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The Synthesis of Bismuth Lactate

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Abstract

A brief review summarizes the results of integrated pharmacological and physicochemical studies carried out in the Russian Academy of Sciences, focused on the supramolecular systems for the delivery of the molecules of medicinal substances based on water-soluble plant metabolites – polysaccharides and glycyrrhizic acid, as well as its derivatives. The promising potential of the development of medicines, dietary supplements and plant protection products of increased efficiency and safety is shown. The advantages of the solid-phase mechanochemical technology for obtaining water-soluble compositions of poorly soluble drugs are demonstrated.

Keywords: drug delivery systems, mechanochemistry, polysaccharides, arabinogalactan, glycyrrhizic acid, saponins, vesicular systems, intermolecular complexes, membrane permeability, pharmacokinetic characteristics, bioavailability, toxicity, pharmacological action

INTRODUCTION

Bismuth compounds are widely used in medicine in the production of antiseptic preparations and medicines to treat gastrointestinal diseases [1, 2]. As a rule, bismuth compounds are almost insoluble in water and in alkaline solutions, and at present the search for water-soluble bismuth compounds is carried out for the purpose of making medicinal preparations.

A known method of obtaining water-stable complex compounds of bismuth is based on the dissolution of bismuth oxide in the ammonia solutions of citric, lactic, glyceric or malic acid, as well as their ammonium salts [3]. Efficient anti-ulcer preparations like DeNol (the Netherlands) were developed on the basis of water-soluble bismuth-potassium-ammonium citrate [1].

The salts of lactic acid (sodium, potassium and ammonium lactates) are used as nutrition additives [4], which determines the urgency of research aimed at obtaining the compounds of bismuth with lactic acid for medicine. The following compositions of bismuth compounds with lactic acid have been described in the literature: $BiC_3H_4O_3$ [5], $BiC_6H_9O_6$ [6-8], $BiC_6H_9O_6 \cdot 7H_2O$ [9] and $BiC_9H_{15}O_9$ [2, 10]. A usual precursor for their synthesis is bismuth hydroxide, which is obtained by bismuth deposition from nitric solutions cooled to 5 °C through the addition of the solutions of an alkaline reagent. However, in this case bismuth hydroxide contains nitrate ions up to 0.4 %; in the gastrointestinal tract, these ions may be reduced into nitrite ions triggering malignant neoplasms. It should be stressed that bismuth carboxylates decompose at relatively low temperatures (400 °C) with the formation of fine-crystalline bismuth oxide, which is of practical interest for the synthesis of functional materials [11, 12].

In the present work, we studied the interaction of bismuth (III) oxide with the solutions of lactic acid fort the purpose of obtaining high-purity bismuth lactate for technology and medicine.

EXPERIMENTAL

Mineral acids, salts and bases of the Kh. Ch. (chemically pure) reagent grade were used in the work. For bismuth (III) oxide, the reagent of varistor grade (HEK, Germany) was used. To study the dissolution of bismuth oxide in the solutions of lactic acid, the weighted portion of bismuth oxide was 10 g. To prepare the initial solution of lactic acid of the required concentration, the necessary aliquot of the concentrated solution of lactic acid (GOST 490–79) was poured into a volumetric flask 100 mL in volume, and distilled water was added to the volume mark. The studied molar concentrations of lactic acid $C_{C_3H_6O_3}$ were within the range 0–9.25 mol/L at the process temperature (T) 23±2 and 70±3 °C. The precipitates were separated from the stock solution by filtering and dried in the air.

The mass concentration of bismuth in solutions C_{Bi} (g/L) and its content in precipitates were determined by means of photocolorimetry in the presence of KI with a KFK-2 instrument. Precipitation products were preliminarily dissolved in nitric acid (1 : 1). The concentration of lactic acid was determined by means of alkalimetric titration with phenolphthalein. X-ray phase analysis (XPA) of reaction products was carried out with the help of Bruker D8 Advance diffractometer (Germany) using CuK_α-radiation, the rate of counter rotation was 0.5 deg/min. The identification of phases was carried out on the basis of the powder database PDF-2 (2008). The curves of differential thermal analysis (DTA), mass changes (TG), differential scanning calorimetry (DSC) of the samples under investigation and the data on water content were obtained with the help of the instrument for synchronous thermal analysis STA 449F1 Jupiter (Netzsch, Germany) in He flow and in a mixture of He with 25 vol. % O_2 (flow rate 50 mL/min, heating to 600 °C, heating rate 10 °C/min, weighted portion of the sample 200 mg, crucibles were made of an alloy of Pt–10 % Rh), combined with a quadrupole mass spectrometer QMS403 CF (Aeolos, Germany). Absorption spectra in the infrared region (400–4000 cm^{-1}) were recorded with an IR Fourier spectrophotometer Varian IR-640. The assignment of characteristic bands was carried out by comparing with the spectrum of lactic acid. Measurements of solution pH were made with an OP-264/1 pH-meter (Hungary) with a glass or renewable solid electrode. Specific surface of the samples was determined using BET procedure with a TermoSorb TPD 1200 instrument (Russia). Electron microscopic images were taken using a scanning electron microscope (SEM) Hitachi TM 1000 (Japan).

RESULTS AND DISCUSSION

The studies of the interaction of bismuth oxide with the solutions of lactic acid of different concentrations showed (Fig. 1) that the solubility curve passes through a maximum in the region of $C_{C_3H_6O_3}$ = 3 mol/L, and C_{Bi} in the solution increases to 96 g/L at the ascending region of the dependence. Other conditions being equal, C_{Bi} is somewhat lower at 23±2 °C than at the process temperature 70±3 °C. This may be due to the formation of a complex of bismuth with lactate ions mainly with the absorption of heat (endothermic reactions) and therefore with an increase in the stability constants of these complexes with an increase in temperature. According to the XPA data, the undissolved precipitate is an X-ray amorphous compound with an admixture of bismuth oxide and oxocarbonate at $C_{C_3H_6O_3} < 1.8$ mol/L and a compound with clear diffraction patterns (d/n 9.56, 4,83, 4.76, 3.65, 3.19 Å) in the case of $C_{C_3H_6O_3} \geq 2$ mol/L. Chemical analysis of the obtained compound provides evidence that bismuth content in it is 43.76 %.

It follows from the results of the studies of bismuth oxide interaction with the solution of lactic acid ($C_{C_3H_6O_3}$ = 3 mol/L) at τ = 0–6 h and

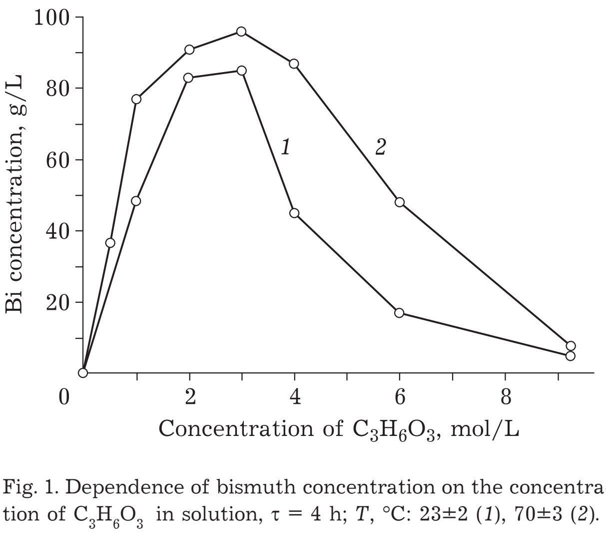

Fig. 1. Dependence of bismuth concentration on the concentration of $C_3H_6O_3$ in solution, τ = 4 h; T, °C: 23±2 (*1*), 70±3 (*2*).

temperature 23±2 and 70±3 °C that at $T = 70\pm3$ °C in 15 min after the start of interaction C_{Bi} in solution is 85 g/L and reaches the maximal value 96 g/L after 2 h. At $T = 23\pm2$ °C, C_{Bi} after 0.5 h is ~30 g/L, and the maximal value (84 g/L) is achieved only after 4 h. So, the solution of bismuth lactate may be obtained at a temperature of 23±2 or 70±3 °C and process time 4 or 2 h, respectively.

The synthesis of bismuth lactate is carried out with lactic acid in excess over bismuth, so this excess amount is to be removed: the products of interaction are washed with distilled water, acetone, ethanol or isopropanol at a temperature of 23±2 °C at the mass ratio of the solvent to bismuth lactate equal to 2 : 1. Investigation of the stage of washing the product of bismuth oxide interaction with the solution of lactic acid ($C_{\mathrm{C_3H_6O_3}}$ = 3 mol/L) with various solvents demonstrated different bismuth content in the solvent phase. According to XPA data, precipitates before and after washing are monophase and identical. According to the results of chemical analysis, bismuth content in the precipitate before washing was 39 %, while after washing it was 43.8 %, which is the evidence of the removal of excess lactic acid and corresponds to the compound $\mathrm{BiC_9H_{15}O_9}$. Washing with distilled water promotes the transition of some amount of bismuth into the solution. The mass concentration of bismuth in the solution after washing is 40.8 g/L. After washing with acetone or ethanol C_{Bi} in solution is 0.105 and 0.225 g/L, respectively, and in the case of isopropyl alcohol it is 0.025 g/L. Somewhat increased bismuth content in the washing solution of ethanol in comparison with isopropanol may be due to the presence of water in the amount of 5 % in ethanol.

For the purpose of revealing the reaction conditions providing a high yield of bismuth lactate, we studied the interaction of bismuth oxide with the solution of lactic acid under the following conditions: the weighted portion of bismuth oxide 100 g, the volume of lactic acid solution 100 mL, the molar ratio of lactate ions to bismuth (n) was varied within the range 1.33–14, $\tau = 1$ h, $T = 23$–70 °C. Precipitates were isolated by filtering, washed from lactic acid with isopropyl alcohol (200 mL) and dried in the air.

As a result of the treatment of bismuth oxide with the solution of lactic acid at $n = 1.33$ and $T = 55\pm3$ °C, X-ray amorphous product with bismuth content 54.88 % was obtained. The diffraction patterns of this product revealed reflections characteristic of bismuth oxocarbonate $\mathrm{(BiO)_2CO_3}$ (PDF [25-1464]).

Similar experiments were carried out at $n = 3$, 4 and 14. The results demonstrated the formation of a monophase product having the diffraction maxima with d/n equal to 9.56, 4,83, 4.76, 3.65, and 3.19 Å. Bismuth content in this product was 43.76 %. At $n = 3$, $\tau = 1$ h, $T = 23\pm2$ °C the product contains bismuth oxide at a level of about 10 %, while at $T = 70\pm3$ °C 30 min is sufficient time for the complete transformation of bismuth oxide into lactate. The studies provide evidence that bismuth lactate may be obtained within temperature range 23–70 °C, but from the technological viewpoint, we recommend to perform the process at 55±3 °C.

Relying on the analysis of IR spectra, we made conclusions concerning the structural features of bismuth lactate. An intense broad absorption band appears at 3498 $\mathrm{cm^{-1}}$ in the spectrum of bismuth lactate. This band is due to the stretching vibrations ν(OH). The presence of a broad absorption band in the region of 2630–3000 $\mathrm{cm^{-1}}$ is also characteristic of the stretching vibrations of a bound OH group ν (OH), these bands are related to dimers. However, it is difficult to determine the exact wavenumbers because of the superposition of the bands related to the stretching vibrations of the C-H group. The disappearance of the band of stretching vibrations of the carbonyl group ν(C=O) at 1730 $\mathrm{cm^{-1}}$, which is present in the spectrum of initial lactic acid, and its replacement by characteristic bands at 1574, 1647 and 1290 $\mathrm{cm^{-1}}$ correspond to the asymmetric and symmetric stretching vibrations of the group $\nu(\mathrm{COO^-})$, which is characteristic of the salts of organic acids. The disappearance of the absorption band ν(C=O) is accompanied by the appearance of up to five bands in the region of 1330-1450 $\mathrm{cm^{-1}}$, characteristic of metal salts with carboxylic acids. The absorption band at 550 $\mathrm{cm^{-1}}$ in the spectrum of bismuth lactate corresponds to the stretching vibrations of the Bi–O band [13–15].

It follows from the data of thermal analysis that the mass loss by bismuth lactate (Fig. 2) with temperature rise is due to its decomposition with the release of water, $\mathrm{CO_2}$ and the formation of bismuth oxide in the monoclinic modification at a temperature above 450 °C, which is confirmed by the XPA data (PDF [14-699]). For $T > 450$ °C sample mass does not change, and the total mass loss is 51.2 %. Theoretically, it is equal to 51.08 % for the compound having the composition $\mathrm{BiC_9H_{15}O_9}$. It should be noted that the thermal decomposition of bismuth lactate is complicated in its nature and requires a separate thorough investigation. Thus, according to XPA data, after annealing bismuth lactate at 300 °C for 8 h, the sample is a mixture of α-Bi_2O_3, β-Bi_2O_3 with a small (~3 %) admixture of metal bismuth. So, relying on the data of thermal and thermogravimetric analyses, as well as theoretical calculations taking into account literature data, we may represent the composition of the resulting bismuth lactate as $BiC_9H_{15}O_9$.

According to the XPA data, initial bismuth oxide of varistor grade is in α-modification; according to the SEM data (Fig. 3, *a*), it is composed of spherical particles about 3–7 μm in diameter; the specific surface of the sample is 0.78 m^2/g. Electron microscopic studies of the products of treatment of initial bismuth oxide with the solutions of lactic acid provide evidence that for the ratio of lactate ions to bismuth $n = 2.1$ the product is composed of the agglomerates of irregular particles ~10–20 μm in size (see Fig. 3, *b*), while for $n \geq 3.0$ it is composed of the plates ≈1 μm thick (see Fig. 3, *c*). A microphotograph of bismuth oxide obtained after annealing bismuth lactate for 4 h at a temperature of 450 °C is shown in Fig. 3, *d*. According to the XPA data, it is a monoclinic modification of α-Bi_2O_3. One can see that the morphology of this oxide differs from that of the initial oxide of varistor grade: it is composed of the particles less than 1 μm in size and has a specific surface of 3.5 m^2/g. This bismuth oxide may possess increased reactivity during the solid-phase synthesis of bismuth-containing functional materials. Bismuth oxide which is usually used for these purposes is obtained through the thermal decomposition of basic bismuth nitrate at a temperature of 620±20 °C (S_{sp} ~0.2 m^2/g).

Solutions containing ammonium-bismuth citrates are used in medicine to prepare the pharmaceutical substance of bismuth tripotassium dicitrate, so it is interesting to study the dissolution of bismuth lactate in ammonium hydroxide for the purpose of obtaining soluble forms of bismuth lactate. The studies at a temperature of 23±2 and 50±2 °C showed (Fig. 4) that process temperature has no substantial effect of the solubility of bismuth lactate for ammonium hydroxide concentration $C_{NH_4OH} = 0.5$ mol/L in the solution with $C_{Bi} = 300$ g/L. With an increase in C_{NH_4OH} to 0.6 mol/L bismuth concentration in the solution decreases to 247.5 g/L, and then, with an increase in C_{NH_4OH} to 9 mol/L, it increases to 380 g/L.

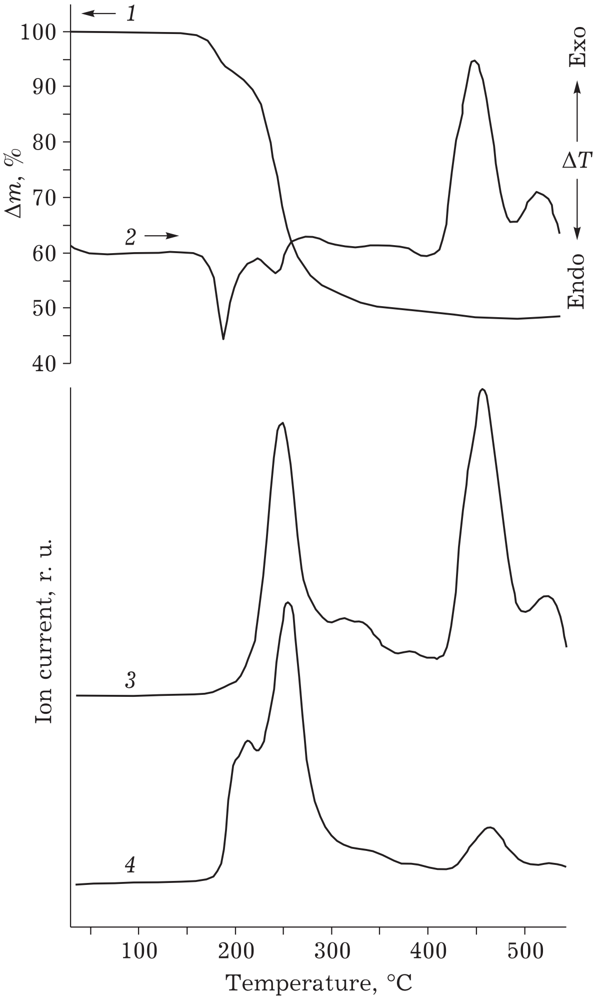

Fig. 2. TG (*1*), DSC (*2*) curves of bismuth lactate sample and recorded masses 18 H_2O (*3*) and 44 CO_2 (*4*) according to the data of mass spectrometry.

According to XPA data, during the treatment of bismuth lactate with the solutions of ammonium hydroxide, at the ascending region up to the value of 0.5 mol/L the solid phase is bismuth lactate. Further increase in the concentration of ammonium hydroxide above 0.6 mol/L leads to the formation of an X-ray amorphous compound in the precipitate. This compound is likely to be ammonium bismuth lactate.

CONCLUSION

Our studies provide evidence that it is reasonable to carry out the synthesis of bismuth lactate $BiC_9H_{15}O_9$ through the interaction of bismuth oxide with the solution of lactic acid at the molar ratio of lactate ions to bismuth equal to 3.0, and at the process temperature of 55±3 °C with subsequent washing of the product with isopropyl

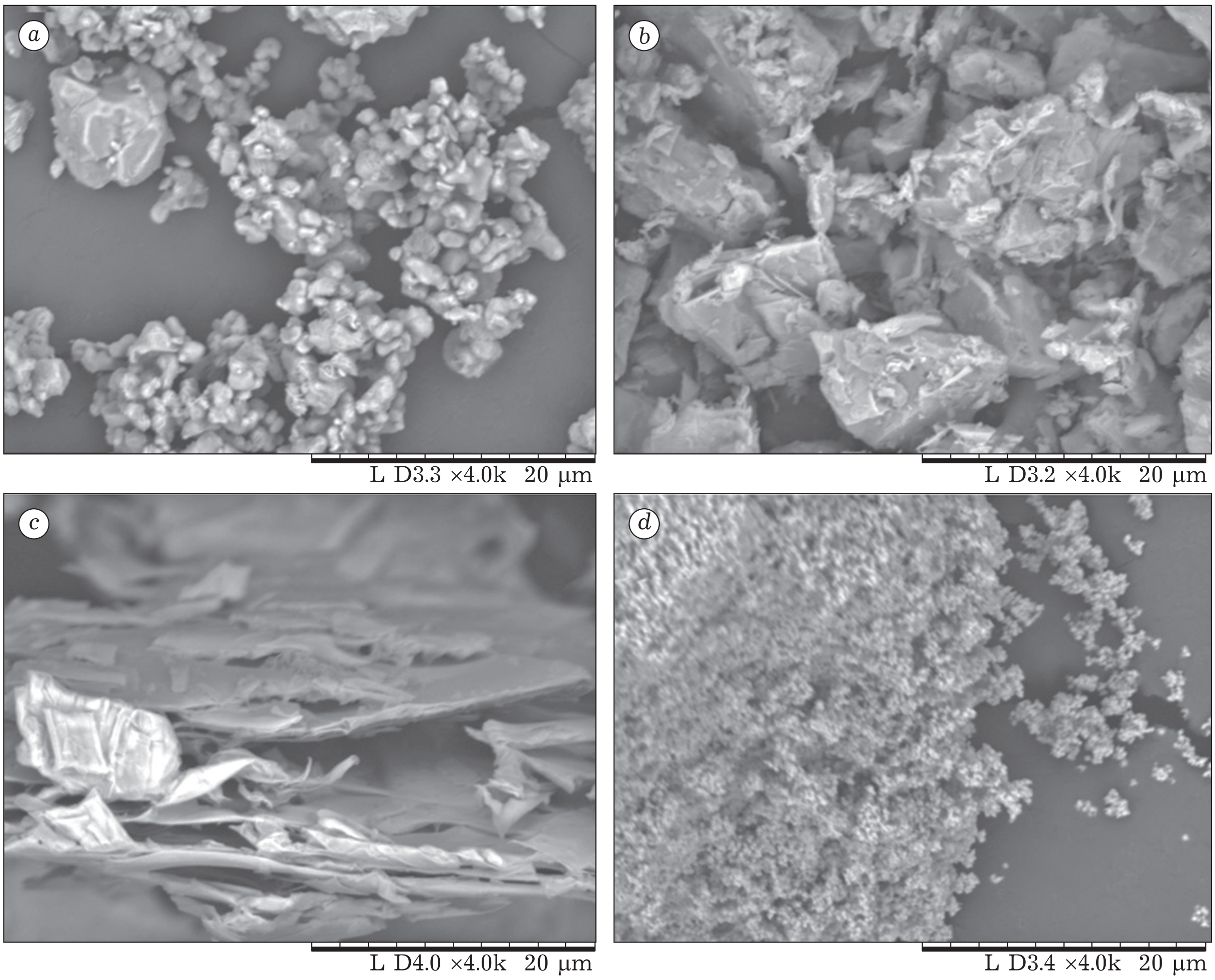

Fig. 3. Electron microphotographs of initial bismuth oxide of varistor grade (*a*), bismuth lactate obtained at $n = 2.1$ (*b*), $n = 3$ (*c*), and bismuth oxide obtained by annealing bismuth lactate for 4 h at a temperature of 450 °C (*d*).

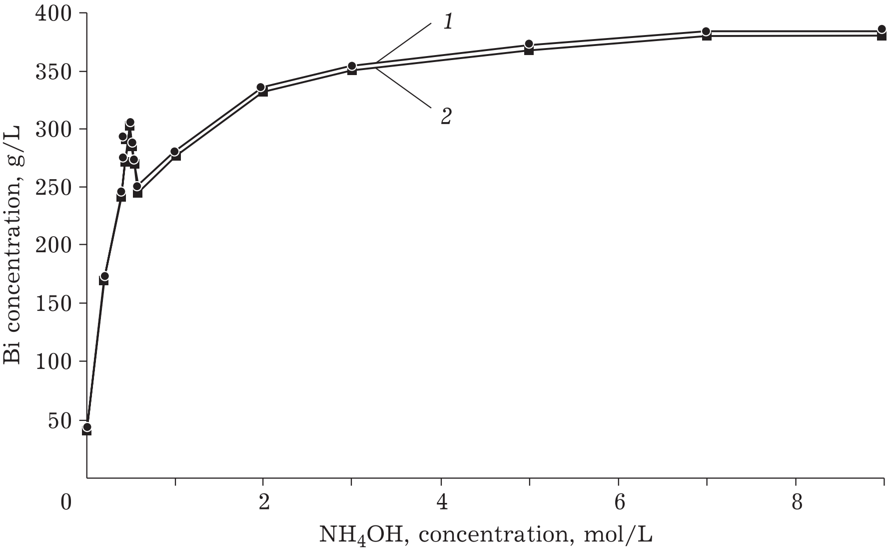

Fig. 4. Dependence of Bi concentration on the NH_4OH concentration in the solution at 50±2 °C (*1*) and 23±2 °C (*2*).

alcohol. The possibility to obtain aqueous and ammonia-containing solutions of bismuth lactate was demonstrated. These solutions may be used to prepare medicinal agents and fine crystalline bismuth oxide through the thermal decomposition of bismuth lactate, which may be used for the synthesis of functional materials.

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