

Solubility of the Preparations of Succinic Acid Obtained Mechanochemically

IRINA A. VORSINA, VERA A. TARASOVA, ANTONINA P. BARINOVA and NIKOLAY Z. LYAKHOV

Institute of Solid State Chemistry and Mechanochemistry, Siberian Branch of the Russian Academy of Sciences, Ul. Kutateladze 18, Novosibirsk 630128 (Russia)

E-mail: barinova_ap@mail.ru

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Abstract

The kinetics of detachment of the acid anions and their transfer into solution is investigated for the preparations of succinic acid obtained mechanochemically. It is established that under the experimental conditions this process goes on almost completely within 1 min for the composites based on talc and for the known pharmaceutical preparations «Yantar-antitox» and «Yantarnaya kislota» (succinic acid). Dissolution of the composites based on kaolinite occurs gradually during 20 min and depends on activation time. The reasons of differences in the solubility of preparations are discussed.

INTRODUCTION

Investigations of the interactions in the systems involving a silicate and biologically active substance showed the possibility to use mechanochemical methods to create new medical products with the required properties, including those of multifunctional and prolonged action [1–4]. In particular, this method can be applied to obtain preparations of succinic acid for use as food additives in order to sustain energy balance of cells for the purpose of prophylaxis of many diseases, especially under unfavourable conditions for an organism, under stress, after severe exhaustive diseases, as well as antioxidants of directive effect. However, the existing preparations of succinic acid are counter-indicative for persons suffering from urolithiasis, gastric and duodenal ulcer, especially under acute condition; they also have a negative effect of enamel.

The preparations of succinic acid which we obtained by means of the joint mechanical activation of the acid and natural layered silicates

[5] are not expected to have a negative effect on human organism because succinic anions are connected in them with the surface Me ions of silicate by the acid protons. As the experiments showed, succinic acid is present in these preparations in the assimilable form because acid anions bound chemically to the surface can detach rather easily under the conditions imitating the acidity of the stomach medium [5].

The efficiency and safety of medical treatment with any medical product depends on the rate and extent of its absorption by a living organism, that is, on its bioavailability. The assimilation of a preparation in an organism is most frequently limited by the rate of dissolution, which depends on particle size and on amorphism of the substance [6].

The present work deals with the investigation of the process (kinetics) of dissolution of succinic acid preparations obtained mechanochemically. Here and below we understand dissolution of succinic acid preparations as detachment of acid anions chemically bound in them and their transition into solution.

EXPERIMENTAL

The preparations of succinic acid used in the present work were layered composites obtained by the joint mechanochemical activation of layered silicates: talc $\text{Mg}_3(\text{Si}_4\text{O}_{10})(\text{OH})_2$ (GOST 20706-75) and kaolinite $\text{Al}_2(\text{Si}_2\text{O}_5)(\text{OH})_4$ (GOST 19608-84) with succinic acid $(\text{COOH})_2(\text{CH}_2)_2$ (hygienic certificate No. 1124-6, GOST 6341-75). Molar ratios of the components in the composites were: talc : acid = 1 : 1; kaolinite : acid = 1 : 0.25 and 0.5 (maximal possible value). The layered composites can be conventionally represented as complex compounds: $[\text{Mg}_3(\text{Si}_4\text{O}_{10})]^{2+}(\text{COO}^-)_2\text{R}$ and $[2\text{Al}_2(\text{Si}_2\text{O}_5)(\text{OH})_3]^{2+}(\text{COO}^-)_2\text{R}$.

In the system with talc, mechanochemical neutralization reaction is possible with the silicate to acid molar ratio $\leq 1 : 1$, and in the system with kaolinite $\leq 1 : 0.5$.

Activation of the preparations, as well as obtaining them, was carried out in a ball mill

of planetary type AGO-2 [7]. For comparison, we also investigated the solubility of commercially available pharmaceutical preparation "Yantar-antitox" (0.4 g of microcrystalline cellulose, 0.1 g of succinic acid).

In order to study solubility of succinic acid preparation, 0.4 g of it was placed in 25 ml of the aqueous solution of hydrochloric acid (pH ~ 1.1) at room temperature under permanent mixing (the rotation frequency of a magnetic mixer was ~ 80 rpm). The dissolution was carried out for a definite time interval τ_{dis} within the range 0.5–20 min. Then the sample was centrifuged; the concentration (g/l) of succinate anions that passed into the solution from the preparation was measured in the aqueous fraction by means of voltammetry basing on the cathode voltammetric signal of maleic acid which is present in succinic acid in trace amounts. For analysis, the solutions under investigation were placed into electrochemical

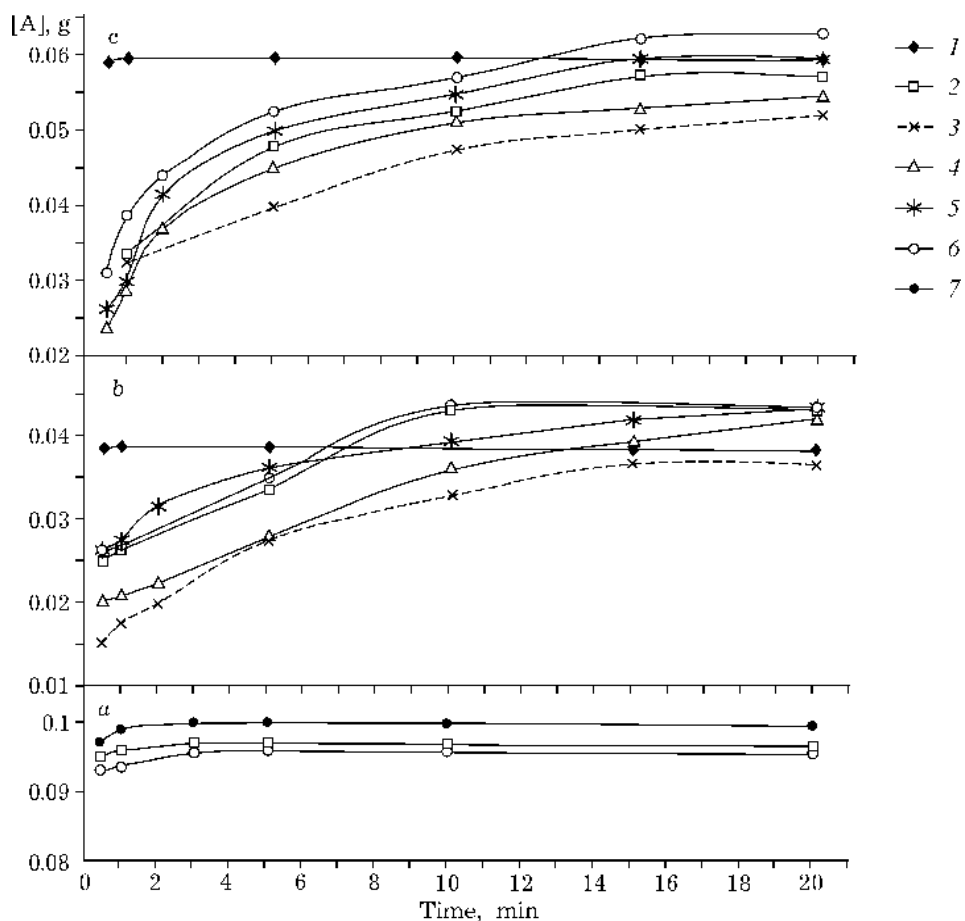


Fig. 1. Dependence of the solubility of succinic acid preparations based on talc (a) and kaolinite (b, c) on mixing time and on activation time: a - $[A]_{\text{max}} = 0.095$ g, curve 7 - Yantar-antitox, b - $[A]_{\text{max}} = 0.041$ g; c - $[A]_{\text{max}} = 0.06$ g; τ_a , min: 0.5 (1), 1 (2), 3 (3), 5 (4), 7 (5).

cell; voltammetric curves were recorded in the cathode mode. Graphite electrode renewed in the solution under investigation directly before determination [8] was used as an indicator (working) electrode. The cathode signal at $E = -0.6$ V was proportional to the concentration of succinic acid in solution. The calibration dependence of the height of the cathode peak on the concentration of succinic acid is a straight line within the range 0.5–5.0 g/l. Relative error of concentration determination does not exceed ± 7 %. No effect of kaolinite and talc on the signal value was revealed.

Specific surface was measured by argon desorption at $T = 77$ K (liquid nitrogen) on the powder surface.

The IR absorption spectra were recorded with Specord 75 IR spectrophotometer; the samples were prepared for recording as tablets with well calcinated potassium bromide.

RESULTS AND DISCUSSION

Figure 1, *a–c* shows the dependencies $[A] = f(\tau_m)$ where $[A]$ is the amount of succinic acid contained in 0.4 g of the preparation, τ_m is the mixing time, min. According to the calculated data, 0.04 g of the preparation based on kaolinite contains 0.041 or 0.06 g of succinic acid, 0.4 g of the talc-based preparation contains 0.095 g.

It follows from Fig. 1, *a* that in the case of talc-based composites the acid anions are detached and pass into solution almost completely within $\tau_m = 0.5$ –1.0 min independently of activation time τ_a . Since the dependencies $[A] = f(\tau_m)$ for the samples taken at the beginning ($\tau_a \geq 0.1$ min) and at the end ($\tau_a = 5$ min) of mechanochemical activation [5] and further activated ($\tau_a = 7$ and 9 min) almost coincide, only three of them are shown in Fig. 1, *a*. The dissolution of the pharmaceutical preparation “Yantar-antitox” occurs with similar rate (see Fig. 1, *a*, curve 7).

Quite different situation is observed with kaolinite-based preparations. In the case of samples taken at the initial stages of preparation ($\tau_a \leq 0.5$ min), when substantial amounts of unbound succinic acid are present [5], the anions of the free acid also pass into solution completely almost from the very beginning of dissolution process (see Fig. 1, *b, c*, curves 1).

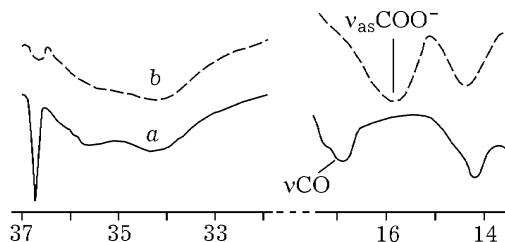


Fig. 2. IR absorption spectra of the mixture of talc with succinic acid before activation (*a*) and after activation for 5 min (*b*). Talc to acid molar ratio 1 : 1.

With a decrease in the content of unbound acid in the samples, the transition of anions into solution is somewhat slowed down. For the samples containing no free acid, that is, taken directly after the finish of mechanochemical reaction¹ ($\tau_a = 3$ (5) min), which depends on the initial kaolinite to acid molar ratio [5] (see Fig. 1, *b, c*) and further activated ($\tau_a = 5, 7, 9$ min), the transition of acid anions into solution becomes dependent on mixing and activating time. Disperse state (specific surface) of the preparations, as suggested by the data shown in Table 1, increases during activation and reaches its maximum after the finish of mechanochemical reaction ($\tau_a = 3$ (5) min). However, these samples exhibit the lowest solubility (see Fig. 1, *b, c*, curves 3). Activation of the ready preparations leads to an increase in their solubility (see Fig. 1, *b*, curves 4–6, and Fig. 1, *c*, curves 5, 6). The observed decrease in specific surface (see Table 1) is connected with the secondary aggregation of particles of the preparations, which does not affect their solubility because solubility is determined in aqueous solution under permanent mixing [9]. The dependence of solubility of kaolinite-based preparations not only of the disperse state but also on mixing time τ_p is the evidence of the possibility to obtain the preparations of succinic acid of prolonged action on the basis of kaolinite.

It follows from the comparison of Fig. 1, *b* and *c* that the character of solubility of the preparations is almost independent on the content of succinate ions in them.

¹The completion of the reaction is evidenced by the presence of bands related to carboxylate ion in the IR absorption spectra of these samples, which characterize the salt of succinic acid, instead of the bands related to the vibrations of carboxylic group: ν_{OH} and $\nu_{C=O}$ (Fig. 2).

TABLE 1

Specific surface of the mixtures of succinic acid with talc and kaolinite in the process of obtaining succinic acid preparations by the mechanochemical method

τ_a , min	S_{sp} , m ² /g		
	mixture with kaolinite		mixture with talc
	1 : 0.25	1 : 0.5	1 : 1
0 (initial)	5.7	5.4	4.2
0.5	9.5	11.8	10.1
1.0	9.9	12.2	10.8
3.0	13.7	12.7	14.3
5.0	12.3	13.0	13.0
7.0	11.5	11.8	12.3
9.0	11.3	10.9	12.0

The established difference in the solubility of talc- and kaolinite-based succinic acid preparations is connected with the difference in the crystal structures of the silicates determining the structure and composition of the resulting composites. Conventionally, the composites can be represented as complex compounds: $[\text{Mg}_3(\text{Si}_4\text{O}_{10})]^{2+}(\text{COO}^-)_2\text{R}$ and $[2\text{Al}_2(\text{Si}_2\text{O}_5)(\text{OH})_3]^{2+}(\text{COO}^-)_2\text{R}$.

It may be assumed that succinate anions which are present in the outer sphere are connected with the complex cation in talc-based composites mainly by electrostatic forces and are easily detached in weakly acidic solution dissociating almost completely according to the strong electrolyte type dissociation. In the case of composites based on kaolinite, the connection between the inner and outer spheres of the complex is enhanced due to the formation of the inner sphere of hydrogen bonds between OH groups and the succinic anions of the outer sphere of the complex. This fact, and also the difference in the structures of the ligands of inner spheres and the properties of the central ions of complexes (Mg^{2+} for talc, Al^{3+} for kaolinite) lead to the difference in the solubility of layered composites which are succinic acid preparations based on talc and kaolinite.

CONCLUSION

The investigation of dissolution kinetics of succinic acid preparations showed that under the experimental conditions ($\text{pH} \sim 1$, $V_m = 80$ rpm) detachment of acid anions and their transfer into solution occurs within $\tau_m \leq 1$ min in the case

of talc-based composites; in the case of kaolinite-based composites, this process is slower and gradual: $\tau_m \geq 20$ min. Pharmaceutical preparations "Yantar-antitox" and "Yantarnaya kislota" (succinic acid) are dissolved similarly to talc-based preparations: within $\tau_m \leq 1$ min.

The established regularities of the solubility of succinic acid preparations are connected with the strength of binding its anions to the support. In the case of kaolinite-based composites, the binding is stronger due to the formation of hydrogen bonds between hydroxy groups of the matrix with acid anions. In talc-based preparations, there are no hydroxy groups, so the succinate anions are bound with the support mainly by electrostatic forces and are easily detached in weakly acidic solution.

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