text{--}5000$   $\text{cm}^{-1}$ , the resolution was  $8$   $\text{cm}^{-1}$ . The samples were prepared by compression into tablets with KBr. The surface morphology was studied using optical microscopes MBS-9.

The statistical data processing was carried out using software StatSoft Statistica 6.0.

### Results and discussion

#### 1. Nucleation parameters

As the result of the research of the dependence of the induction time on supersaturation (Fig. 1), it is established that the curves are not linear and consist of three parts: for higher supersaturations, the induction times are very small; for average supersaturations, the induction times range from several seconds to several minutes; and for small supersaturations, the induction times increase rapidly, tending to infinity. This regularity can be explained by the fact that with the increase of supersaturation, the concentration of deposit-forming ions increases. The obtained values of the induction periods were used to calculate the overall order of the reaction by the graphical method [18]. The value of the order indicates the number of particles that make up the composition of the nucleus, and the constant value  $e$  characterizes the total number of the formed particles [18].

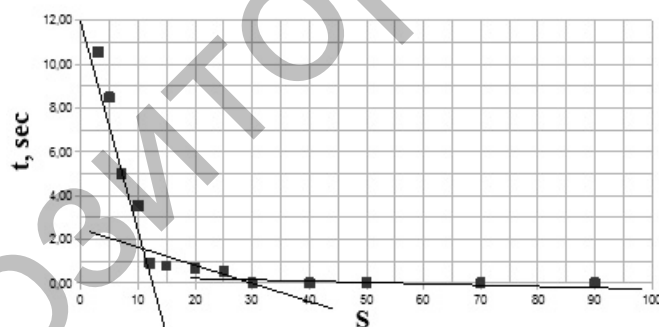


Figure 1. Dependence of the induction period on supersaturation in simulated solutions of blood plasma

In the first section of the induction time is changing quickly. In the third section the induction does not depend on the degree of supersaturation of the system and is practically unchanged.

Calculated overall reaction order is fractional and is equal to  $1.62 \pm 0.11$ . The set value of the rate constant was  $87.09 \pm 0.68$   $\text{mole}^{1-n} \text{s}^{-n}$ . It is well known that a value of the order indicates the number of particles entering into the embryo, and the constant value describes the total amount of particles formed [17].

The specific surface energy was calculated according to the Gibbs-Volmer theory based on the data of dependence of the nucleation on supersaturation [19]. As a result, it was discovered that at low supersaturation, specific surface energy is low, and at high supersaturation, it increases (Table 2). This points to the fact that with the increase in supersaturation, the transition from heterogeneous nucleation of crystallites to a homogeneous one is observed. Herewith, a smaller value of the specific surface energy is «effective», reflecting the adhesion of the nucleus in the active centre.

Table 2

## Dependence of the nucleation parameters from the supersaturation

S	Induction period, s	$\sigma$ , mJ/m <sup>2</sup>	R <sub>crit</sub> , nm
3	Stable system	2.2	0.52
5	10.56		0.35
10	8.48		0.24
15	5.02		0.21
20	3.54		0.21
30	0.92	2.4	0.18
40	0.80		0.17
50	0.70	3.2	0.20
60	0.52		0.20
70	0.10		0.19
90	0.06		0.18

On the basis of the thermodynamic model of nucleation and the calculated value of the specific surface energy, the size of the critical nucleus can be calculated according to equation (4) [17]. The nuclei with a size greater than the critical one are capable of further growth since their free energy decreases.

$$r^* = \frac{2\sigma}{RT \ln S} \quad (2)$$

The obtained results show that the size of the critical nucleus for two systems is in the range of 3–20  $\mu\text{m}$ , and with the increase of supersaturation in the solution, the size of the critical nucleus reduces, which is in agreement with the data reported in [17, 19].

It was found that in the simulated solution of blood plasma, the pH variation does not influence the induction periods. In our opinion, this is due to the presence of powerful buffer systems in the blood plasma-carbonate and phosphate. Additionally incorporated  $\text{H}^+$  and  $\text{OH}^-$  ions interact with the components of the buffer systems, and at that, no significant changes in the pH value and, therefore, in the properties of the system can be observed. The values of the constants are independent of pH both in the first and in the second regions. Thus, the change of pH in the range 7.0–8.0 is found to have no influence on the parameters of the process of crystallization of the simulated human blood plasma system.

It is known that inorganic and organic additions influence the processes of crystallization in biological matrixes [19]. In the study of the influence of magnesium ions on the stage of nucleation for two simulation solutions, it was found that the inhibitory effect of this additive increases as the ion concentration increases. Effect of the additions on the nucleation rate is shown in Table 3. It should be noted that for blood plasma, the influence of magnesium ions does not depend on supersaturation. The inhibitory effect of magnesium ions can be due to the formation of slightly soluble compounds of magnesium —  $\text{Mg}_3(\text{PO}_4)_2$  ( $p\text{PR}=13$ ).

Table 3

## The magnitude of induction periods when various concentrations of additions (S = 10, pH = 7.4)

Substance	Concentration, mmol/l	Induction period, s	$\sigma$ , mJ/m <sup>2</sup>	R <sub>crit</sub> , nm
1	2	3	4	5
Without additions	–	8.48	2.2	0.24
Magnesium ions	C <sub>phys.</sub> *2	10.56	1,7	0.08
	C <sub>phys.</sub> *4	15.52		0.08
	C <sub>phys.</sub> *6	23.22		0.06
Lactic acid	C <sub>phys.</sub>	5.24	3,2	–
	C <sub>phys.</sub> *50	15.65		0.21
	C <sub>phys.</sub> *100	no precipitation		0.17
Citric acid	C <sub>phys.</sub>	10.26	2,5	–
	C <sub>phys.</sub> *50	17.41		0.16
	C <sub>phys.</sub> *100	no precipitation		0.14
Glucose	C <sub>phys.</sub>	375.48	2,1	–
	C <sub>phys.</sub> *50	461.94		0.14
	C <sub>phys.</sub> *100	737.21		0.12

Continuation of Table 3

1	2	3	4	5
Glycine	$C_{phys.}$	365.24	0,6	–
	$C_{phys.}^*50$	368.32		0.37
	$C_{phys.}^*100$	365.94		0.31
Alanine	$C_{phys.}$	384.41	2,3	–
	$C_{phys.}^*50$	626.39		0.15
	$C_{физ.}^*100$	925.58		0.13

Thus, it is experimentally found that all of the selected additions effect on the nucleation step, namely, reduces the nucleation rate. By comparing the effect of additions, they can be ranked in a series to reduce the effect on the induction time: alanine > glucose > glycine > citric acid > lactic acid > magnesium ions.

In our opinion, organic supplements can provide two-way influence: organic molecules may adsorb on the surface of the formed crystals, thereby poisoning their growth and slowing growth; they can form sustainable integrated compound with calcium ions.

### 2. Kinetics of crystallization

To study the kinetics of crystal growth, a range of supersaturation was selected and the kinetic curves were taken (Fig. 2). In all the observed dependences for both considered systems, two distinct parts can be observed: first section corresponds to the increase in the number of particles in the volume; second section corresponds to the growth of the formed particles.

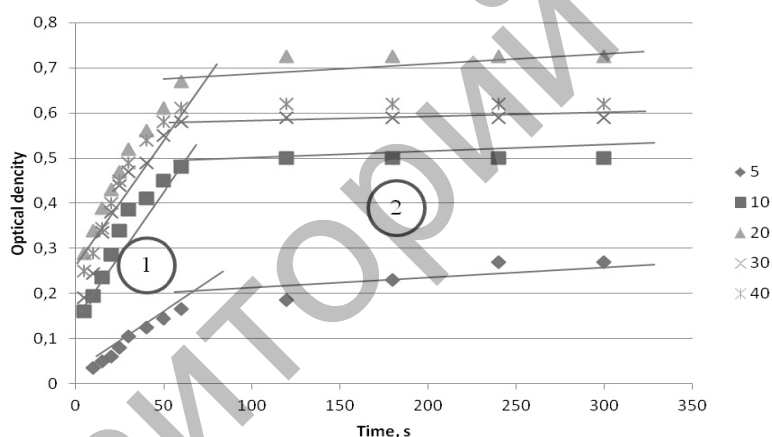


Figure 2. Example of the kinetic curves

The order reaction was determined by the graphical method for each of the sections (Table 4). Both for the first and for the second sections, the order is equal to zero which is characteristic of ion-exchange heterogeneous reactions that occur in the solution.

Table 4

The crystal growth rate constants, depending on the pH and supersaturation

Section	Supersaturation	Order	$k \cdot 10^3$ , mole/l*s
1	5	0	18.36
	10		6.50
	20		6.60
	30		6.90
	40		6.85
2	5	0	4.45
	10		0.20
	20		0.25
	30		0.15
	40		0.15

The rate constants were found. The calculations showed that for the first section, the rate constant is by an order of magnitude greater than for the second section for all considered supersaturations. The observed dependences and statistical processing of data indicate that an increase in supersaturation over 10, it does not influence significantly the magnitude of the rate constant. In our opinion, this is due to the high content of deposit-forming components: their concentration is so high that the expenditure of concentration on the formation and growth of crystals does not affect their contents.

Experimental dependence and statistical processing of data indicate that the increase in supersaturation ceases to significantly influence the value of the constant. This, in our opinion, due to the high content of sediment-components: their concentration is so high that the rate of formation and the growth of crystals do not affect their concentration.

It is noted that the dependence of the constants on the pH, and the supersaturation but the order of the values of the constants are not much different.

In our view the pH dependence of the constants associated with finding a form of phosphate ions in the solution. Hydrogenphosphate and dihydrogenphosphate ions present in the range of pH 7 to 8, therefore calcium octophosphate (pH 5.5–7.0), calcium-deficient hydroxyapatite (pH = 6.5–9.5), and amorphous calcium phosphate (pH = 5–12) can crystallize in this pH range. This confirms the complexity of the processes.

To compare the crystallization processes that occur at different supersaturations, the value of the efficiency of the crystallization behavior (conversion  $\alpha$ ) was used [18]. The second section is of greatest interest in the study of kinetic curves (Fig. 2). It corresponds to the crystal growth, so it was used to calculate the basic kinetic characteristics. The order of the rate constant (for the second stage) obtained in the experimental data processing is shown in Table 5.

Table 5

#### Kinetic characteristics of the crystallization process in blood plasma

Supersaturation, S	Order	$R^2_{\text{tabl}}$	$R^2_{\text{calc}}$	$\lg K'$
5	0.59±0.12	0.514	0.6585	2.56±0.20
10	0.58±0.14		0.7641	2.01±0.35
20	0.46±0.11		0.8035	2.00±0.53
30	0.41±0.17		0.6367	2.04±0.58
40	0.32±0.09		0.8452	2.00±0.46

The analysis showed that the particular order by calcium ions for simulated systems does not exceed a unit; this value is typical of the systems where heterogeneous nucleation and further growth prevail. The solutions with supersaturation were used to study the influence of various additions on the stages of crystal growth: blood plasma S=10. The data processing showed that the order for the systems in the presence of additions, as well as for the system in the absence of additions is less than a unit. The value of the rate constant is less than that for the system in the absence of additions.

The constants of the order of the reaction and the rate is determined by the graphical method for obtaining kinetic curves. The equation for the second-order reaction describes the growth kinetics in studied system most adequately. Accordingly, the rate constant was calculated (Table 6).

Table 6

#### The rate constants of crystal growth in the presence of additions

Substance	Concentration	Rate constant, $1/s \cdot 10^{-3}$
Without additions	–	37800
Magnesium, mmol/l	$C_{\text{phvs.}} \cdot 2$	5.00
	$C_{\text{phvs.}} \cdot 4$	5.00
	$C_{\text{phvs.}} \cdot 6$	5.00
Alanine, mol/l	$C_{\text{phvs.}}$	2.50
	$C_{\text{phvs.}} \cdot 50$	3.33
	$C_{\text{phvs.}} \cdot 100$	5.00
Glucose, mmol/l	$C_{\text{phvs.}}$	1.67
	$C_{\text{phvs.}} \cdot 50$	3.33
	$C_{\text{phvs.}} \cdot 100$	16.7

Magnesium ions, at concentrations of five or ten times exceeding the value of biological pH, reduce the rate of crystallization proportionally to the increase in the content of this component, but herewith do not influence the corresponding constants and the order. If the concentration fifteen-fold increases, not only the rate of crystallization, but also the constants in each of the plots decrease. Glucose enhances the rate of crystallization in the simulated solution of saliva, and its effect appears for both studied stages. This may occur because of the formation of complex compounds of calcium ions with glucose.

For the simulated solution of blood plasma, it was found that the greater the concentration of glucose and alanine in the solution, the lower the concentration of calcium ions in solution.

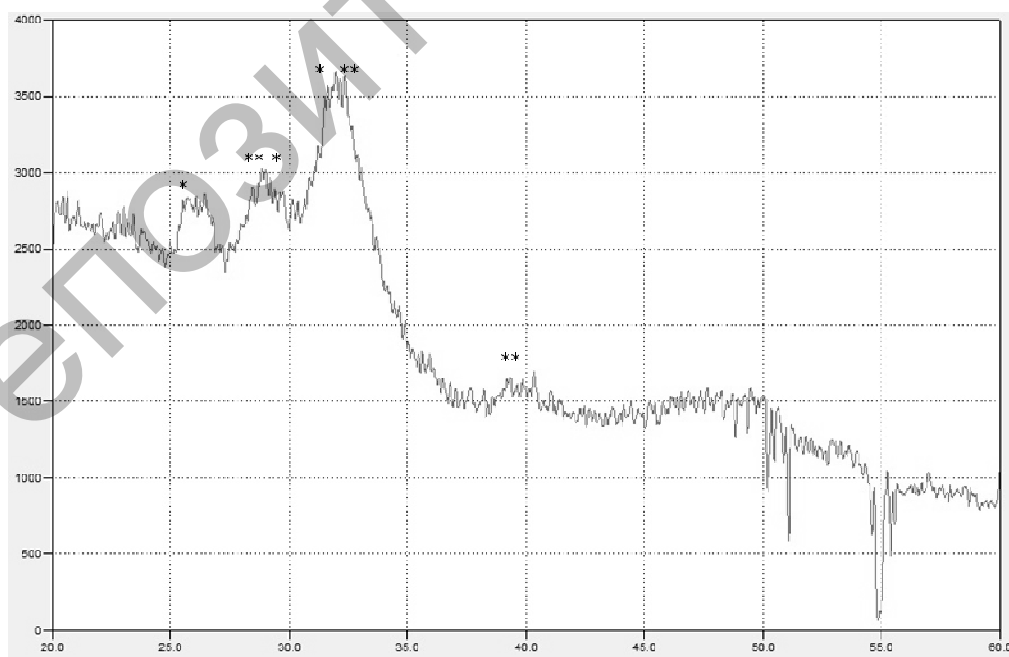
Comparing the influence of additions on the nucleation phases and on the crystal growth, it should be noted that the effect is more distinct at the stage of nucleation.

The pH of the solution plays an important role in the formation of a mineral component from the bioliquid prototypes. It is known [20] that in a three-component system  $\text{Ca}(\text{OH})_2\text{-H}_3\text{PO}_4\text{-H}_2\text{O}$ , can be found eleven known unsubstituted calcium phosphate with atomic ratio of Ca/P in the range 0.5 and 2.0. The most important parameters are the value of the atomic ratio of Ca/P, basicity/acidity and solubility. These parameters strongly depend on the pH of the solution. The lesser the value of Ca/P, the more acidic and water-soluble calcium orthophosphate is. Due to the three-fold ionic equilibrium in the solution containing phosphate ions, the pH change leads to the change in relative concentrations of the four polymorphic forms of phosphoric acid, and hence, the chemical composition and the amount of calcium orthophosphate, which are formed as a result of direct deposition.

In the study of kinetic regularities depending on the pH, we found that as pH grows, the order and the constant of crystallization remain the same, but the rate of the deposit formation changes. Thus, at the  $\text{pH}=6.80\pm 0.01$ , the rate of crystallization in both regions for two systems is reduced on average by 1.3 times, while as pH increases to  $7.10\pm 0.01$ , the rate increases in both stages in 1.3–1.6 times that can be explained by the predominance of one of the forms of the phosphate ions in the solution.

### 3. The results of XPA and IR spectroscopy

X-ray diffraction analysis of the synthesized solid phases obtained from the simulated solution of the blood plasma showed that carbonated hydroxyl-apatite ( $\text{Ca}_{10-x/2}(\text{PO}_4)_{6-x}(\text{CO}_3)_x(\text{OH})_2$ ) and whitlockite ( $\text{Ca}_9\text{Mg}(\text{PO}_4)_6(\text{PO}_3\text{OH})$ ) are found in the deposit. Low intensity and half-width of the diffraction reflections indicate low crystallinity of the obtained powders (Fig. 3). The crystallite size was estimated from the parameters of the most resolved peaks, it was 8.2 nm.

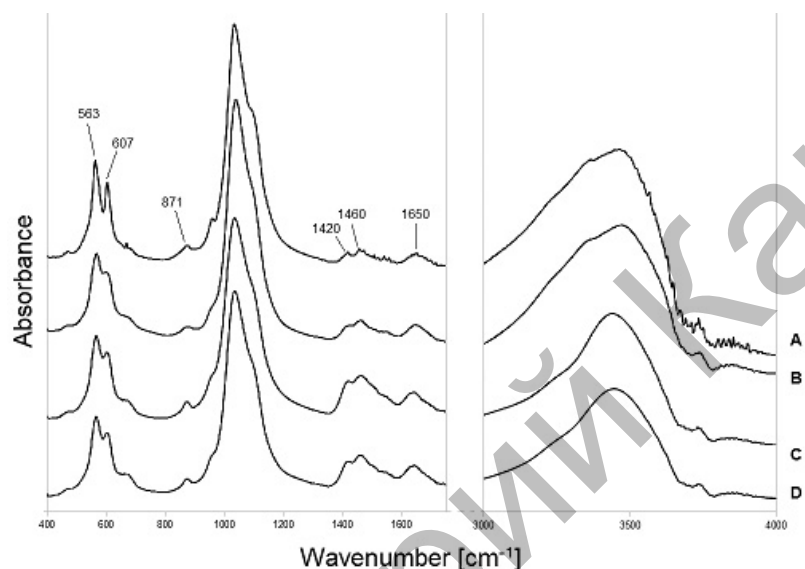


\* — the peak of whitlockite; \*\* — the peak of carbonate hydroxylapatite

Figure 3. The results of X-ray phase analysis of sediments from supersaturation 10

The diffraction patterns of solid phases, synthesized in the presence of the investigated additions, were obtained, wherein the peaks on the diffraction patterns of the samples in the presence of additions become more fuzzy as the additive ratio increases. The size of the crystallites in the presence of additions and without them was calculated. It was found that the size of the crystallites in the presence of additions decreases by an order of magnitude. This may be due to the adsorption of molecules on the surface of the faces, crystal face poisoning and deceleration in growth of the rate of crystallites which is in agreement with the previously obtained kinetic data.

Examination of the samples by IR spectroscopy allows making adjustments to the composition and structure of the prepared samples. Interpretation of the data was carried out by qualitative identification of the absorption bands of oscillations groups in the IR spectra of the samples (Fig. 4).



Supersaturation — 50; experiment time, weeks: A — 2; B — 4; C — 10; D — 12

Figure 4. Typical IR-spectra of the synthesized apatites

Thus, the composition of the obtained solid phase is detected the mixture of whitlockite and carbonate hydroxylapatite A-type. It is known that whitlockite is a precursor of hydroxyapatite. Consequently phase mixture may be formed due to insufficient crystallization time.

The obtained results are confirmed by optical microscopy of the test solutions. With a large supersaturation inclusions of hydroxyapatite aggregates are well observed in the images (Fig. 5).

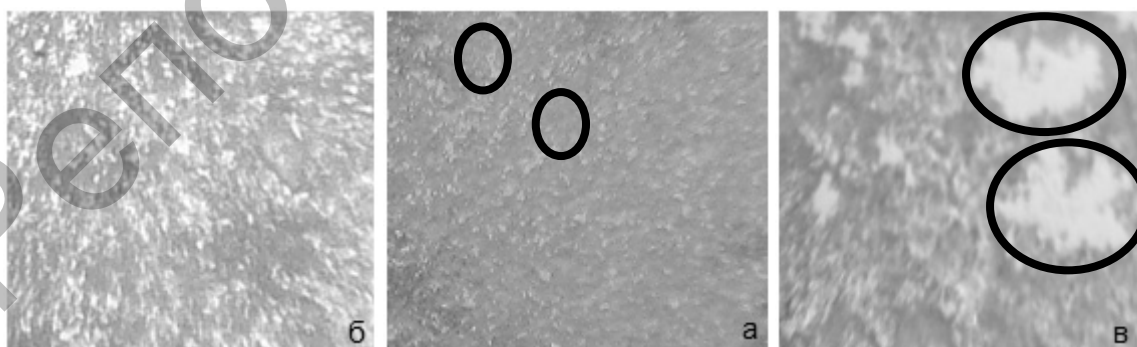


Figure 5. Optical microscopy results of supersaturation 5 (a) and 20 (b), 40 (c), increase  $\times 120$

The obtained results are confirmed by optical microscopy of the test solutions. With a large supersaturation inclusions of hydroxyapatite aggregates are well observed in the images (Fig. 5).

### Conclusion

As the result of this research, the crystallization process from solutions simulating the composition of human plasma under near physiological conditions is studied. The kinetic characteristics of the processes are obtained: defined order and constant of nucleation; found that with increasing supersaturation transition from heterogeneous nucleation of crystallites to a homogeneous is observed; estimate the critical size of nuclei; defined order and constant crystallization; at the nucleation stage and the stage of their growth  $n = 0$ .

The influence of a number of additions in biological fluids on the processes of crystallization in the prototype of blood plasma is found. By comparing the effect of additions, they can be ranked in a series to reduce the effect on the induction time: alanine > glucose > glycine > citric acid > lactic acid > magnesium ions.

In composition of the obtained solid phase is detected the mixture of whitlockite and carbonate hydroxylapatite A-type.

### References

- 1 *Баринов С.М.* Тенденции в разработке керамических и композиционных материалов на основе фосфатов кальция // Рос. хим. журн. — 2009. — Т. LIII, № 2. — С. 123–130.
- 2 *Герк С.А., Голованова О.А., Клушин В.А.* Фазовый, элементный, аминокислотный и структурный состав физиогенных минералов // Бутлеровские сообщения. — 2012. — Т. 32, № 12. — С. 80–89.
- 3 *Le Geros R.Z.* Formation and transformation of calcium phosphates: relevance to vascular calcification // Zeitschrift fur Kardiologie. — 2001. — No. 3. — P. 116–124.
- 4 *Титов А.Т., Ларионов П.М., Зайковский В.И., Иванова А.С.* Гидроксилapatит в крови человека // Поверхность, рентгеновские, синхротронные и нейронные исследования. — 2000. — № 7. — С. 66.
- 5 *Becker M., Epple K., Mueller M., Schmitz I.* A comparative study of clinically well-characterized human atherosclerotic plaques with histological, chemical and ultrastructural methods // J. of Inorganic Biochemistry. — 2004. — P. 2032–2038.
- 6 *Росеева Е.В., Николаев А.М., Морозов М.В., Франк-Каменецкая О.В., Ламанова Л.М.* Биоapatит кальцификатов сердечных клапанов // Материалы докл. годичного собрания РМО и Федоровской сессии. — 2012. — С. 306–308.
- 7 *Pigozzi F., Rizzo M., Fagnani F., Parisi A., Spataro A., Casasco M., Borriore P.* Endothelial (dys)function: the target of physical exercise for prevention and treatment of cardiovascular disease // J. Sports Med. Phys. Fitness. — 2011. — P. 260–267.
- 8 *Гилинская Л.Г., Григорьева Т.Н., Окунева Г.Н., Власов Ю.А.* Исследование минеральных патогенных образований на сердечных клапанах человека. I. Химический и фазовый состав // Журн. структ. химии. — 2003. — Т. 44, № 4. — С. 678.
- 9 *Гилинская Л.Г., Окунева Г.Н., Власов Ю.А.* Исследование минеральных патогенных образований на сердечных клапанах человека. II. ЭПР спектроскопия // Журн. структ. химии. — 2003. — Т. 44, № 5. — С. 882.
- 10 *Гилинская Л.Г., Рудина Н.А., Окунева Г.Н., Власов Ю.А.* Исследование минеральных патогенных образований на сердечных клапанах человека. III. Электронная микроскопия // Журн. структ. химии. — 2003. — Т. 44, № 6. — С. 1122.
- 11 *Gibson I.R., Bonfield W.* Novel synthesis and characterization of an AB-type carbonate-substituted hydroxyapatite // J. Biomed. Mater. Res. — 2002. — P. 697–708.
- 12 *Danilchenko S.N., Kuznetsov V.N., Stanislavov A.S., Kalinkevich A.N., Starikov V.V., Moskalenko R.A., Kalinichenko T.G.* The mineral component of human cardiovascular deposits: morphological, structural and crystal-chemical characterization // J. Cryst. Res. Technol. — 2013. — No. 3. — P. 153–162.
- 13 *Jono S., Shioi A., Ikari Y., Nishizawa Y.* Vascular calcification in chronic kidney disease // J. Bone Miner. Metab. — 2006. — P. 176–181.
- 14 *Голованова О.А.* Биоминеральные композиты из организма человека: теория, практика, перспективы // Бутлеровские сообщения. — 2011. — Т. 24, № 3. — С. 113–122.
- 15 *Голованова О.А.* Особенности патогенного минералообразования // Вестн. Томск. гос. ун-та. — 2008. — № 313. — С. 215–224.
- 16 Биохимия / Под ред. Е.С. Северина. — М.: ГЭОТАР-Медиа, 2003. — 356 с.
- 17 *Голованова О.А., Ачкасова Е.Ю., Пунин Ю.О., Желяев Е.В.* Основные закономерности кристаллизации оксалата кальция в присутствии аминокислот // Кристаллография. — 2006. — Т. 51, № 2. — С. 376–382.
- 18 *Тодес О.М., Себалло В.А., Гольцикер А.Д.* Массовая кристаллизация из растворов. — Л.: Химия, 1984. — 232 с.
- 19 *Голованова О.А.* Патогенные минералы в организме человека. — Омск: Изд-во ОмГУ, 2007. — 396 с.
- 20 *Солоненко А.П., Голованова О.А.* Термодинамическое моделирование формирования ортофосфата кальция // Бутлеровские сообщения. — 2011. — № 2. — С. 106–112.

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### Адам қаны плазмасының прототиптерінде кристалданудың кинетикалық сипаттамалары

Оптикалық тығыздық, электрөткізгіштік және рН көрсеткіштерінің көмегімен қан плазмасының құрамын үлгілеуші жүйесінің қасиеттерінің шамадан тыс қанықтырылуына байланысты өзгеру аралықтары 3–15, 15–30, 30–90 айқындалды. Қан плазмасының үлгі ерітіндісінде пайда болатын кальций фосфаттарының нуклеациясының тұрақтылығы және реттілігі ( $n = 1.6$ ;  $k = 88.61$ ) анықталды. Бастапқы шамадан тыс қанықтырулары әр түрлі жүйелер үшін қан плазмасының үлгі ерітінділерінің кристалдану түрлеріне салыстырулар жүргізілді, тұнбаның құрамында фосфаттың октокальцийі және тапшы-кальций гидроксипатиттің бар екендігі белгілі болды. Адамның қан плазмасының түптулғасының кристалдану кинетикасына кейбір бейорганикалық (магний иондарының) және органикалық (аланиннің және глюкозаның) қоспаларының әсері зерттеліп, көрсетілді.

*Кілт сөздер:* кристалдардың пайда болу және өсу кинетикасы, қан плазмасы ерітіндісі, реакция жылдамдығының реті және тұрақтылығы, бейорганикалық және органикалық қоспалар, шамадан тыс қанықтырылу, кальций фосфаты.

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### Кинетические характеристики кристаллизации в прототипах плазмы человеческой крови

В статье представлены результаты исследований кинетики нуклеации и процесса роста кристаллов в растворах, моделирующих состав плазмы крови человека. С помощью оптической плотности, электропроводности и рН выявлены интервалы изменения свойств системы, моделирующей состав плазмы крови, в зависимости от пересыщения: 3–15, 15–30, 30–90. Определены порядок и константа нуклеации ( $n = 1.6$ ;  $k = 88.61$ ) фосфатов кальция, образующихся в модельном растворе плазмы крови. Проведено сравнение типов кристаллизации модельных растворов плазмы крови для систем с различным исходным пересыщением. В составе осадка обнаружено присутствие октокальцийфосфата и кальций-дефицитного гидроксипатита. Установлено, что при изменении пересыщения изменяется состав осадка — октофосфат кальция переходит в гидроксипатит. Показано влияние некоторых неорганических (ионов магния) и органических (аланина и глюкозы) добавок на кинетику кристаллизации протопита плазмы крови человека.

*Ключевые слова:* кинетика зародышеобразования и роста кристаллов, раствор плазмы крови, порядок и константа скорости реакции, неорганические и органические добавки, перенасыщение, фосфат кальция.

### References

- 1 Barinov S.M. *Russian chemical Journal*, 2009, 2, p. 123–130.
- 2 Herk S.A., Golovanova O.A., Klushin V.A. *Butlerov Communications*, 2012, 32(12), p. 80–89.
- 3 Le Geros R.Z. *Zeitschrift fur Kardiologie*, 2001, 3, p. 116–124.
- 4 Titov A.T., Larionov P.M., Zaikovskiy V.I., Ivanova A.S. *J. of Surface Investigation. X-ray, Synchrotron and Neutron Techniques*, 2000, 7, p. 66–73.
- 5 Becker M., Epple K., Mueller M., Schmitz I. *J. of Inorganic Biochemistry*, 2004, p. 2032–2038.
- 6 Rosseeva E.V., Nikolaev A.M., Morozov M.V., Frank-Kamenetskaya O.V., Lamanova L.M. *Proceedings of the Annual Session combined with the Fedorov Session*, 2012, p. 306–308.
- 7 Pigozzi F., Rizzo M., Fagnani F., Parisi A., Spataro A., Casasco M., Borrione P. *Sports Med. Phys. Fitness*, 2011, p. 260–267.
- 8 Gilinskaya L.G., Grigor'eva T.N., Okuneva G.N., Vlasov Yu.A. *J. of Structural Chemistry*, 2003, 44, 4, p. 678.
- 9 Gilinskaya L.G., Okuneva G.N., Vlasov Yu.A. *J. of Structural Chemistry*, 2003, 44, 5, p. 882.
- 10 Gilinskaya L.G., Rudina N.A., Okuneva G.N., Vlasov Yu.A. *J. of Structural Chemistry*, 2003, 44, 6, p. 1122.
- 11 Gibson I.R., Bonfield W. *J. Biomed. Mater. Res.*, 2002, P. 697–708.
- 12 Danilchenko S.N., Kuznetsov V.N., Stanislavov A.S., Kalinkevich A.N., Starikov V.V., Moskalenko R.A., Kalinichenko T.G. *Cryst. Res. Technol.*, 2013, 3, p. 153–162.
- 13 Jono S., Shioi A., Ikari Y., Nishizawa Y. *Bone Miner. Metab.*, 2006, p. 176–181.
- 14 Golovanova O.A. *Butlerov Communications*, 2011, 24, 3, p. 113–122.

- 15 Golovanova O.A. *Bulletin of the Tomsk State University*, 2008, 313, p. 215–224.
- 16 *Biochemistry*, Ed. by E.S. Severin, Moscow: GEOTAR-Media, 2003, 356 p.
- 17 Golovanova O.A., Achkasova E. Yu., Punin J.O., Zhelyaev E.V. *Crystallography*, 2006, 2, p. 376–382.
- 18 Todes O.M., Seballo V.A., Goltsiker A.D. *Mass crystallization from solutions*, Leningrad: Khimiya, 1984, 232 p.
- 19 Golovanova O.A. *Pathogenic minerals in the human body*, Omsk: OmGU Publ., 2007, 396 p.
- 20 Solonenko A.P., Golovanova O.A. *Butlerov Communications*, 2011, 2, p. 106–112.

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