UDC 577.118.543.422

Effect of Organic and Inorganic Impurities on the Nucleation of Calcium Oxalate Monohydrate

O. A. GOLOVANOVA[1], YU. O. PUNIN[2], A. S. VYSOTSKIY[1] and V. R. KHANNANOV[1]

[1]*Dostoevsky Omsk State University, Pr. Mira 55A, Omsk 644077 (Russia)*

E-mail: golovanoa2000@mail.ru

[2]*Saint Petersburg State University, Universitetskaya Naberezhnaya 7/9, Saint Petersburg 199034 (Russia)*

(Received February 16, 2011)

Abstract

On the basis of the experimental data, a set of problems connected with the features of the crystallization of wavellite in the presence of additives is considered. It is established with the help of X-ray phase analysis that the precipitates formed under the conditions studied are presented by calcium oxalate monohydrate. The presence of magnesium ions, hydrophosphate, phosphate and sulphate ions in solution has an inhibiting action on the crystallization of calcium oxalate monohydrate. The hindering effect of the additive increases proportionally to an increase in the concentration of the additive. It was proved experimentally that amino acids have diverse effects on nucleation: some of them (glutamic acid, glycine, lysine *etc.*) inhibit the process, whereas the others (proline, alanine, valine *etc.*) act as catalysts; a number of amino acids (serine, phenylalanine) exhibit an insignificant effect on nucleation.

Key words: calcium oxalate monohydrate, induction period, amino acids, inhibition, crystallization

INTRODUCTION

Predicting the behaviour of a biological system when changing either parameters is especially important in the course of studying the processes caused by abnormal functioning of an organism. One of the results inherent in such processes consists in forming the neoplasms of pathogenic nature, in particular human urinary calculi, composed of 80 % calcium oxalate monohydrate [1–8].

Calcium oxalate monohydrate within the range of supersaturation level values inherent in biological fluids represents a thermodynamically stable phase [8]. However, numerous studies [9–15] demonstrated that the mechanism of forming the mentioned phase is complicated and multi-stage, and the features of its realization depends on the conditions of performing the synthesis as well as on the presence of various additives in the solution. In this connection, of current importance is studying the crystallization of calcium oxalate as well as the influence of various impurities thereon, including organic impurities as the integral components of the physiological salt solution.

A lot of papers were published concerning the effects of organic and inorganic impurities on the nucleation and growth of calcium oxalate crystals as well as the phase composition of the precipitate [16–23]. Many authors [23–31] emphasize a particular importance of organic compounds (various amino acids, proteins, citrate ions) and inorganic substances (magnesium, calcium, potassium and sodium salts and others) in the course of the formation and growth of calcium oxalate minerals. However, any mechanism of their action is not completely understood yet. Metabolic disorders, and, consequently, the ratio between organic and inorganic components in physiological fluids (*e. g.*, urine) in humans often results in the deposition

of calcium oxalate within urinary organs, *i. e.* in appearing the pathogenic mineral formations in an organism. In this connection the studies concerning the interaction between amino acids and calcium oxalate is very important, especially taking into account increasing the number of diseases and the necessary for finding novel methods of treatment and prevention of urolithiasis.

In this regard, to establish the role of the components of the natural crystal-forming environment in the formation of calcium oxalate monohydrate is crucial for the development of the ways to prevent its crystallization in an organism.

The aim of this work consisted in studying the laws of the nucleation of calcium oxalate monohydrate in the presence of organic and inorganic impurities those are contained in human urine.

EXPERIMENTAL

The crystallization process was studied at a temperature of 20–23 °C and at the supersaturation level of calcium oxalate solution $\gamma = C_0/C_s$ (C_0 is the concentration of calcium oxalate in the supersaturated solution; C_s is the solubility of calcium oxalate amounting to $0.7 \cdot 10^{-4}$ mol/L) equal to 5, 7 and 10. The choice of the basic γ values is connected with the fact that these values are typical for biological media, in particular for the urine of a healthy average adult human [32]. Additional experiments were also carried out at $\gamma = 12, 15, 20, 25$ for more complete information.

The supersaturation with respect to calcium oxalate was produced by the following chemical reaction:

$$Ca^{2+} + C_2O_4^{2-} \rightarrow CaC_2O_4$$

that was realized *via* stoichiometric mixing the initial solutions of soluble compounds such as calcium chloride and ammonium oxalate. For each series of experiments we prepared the solutions those under the experimental conditions do not contain cations and anions do not form low-soluble compounds. Further, the solutions were mixed in equivalent amounts. Ready solution was poured into a conical flask and stirred during 5–10 s.

In order to determine the parameters of nucleation, we used a method based on the measurement of induction period values. The method is based on the dependence of the induction period values on the initial concentration of supersaturated solutions. The determination of induction period values was carried out in a visual manner from the turbidity of the solution.

As a solvent we used double-distilled water. For the preparation of the initial solutions, we used analytical grade salts. Since the fact that calcium chloride is able of hydratation in the course of storage, we standardized its solution *via* complexometric titration by Trilon B prior to the experiment [33].

The standardization of the nucleation process was carried out at the expense of maintaining the experimental conditions to be constant. The system under investigation was prepared in a crystallizer *via* rapid mixing of the initial solutions. The clouding time for the solutions was determined with the help of stopwatch; the countdown began at the end of mixing the initial solutions. For each concentration we conducted several parallel experiments (5–6), whereby the relative standard deviation of the induction period values (τ_{ind}) was equal to $S_r = 0.01–0.02$. All the experiments were carried out without stirring.

Impurities were introduced into one of the initial solutions before mixing. Thereby inorganic anions added to the solution of ammonium oxalate, whereas inorganic cations and organic impurities were added to the calcium chloride solution. As organic additives we used amino acids (*L*-proline ($CH_2(COOH)CH_2CH_2CH_2)NH$), *L*-threonine ($CH_3CH(OH)CH(NH_2)COOH$), *DL*-valine ($(CH_3)_2CHCH(NH_2)COOH$), *L*-asparagine ($HOOCCH(NH_2)CH_2COOH$), *L*-serine ($CH_2(OH)CH(NH_2)COOH$), *L*-phenylalanine ($C_6H_5CH_2CH(NH_2)COOH$), *L*-isoleucine ($C_2H_5CH(CH_3)CH(NH_2)COOH$), *L*-arginine ($C_2H_5CH(CH_3)CH(NH_2)COOH$), *L*-lysine ($H_2NCH_2CH_2CH_2CH_2CH(NH_2)COOH$), *DL*-methionine ($CH_3SCH_2CH_2CH(NH_2)COOH$), *DL*-leucine ($((CH_3)_2CHCH_2CH(NH_2)COOH$), *L*-α-alanine ($CH_3CH(NH_2)COOH$), aminoacetic acid (glycine) ($CH_2(NH_2)COOH$), *DL*-glutamic acid ($HOOCCH(NH_2)CH_2CH_2COOH$), *DL*-tyrosine ($(OH)C_6H_2CH_2CH(NH_2)COOH$). In general, these amino acids were found in the composition renal calculi [28].

As the inorganic additives, basing on the data published concerning the composition of urine [3, 6, 7], we used magnesium ions in the form of $MgCl_2 \cdot 2H_2O$, iron (III) ions ($Fe(NH_4)(SO_4)_2 \cdot 12H_2O$), hydrophosphate ions ($(NH_4)_2HPO_4$), phosphate ions ($Na_3PO_4 \cdot 12H_2O$), sulphate ions ($(NH_4)_2SO_4$). The concentration values for the additives corresponded to the physiological ones (for amino acids the biological concentration is equal to 0.004 mmol/L) to be varied depending upon the requirements of the experiment.

The mineral (phase) composition of precipitates obtained in the course of the synthesis were studied using XRD phase analysis. The diffraction patterns were obtained by means of a powder technique using a DRON-3 X-ray diffractometer. The qualitative analysis of the phase composition of samples was carried out by comparing the experimental values of interplanar spacing and relative intensities of diffraction peaks with a set of corresponding tabular values for each of the phases proposed. The identification of phases was performed using international ASTM card-file. The accuracy of X-ray diffraction phase analysis depends on the dispersion level and could be equal to 2–10 % of the value determined.

RESULTS AND DISCUSSION

The studies concerning solid phases formed during crystallization analysis by means of XRD phase analysis demonstrated that the precipitate obtained represents, in all cases, calcium oxalate monohydrate (Fig. 1), no other impurity phases were revealed. At the same time, several

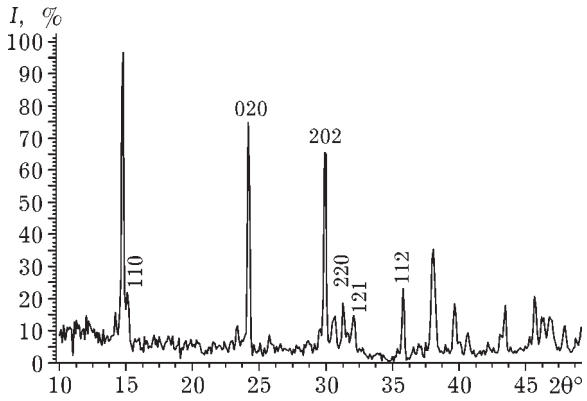

Fig. 1. XRD profile of calcium oxalate monohydrate.

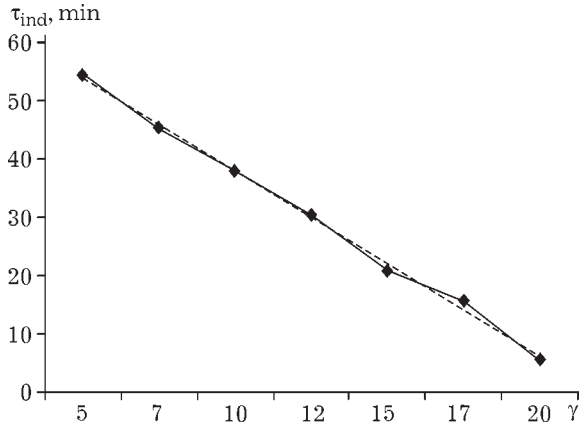

Fig. 2. Induction period of calcium oxalate monohydrate nucleation (τ_{ind}) depending on the supersaturation level (γ). $y = -7.9732x + 61.893$, $R^2 = 0.9968$.

papers [34, 35] reported the formation of two calcium oxalate trihydrate in similar experiments.

At the first stage we studied the effect of supersaturation on the induction period of calcium oxalate monohydrate with no additives. We determined the induction period values for γ = 5, 7, 10, 12, 15, 17, 20 (Fig. 2). It can be seen that the resulting dependence is linear, but this does not agree with the theory of nucleation.

It is known that the induction period (τ_{ind}) is inversely proportional to the nucleation rate (J) to depend exponentially on the inverse square of supersaturation level:

$$J \sim \exp(-16\pi\sigma^3 v^2 / 3k^3T^3(m\ln\gamma)^2$$

where σ is the specific surface energy; v is the volume of the molecule; k is the Boltzmann constant; T is the temperature; m is the number of ions formed in the course of calcium oxalate dissociation in solution equal to 2 [34]. Hence $\ln \tau_{ind}$ should depend linearly on the $(\ln \gamma)^{-1/2}$. However, this plot demonstrates two lines with a knee at $\gamma = 12$. Such behaviour corresponds to the transition from heterogeneous nucleation at $\gamma < 12$ to the homogeneous one at $\gamma > 12$ [28, 34]. Thus, the "linear" curve in Fig. 2 represents really a composition of two exponential dependences with different exponent values. The values of the surface energy for the two parts of the kinetic curve are equal to 15.3 and 36.0 mJ/m^2 for the heterogeneous and homogeneous nucleation, respectively, which is close to the results obtained earlier [28]. However, these values differ to a considerable extent from the data available in the literature

[34], which we attributed to the absence of impurities in our system, unlike the conditions used by the authors of [34].

Effect of organic additives of various amino acids on the induction period of calcium oxalate monohydrate nucleation

A number of research works [28–31] demonstrated that the formation of calcium oxalate monohydrate is to a great extent influenced by amino acids those are contained in the physiological salt solution and were in renal oxalate calculi [36]. In the organic component of the renal calculi there are up to ten amino acids registered, among those glutamic acid, glycine and certain other amino acids represent a basis of the organic matter. For this reason, we have chosen these amino acids as additives in order to determine their impact on the process of calcium oxalate nucleation.

The diagram in Fig. 3 illustrates the effect of amino acids on the induction period of calcium oxalate monohydrate. It can be seen that amino acids can both inhibit the crystallization of calcium oxalate monohydrate, and catalyze this process. However, some amino acids exert a little effect on the crystallization. It is assumed that the amino acid inhibitory effect could be connected with their adsorption onto active surface centers of crystals formed in the course of the interaction between the positively charged surface of crystals and the aggregates of calcium oxalate and the amino acid that is in the most probable conformation. In this case one could expect an increase in the inhibitory effect to result in increasing the amino acid content in renal calculi.

Let us compare the obtained series of amino acids with respect to increasing the inhibitory properties as it follows: *L*-proline < *L*-threonine < *DL*-valine < *L*-asparagine < *L*-serine < *L*-phenylalanine < *L*-isoleucine, *L*-arginine < *L*-lysine < *DL*-methionine < *DL*-leucine <*L*-α-alanine < aminoacetic acid (glycine) <*DL*-glutamic acid with a number of amino acids with respect to increasing their content in renal calculi: methionine < arginine < phenylalanine < threonine < valine < serine < alanine < glycine < lysine < glutamine. It is seen that at least for the main four amino acids in oxalate renal calculi our hypothesis is confirmed.

The results we obtained differ in several respects with the data published in the literature those, however, are contradictory to a considerable extent. So, according to data obtained by different authors, glutamic acid being the most potent inhibitor in our experiments enhances the nucleation [35], weakens it [30] or exerts no effect on the nucleation of calcium oxalate [37]. Threonine, according to [30], does not affect the nucleation, whereas to our knowl-

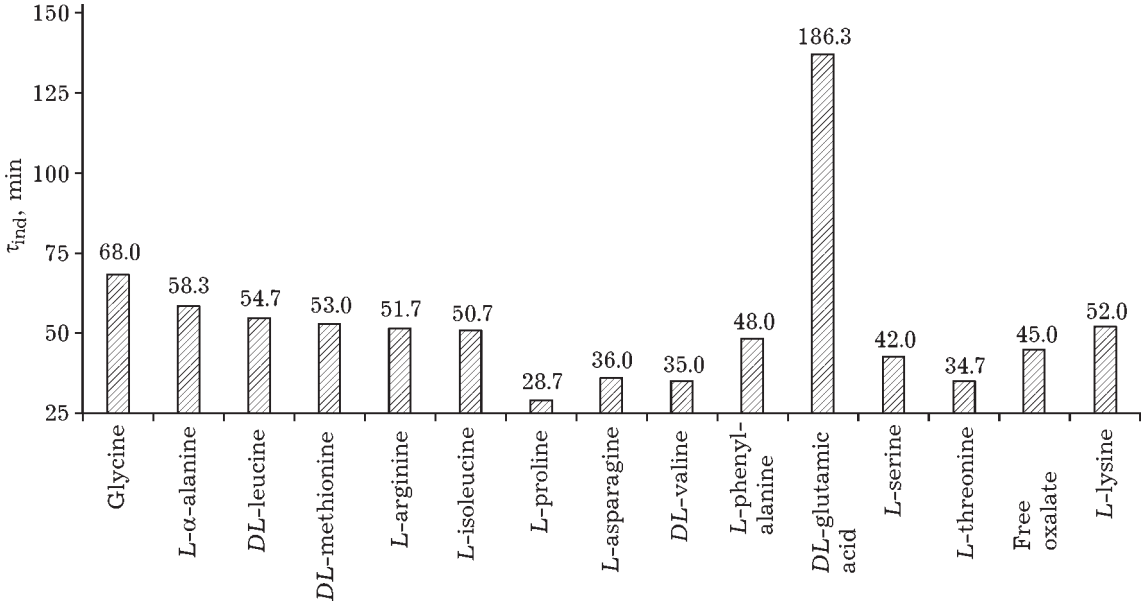

Fig. 3. Influence of amino acids upon the induction period of calcium oxalate monohydrate.

edge, it promotes it. The most significant discrepancy between our results and data published is observed with respect to aspartic acid. According to [30, 37, 38] the mentioned acid to a greater or lesser extent inhibits the nucleation and growth of calcium oxalate monohydrate, however, according to our work, in the presence of this amino acid there is a significant promotion of nucleation observed.

The results of the investigation of influencing amino acids upon the induction period demonstrates that the action is not connected with the main characteristics of amino acids determining their adsorption on the surface of calcium oxalate [38]: a) acidity–basicity, *i. e.*, p*I* (among the inhibitors there are acidic, neutral and basic amino acids present); b) the dissociation constant (the pK_1 range for promoters and inhibitors is the same being equal to about 2.0–2.3); c) the stability constants for the complexes with calcium (for inhibitors pK = 1.2–2.2, for promoters pK = 1.4–1.6) and d) the number of carboxyl groups among inhibitors and promoters there are both mono- and dicarboxylic amino acids). To reveal any common characteristic of an amino acid determining its action on the nucleation of calcium oxalate monohydrate remains elusive yet.

Particular attention is attracted by the fact that there is an opposite behaviour of aspartic and glutamic acid observed. The differences between these amino acids are relatively low according to the values of the second dissociation constants (pK_2 = 3.75 and 4.15 for aspartic and glutamic acid, respectively) and the isoelectric point (pI = 2.77 and 3.22, respectively), as well as the length of the carbon chain (glutamic acid has only one CH_2 group more). The opposite action of these acids on the nucleation of calcium oxalate could be explained only by the fact that both the inhibition and promotion of nucleation is realized on the nucleus surface (inhibition) or in the solution (promotion) at the expense of the same mechanism such as strong binding the calcium ions with an amino acid. Owing to a smaller value of the second dissociation constant, aspartic acid at pH ~ 6 is much more highly ionized, which should weaken its adsorption on the surface of calcium oxalate [38]. On the other hand, in this case one should observe amplifying the formation of calcium carboxylate complex in the solution those could serve as the centers of calcium oxalate nucleation.

Effect of inorganic additives on the induction period of calcium oxalate monohydrate nucleation

Inorganic additives (magnesium and iron (III) ions, phosphate, hydrogen phosphate and sulphate ions) were chosen basing on the composition of the physiological salt solution and on the results of previous studies [3, 6, 7, 39].

First of all, it is necessary to clarify the role of magnesium. In the natural oxalate forming environment there are magnesium ions present those represent one of the most important activator of many enzymatic processes. A considerable part of magnesium comes to an organism from plant foods. Although the absorption of magnesium is regulated by the same substances as the calcium absorption (for example, proteins and vitamin D), a certain antagonism in an organism is observed for magnesium and calcium [40].

In the course of studying the effect of adding the additives of magnesium on the nucleation of calcium oxalate monohydrate we created the concentration related to the natural biological concentration range: maximum concentration (11 mmol/L), medium concentration (8.15 mmol/L) and minimum concentration (5.30 mmol/L). From the data of Fig. 4 one can see that the inhibitory effect from the addition of magnesium ions increases in proportion to the concentration of magnesium ions. The linear relationship is observed for all the values of the supersaturation levels created. The inhibitory effect of the addition of magnesium ions is considerable; it is manifested at all the supersaturation levels to exhibit about the same extent. So, for the supersaturation level γ equal to 7 and the concentration of additives equal to 8.15 mmol/L, the nucleation time exhibits a 1.5-fold decrease, whereas for C_{add} = 11 mmol/L the decrease value is about 2 times. The induction time exhibits an increase at the same proportions for γ = 15. Strong inhibitory effects of magnesium on the crystallization kinetics could be, first of all, associated with the increased solubility of calcium oxalate monohydrate in the presence of magnesium. The estimative cal-

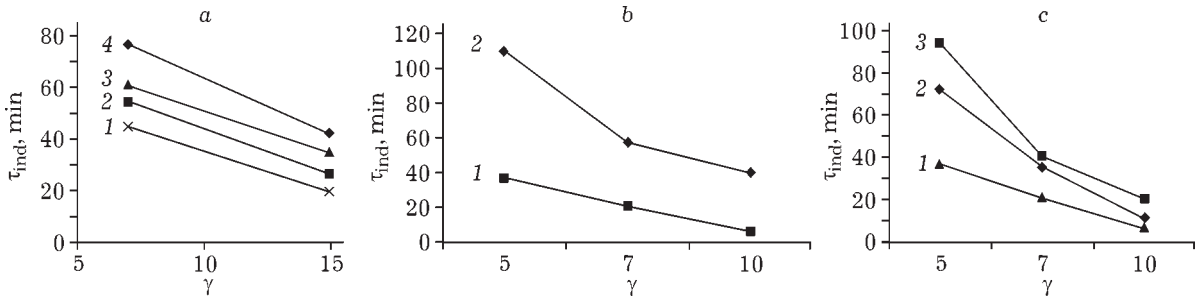

Fig. 4. Effect of adding magnesium ions (*a*), hydrophosphate ions (*b*) and sulphate ions (*c*) on the induction period of calcium oxalate monohydrate nucleation: *a* – no adding (*1*), 5.3 mmol/L (*2*), 8.15 mmol/L (*3*), 11 mmol/L (*4*); *b* – no adding (*1*), 3.75 mmol/L (*2*); *c* – no adding (*1*), 3.34 mmol/L (*2*), 6.69 mmol/L (*3*).

culations demonstrate that at the concentration of magnesium equal to 10 mmol/L the solubility of calcium oxalate monohydrate demonstrates a 5.3-fold increases. Approximately the same results were obtained by the authors of [41]. It should be noted that these data take into account the effect of complexation only. As a matter of fact, due to salting-out the increase in solubility should be less. In any case, the real supersaturation level of the solution with respect to calcium oxalate is less than the preset one, which just results in an increase in the induction time and in decreasing the rate of nucleation in the presence of magnesium impurities.

As far as the adsorption action of magnesium on the nucleation of calcium oxalate monohydrate is concerned, this effect, to all appearance, could be neglected. At least, the effective surface energy values for nuclei in the presence of magnesium determined from the nucleation kinetics data are comparable with those for the system containing no additives, being equal to 13.8 and 34.2 mJ/m^2 for the case of homogeneous and heterogeneous nucleation, respectively.

The effect of adding Fe^{3+} cations on the induction period of calcium oxalate monohydrate was investigated at the biological concentration amounting to 3 μmol/L. It was found that iron (III) ions have almost no affect the induction period of calcium oxalate monohydrate: the difference is within the experimental error. The authors of [6, 7] reported a strong inhibition of the growth of calcium oxalate monohydrate crystals by iron impurities. The negligible iron effect on on the nucleation process is connected, to all appearance, with a very low concentration of iron ions in the physiological salt solution.

Further, we studied an effect of adding phosphate and hydrophosphate ions those represent essential components of physiological fluids, on the formation of calcium oxalate monohydrate. For the phosphate ion, we preset biological concentration equal to 23 mmol/L as well as lower concentration values (11, 5.7, 2.8 and 1.4 mmol/L). For all the concentration values and at $\gamma = 5$, 7, and 10 we noted the formation of calcium phosphate precipitate, which did not disappear within a few days. It should be noted that phosphate ions at the concentration that is 16 times lower than biological one completely inhibited the nucleation process of calcium oxalate monohydrate due to the formation of a low-soluble precipitate of calcium phosphate (the solubility product constant being equal to $K_{p.s} = 2.0 \cdot 10^{-29}$).

For the hydrophosphate ions we used the biological concentration of the additive equal to 60 mmol/L; the following values of concentration were preset, mmol/L: 30, 15, 7.5, 3.75.

We have found that calcium oxalate precipitates only at the concentration of hydrophosphate ions amounting to 3.75 and 7.5 mmol/L, which is five and four times less than its physiological concentration. The induction time in this case is significantly higher even for a minimal impurity concentration (3.75 mmol/L) as compared to that for pure system (see Fig. 2, *b*). When the concentration of hydrophosphate is equal to 7.5 mmol/L and $\gamma = 10$ the precipitate begins to form only in 2 h. With decreasing the supersaturation level the inhibitory effect is enhanced (see Fig. 4, *b*). At a higher concentration of hydrophosphate ion there is a slightly soluble precipitate of calcium hydrophosphate

($K_{p.s} = 2.7 \cdot 10^{-7}$) that does not disappear within 1 day. Further, there is substitution of hydrophosphate by oxalate ion observed, *i. e.*, calcium oxalate monohydrate if formed ($K_{p.s}$ of calcium oxalate < $K_{p.s}$ of calcium hydrophosphate). The inhibitory effect of phosphate ions could be, to all appearance connected with their adsorption on the nuclei of calcium oxalate, according to the Faience –Peskov – Paneth rule [23].

An essential component of the physiological fluid is presented also by sulphates. The influence of adding sulphate ions upon the induction period of calcium oxalate monohydrate was studied at the biological concentration of 53.5 mmol/L, and at the concentration values amounting to 26.7, 13.3, 6.7 and 3.3 mmol/L. In this case the precipitate of calcium oxalate monohydrate is formed only at the concentration values of sulphate ion equal to 6.7 and 3.3 mmol/L, *i. e.*, for the values being four or five times, respectively, lower as to compare with the physiological concentration. It can be seen that the sulphate ions as well as the phosphate ions exert an inhibitory effect. Increasing the concentration of the additive results in increasing the induction period. With decreasing in the value of the solution supersaturation level the inhibitory effect demonstrates enhancing (see Fig. 4, *c*). In the case when the concentration of sulphate ions is higher than 6.7 mmol/L and the supersaturation level is equal to the values chosen, the crystallization does not occur, and the nucleation is completely inhibited. However, unlike the action of hydrophosphate ions, there is no precipitation of other phases (gypsum or hemihydrate), too, *i. e.*, the inhibition of nucleation occurs in the pure form, which could also be explained by the adsorption of impurities according to the Faience–Peskov–Paneth rule [23].

CONCLUSIONS

In the course of the studies concerning the nucleation of calcium oxalate monohydrate in model solutions with no additives as well as with adding inorganic compounds and amino acids with the concentration close to physiological values, the following results were obtained:

1. For the solutions with no contaminants added, a transition from heterogeneous to homogeneous nucleation is observed with increasing the supersaturation level > 12, with a more than twofold increase in the efficient surface energy.

2. Different amino acids exert either inhibiting or promoting effect on the nucleation of calcium oxalate monohydrate [42].

3. Increasing the inhibitory properties of amino acids correlates with increasing the content of the latter in oxalate renal calculi.

4. The admixture of magnesium inhibits the nucleation of calcium oxalate monohydrate via increasing its solubility and decreasing the effective supersaturation level.

5. Other inorganic additives (sulphate, phosphate, hydrophosphate ions) inhibit the formation of precipitate at physiological concentration values of ions owing to the adsorption on the nuclei, with worsening the inhibiting properties in the series phosphate > phosphate > sulphate > iron(III).

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