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Cryochemical Modification of Medicinal Substances: the Effect of the Carrier Gas Flow Rate on the Physicochemical Properties of Nanoforms of the Antibacterial Drug Dioxidine

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Abstract—A combined cryochemical method is proposed for the dimensional and structural modification of drugs. This method forms a molecular flow of a substance combined with a flow of carrier gas, with subsequent condensation of the substance's molecules on a cold surface. This method is used to synthesize nanoforms of the dioxidine antibacterial drug. The molecular structure of the drug is found to remain unaltered during the cryochemical dimensional and structural modification. A regular decrease in the particle size and a change in the phase composition of the cryochemically modified dioxidine with an increase in the carrier gas (carbon dioxide, CO_2) flow rate are shown.

Keywords: cryochemical modification of drugs, combined cryochemical method, nanoparticles and nanoforms of drugs, dioxidine

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To date, well-known proven medicinal substances do not meet modern requirements, and this determines the need for the development of new drugs. However, the development and approval of new molecular forms of drugs (drug discovery) require not only huge material costs (several billion dollars) but also a long time (up to several years) spent on various clinical and preclinical trials. Such a lengthy process of obtaining the right drugs can cost many lives.

From this point of view, another approach that is aimed at increasing the efficiency of known medicinal drugs and improving the methods of their targeted delivery (drug delivery) seems to be more promising. For instance, the desired result can be achieved by reducing the particle size of the active drug to the nanoscale forms [1] and synthesizing new forms of thermodynamically metastable polymorphic modifications of the previously known drugs [2].

To obtain drug nanoforms, various physical and chemical methods are used [3]. These are subdivided into top-down and bottom-up methods [4–6].

The top-down methods reduce the particle size by mechanical action on the initially large particles of the original material. For these purposes, dry and wet mechanical milling in special mills [7], including cryomilling at low temperatures [8], is commonly used. Methods for the homogenization of components under high pressure [9] and methods for selecting particles by size using nanoporous membranes, filters, etc. [10, 11] have been developed.

The bottom-up approach is used to transfer the original pharmacopoeial drug into a homogenous state (a group of individual molecules or small molecular clusters) and to create conditions for the subsequent assembly of the nuclei of the new phase, their growth, and nanoparticle formation [12–14]. The solvent exchange method [15], synthesis using supercritical fluids [16–18], techniques involving spray drying [19–21], and cryochemical synthesis [22–24] are examples of the bottom-up approach.

Size is of primary importance since the dimensional parameters largely determine the bioavailability of the drug [25]. For instance, decreasing the particle size of the antigonadotropic danazol drug in an aqueous suspension from 10 μm to 169 nm results in an increase in the absolute bioavailability from 5.1 ± 1.9 to $82.3 \pm 10.1\%$ [26]. Increased bioavailability makes it possible to reduce the therapeutic dose and, therefore, possible side effects.

The particle size may not only change the solubility and the dissolution rate but also allow the penetration

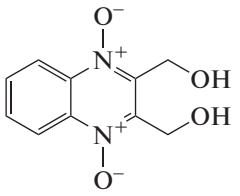

Fig. 1. The molecular formula of dioxidine.

of the drug particles through the biological barriers of the organism [27, 28].

The effect of polymorphism (the existence of several crystalline forms of the substance of the same molecular structure) has attracted close attention of both scientists and surveillance services in the healthcare sector. Changes in the polymorphic modification can alter the therapeutic characteristics of the drug: bioequivalence and bioavailability [29–33]. When one polymorphic modification is changed to another, the physicochemical characteristics, such as melting point, density, thermodynamic stability, solubility in various media, and the dissolution rate [29–33], also alter. Thus, the control of the phase composition of crystalline drugs is of great importance to biomedical research.

The aim of this research is to synthesize drug nanoforms by cryochemical modification and to study the dependence of the physicochemical properties of the obtained samples on the rate of the carrier gas (CO_2) flow.

EXPERIMENTAL

For cryochemical modification, a broad-spectrum antibacterial drug 2,3-bis-hydroxymethyl-quinoxaline-N,N'-dioxide (dioxidine) was selected (Fig. 1). The therapeutic effect of this drug is based on its selective destruction of the DNA of cells of the infectious agent [34, 35]. The original dioxidine drug (98.9%; MirFarm, Russia) was used without additional purification.

The cryochemical synthesis of dioxidine nanoforms was carried out by the combined method. It included the sublimation of the original dioxidine, the combination of the molecular flow of the substance with the flow of the carrier gas, and the combined low-temperature condensation of the flows of the substance and the carrier gas. For sublimation of the original pharmacopoeial dioxidine, special mesh evaporators, the design of which was described in the patent [36], were used. Carbon dioxide (CO_2) was used as a carrier gas, which is almost completely condensed on the inner surface of the preparative cryostat cooled with liquid nitrogen. Figure 2 shows a schematic diagram of the cryochemical synthesis unit.

In all experiments, the temperature of the metal mesh was maintained in the range of 140 ± 2°C. The weight of the loaded original dioxidine was 0.5 g. At the beginning of each test, the reactor was pumped out to a residual vacuum of 5×0^{-5} Torr. In all cases, the experiment time was 30 min. During this time, all the original dioxidine passed into the gas phase. After the experiment, the reaction surface of the cryostat was heated to room temperature, while the condensed carbon dioxide was sublimated. After this, the cryochemically modified dioxidine was removed from the reactor. The product yield was 50–60% of the initial amount.

The carrier gas (CO_2) flow was changed during the cryochemical modification of dioxidine. The other conditions (the temperature of the metal mesh of the evaporator (140°C) and the temperature of the cooled surface (–196°C), as well as geometric arrangement of the evaporator and nozzles for supplying carbon dioxide to the cryostat) were unaltered. The surface area on which the combined low-temperature condensation of the flows of the dioxidine drug and the carrier gas was carried out was 100 cm^2.

The flow of dioxidine molecules onto a surface cooled with liquid nitrogen was 7.53 ± 10^{15} molecules/(cm^2 s).

Carbon dioxide was supplied with gas pipelines (Eltochpribor, Russia) equipped with gas flow rate regulators, which allowed accurately regulating the carrier gas flow rate.

To obtain the characteristics of the original and cryochemically modified dioxidine, the following methods were used. These were UV/Vis spectrophotometry (Jasco V-770, JASCO Corporation, Japan), FTIR spectroscopy (Tenzor II equipped with the A225/Q Platinum ATR accessory, Bruker, Germany), and powder X-ray diffraction (PXRD) analysis (Rigaku D/MAX-2500, Rigaku, Japan, $\lambda = 1.54056$ Å). The particle size was measured with a QUANTA 650 FEG scanning electron microscope equipped with a field emission cathode (Center for Collective Use of the Frumkin Institute of Physical Chemistry and Electrochemistry, Russian Academy of Sciences). The specific surface area measurements were also carried out by determining the amount of adsorbed argon from a helium-argon mixture (95 : 5%) with a Khrom 5 gas chromatograph equipped with a katharometer [37]. Figure 2 shows a layout of the cryochemical unit for the dimensional and structural modification of dioxidine.

RESULTS AND DISCUSSION

UV/Vis spectra of aqueous solutions of the initial and cryochemically modified dioxidine contain an intense doublet band with maxima at 241 and 259 nm, which is due to the $\pi \rightarrow \pi^*$ electron transition of the aromatic system, and a low-intensity band with a max-

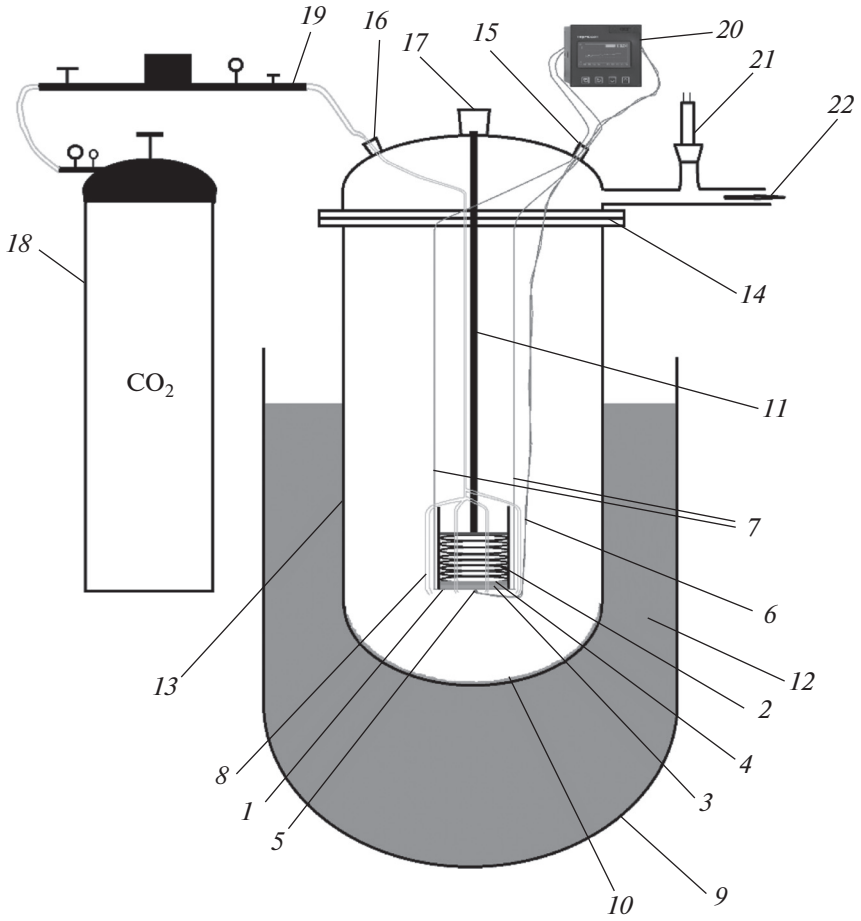

Fig. 2. The unit layout for cryochemical synthesis by the method of sublimation: joint low-temperature condensation: (1) metal mesh heated by passing electric current through it; (2) spring that presses the layer of the original drug compound to the metal mesh; (3) layer of the original drug compound that is pressed against the metal mesh; (4) rod to uniformly press the layer of the original drug compound to the metal mesh; (5) junction of the thermocouple used to measure the temperature of the metal mesh; (6) copper-constantan thermocouple used to measure the temperature of the metal mesh; (7) wires connected to the metal mesh; (8) comb designed for uniform distribution of the carrier gas flow (CO_2); (9) Dewar vessel filled with liquid nitrogen; (10) layer of mixture of cryomodified dioxidine and solid carbon dioxide; (11) pin regulating the position of the sublimator along the height of the submersible reactor; (12) liquid nitrogen; (13) vacuumized submersible reactor; (14) mobile vacuum connection; (15) vacuum inlet for thermocouple and wires; (16) vacuum inlet for carrier gas (CO_2) flow; (17) vacuum input for the pin regulating the position of the sublimator along the height of the submersible reactor; (18) metal tank containing carbon dioxide; (19) gas main (gas flow regulator); (20) temperature controller; (21) vacuum sensor; (22) output to the vacuum system.

imum at 375 nm, determined by the $n \rightarrow \pi^*$ electron transition of *n* electrons of nitrogen atoms composing the dioxidine molecule. According to the UV/Vis spectrophotometry data, the molecular structure of dioxidine does not change during cryochemical modification since the UV/Vis spectra of aqueous solutions of the original and cryochemically modified dioxidine are identical.

According to the powder X-ray diffraction (PXRD) analysis, the phase compositions of the original and cryochemically modified dioxidine differed significantly (Table 1). The original dioxidine is a monohydrate of a 1 : 1 composition, the crystal structure of which is known (included in the SOKGAA Cambridge Structural Database) [38]. According to the data on argon adsorption, the average particle size of the original pharmacopoeial dioxidine is 5700 ± 1200 nm.

The phase composition of the cryochemically modified dioxidine and the average particle size depended on the carbon dioxide flow as can be seen from Table 1. Note that all samples obtained as a result of cryochemical modification did not contain the original dioxidine monohydrate. The main structural components of the samples are the following dioxidine phases, which have been recently discovered and crystallographically deciphered: triclinic (T-) and monoclinic (M-) phases [39]. The sample obtained by sublimation of dioxidine in the absence of the carrier gas also contained a small amount of the new crystalline hydrate: the H-phase with a composition of 3 : 1 (three dioxidine molecules per one water molecule) [39].

Table 1. Dimensional and structural characteristics of cryochemically modified dioxidine samples at different rates of the carrier gas (carbon dioxide, CO_2)

CO_2 consumption, L/h	CO_2 flow, molecules s^{-1} cm^{-2} × 10^{-16}	Dioxidine/CO_2 flow ratio	Phase composition	Specific surface area, S/m, m^2/g	Average particle size, nm
0	0.0	0	T : H = 7 : 1	9.6	414 ± 80
0.2	1.4	1.85	T : M = 2 : 1	33	120 ± 24
0.45	3.1	4.16	T : M = 1 : 1	34	118 ± 23
1.00	7.0	9.24	T : M = 1 : 1.5	37	108 ± 22
4.5	31.4	41.63	T : N = 3 : 2	71	56 ± 11
10.0	69.7	92.50	T : N = 3 : 2	78	51 ± 10

The samples obtained at low and medium flows of the carrier gas were shown to contain only the T- and M-phases, and the ratio of these phases changed regularly with the change in the flow of the carrier gas. With an increase in the flow, the content of the M-phase increased from 33% (a flow of 1.4×10^{16} molecules s^{-1} cm^{-2} to 60% (a flow of 7.0×10^{16} molecules s^{-1} cm^{-2}). Note that in the absence of the carrier gas, a nanoform of dioxidine in the form of the dioxidine triclinic modification (more than 95%), or the T-phase, was obtained. Previously, heating dioxidine crystalline hydrate by freeze-drying at 120°C for 8 h was required to obtain the T-phase [39]. During this temperature treatment, the sample may lose the properties of a nanoform since the particles of the preparation become enlarged. The samples obtained at high rates of the carrier gas flow, along with the T-phase, contain a new unidentified phase (N-phase).

The average particle size of the original pharmacopoeial dioxidine, according to the low-temperature adsorption of argon, is 5700 ± 1200 nm. The average particle size of cryochemically modified dioxidine samples decreased regularly with an increase in the carrier gas (CO_2) flow from 414 ± 80 nm (in the absence of the carrier gas flow) to 108 ± 22 nm (6.97×10^{16} molecules s^{-1} cm^{-2}) and 51 ± 10 nm (flow of 6.97×10^{17} molecules s^{-1} cm^{-2}).

The dependence of the average particle size of cryochemically modified dioxidine on the carrier gas flow is probably due to the competition between two nucleation mechanisms: a heterogeneous mechanism on the cooled surface of the cryostat and a homogeneous gas-phase mechanism. In the absence of the carrier gas, the stationary concentration of dioxidine molecules (1.5×10^{21} molecules/m^3) corresponds to the conditions of Maxwell's gas, the thermal conductivity of which is independent of the concentration. Therefore, heat exchange between the cooled surface and the molecular flow of dioxidine occurs via the mechanism of heat conduction. Probably, the cooling rate of the molecular flow of dioxidine is insufficient for the efficient homogeneous gas-phase nucleation; therefore, the nucleation and growth of dioxidine crystallites occur through a less effective surface heterogeneous mechanism.

The use of CO_2 as a carrier gas leads to much faster cooling of the molecular flow of dioxidine as it moves to the cold surface. It is achieved due to both the convective mixing of molecular flows (a hot flow of dioxidine and a relatively cold flow of the carrier gas) and higher thermal conductivity of the molecular mixture of dioxidine and CO_2. According to the molecular-kinetic theory of gases, the following formula for the thermal conductivity of Maxwell's gases can be used [40]:

$$\lambda = \frac{2}{3\pi^{3/2}} \frac{C_V}{d_0^2 N_a} \sqrt{\frac{RT}{\mu}}.$$

It is known that in the absence of activation of the vibrational degrees of freedom, $C_V(CO_2) = 5R$ (as a linear molecule), C_V (dioxidine) = $6R$. The thermal conductivity of gas mixtures depends on their composition; however, when any gas prevails considerably in the mixture, the thermal conductivity of the gas mixture is determined by this particular gas. Thus, the use of carbon dioxide as a carrier gas leads to more pronounced cooling of the dioxidine molecular flow. As a result, conditions that favor homogeneous gas-phase nucleation and the formation of nanoparticles in the gas phase are created. Moreover, molecules of the carrier gas (CO_2) can be adsorbed onto the surface of the formed nuclei of the new phase, reducing their surface energy, which results in a significant increase in the nucleation rate. According to the classical theory of nucleation [41],

$$J = C \exp\left(\frac{\Delta G^*}{kT}\right); \quad \frac{16}{3} \frac{\pi\sigma 3\nu_1^2}{(kT \ln S)^2}.$$

Here, J is the nucleation rate; C is the pre-exponential factor that is almost independent of temperature and supersaturation; S is supersaturation; σ is the surface energy; ν_1 is the volume occupied by one molecule in the condensed phase; and k is the Boltzmann constant.

This formula indicates a pronounced dependence of the nucleation rate on the surface energy. The effect

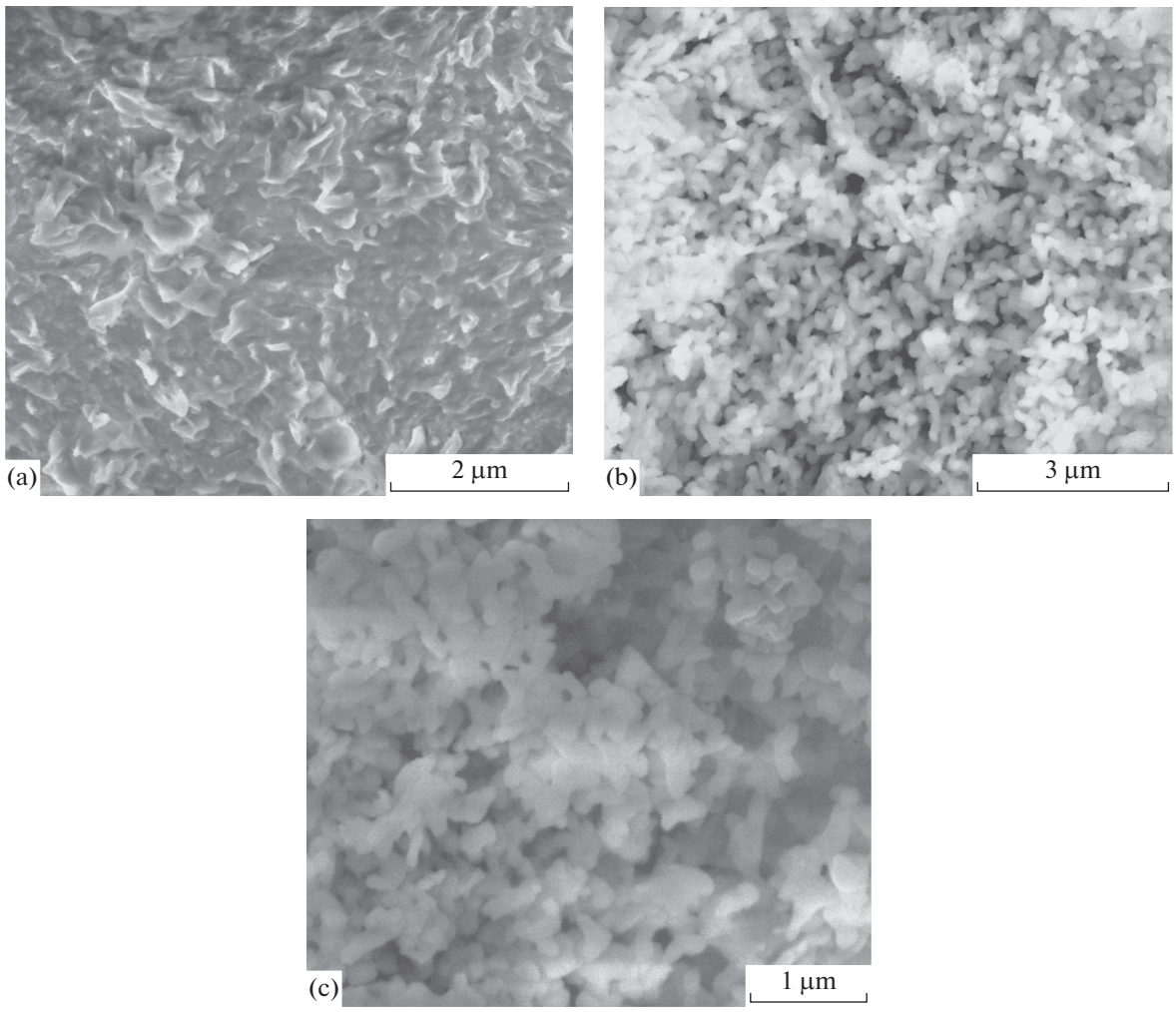

Fig. 3. SEM micrographs of cryomodified dioxidine samples obtained at the following carrier gas flow rates (molecules s^{-1} cm^2): 0 (a); 7.0×10^{16} (b); 7.0×10^{17} (c).

of the carrier gas nature on the nucleation rate is well known [42].

An increase in the carrier gas flow results in the more efficient cooling of the dioxidine molecular flow, primarily, due to convective mixing. In this case, the contribution of the homogeneous gas-phase mechanism to the processes of nucleation and growth of crystals increases, which leads to a decrease in the average particle size of the cryochemically modified dioxidine. At a certain value of the carrier gas flow, the contribution of the homogeneous gas-phase mechanism prevails, and a further increase in the flow rate does not lead to changes in the average particle size, which agrees with the experimental data obtained in this study.

The effect of the carrier gas flow rate on the structural-phase state of cryochemically modified dioxidine can be explained as follows. Anhydrous dioxidine modifications (monoclinic (M-) and triclinic (T-) phases) are characterized by the difference in the arrangement of the hydrogen bond system.

The triclinic phase (T-phase) of dioxidine consists of endless chains of molecules connected by intermolecular hydrogen bonds, with two N-oxide and two hydroxyl groups forming cross-hydrogen bonds (N → O...H–O) with two neighboring dioxidine molecules.

In the monoclinic phase (M-phase), the arrangement of the system of hydrogen bonds is more complex. One of the N-oxide groups of the dioxidine molecule does not participate in the formation of classical hydrogen bonds. The dioxidine molecule binds with two neighboring molecules due to the formation of a three-center hydrogen bond of the hydroxyl group of the molecule under consideration with the hydroxyl group of one neighboring molecule (molecule 1) and the N-oxide group of the other neighboring molecule (molecule 2) (N → O...H–O...H–O). The second hydroxyl group of the molecule under consideration forms a two-center hydrogen bond with the hydroxyl

group of the neighboring molecule (molecule 1), which participates in the formation of a three-center hydrogen bond with another molecule (molecule 3).

The primary nucleation process is the formation of molecule dimers. By joining additional molecules, dimers form trimers, tetramers, and more complex molecular clusters, which, when enlarged, form stable nuclei of the new phase. From this point of view, molecular dimers in which dioxidine molecules are linked by cross hydrogen bonds (N → O...H–O) can be distinguished in the crystal structure of the T-phase. Such dimers are likely the predominant dimeric form in the gas phase. The addition of dioxidine molecules to the natural dimer occurs by saturation of the existing active centers. Thus, the molecular assembly of the T-phase crystal structure does not require any significant structural rearrangements.

In the M-phase, a tetramer (rather than a dimer) serves as the initial structural unit that allows obtaining this crystal structure. The processes of nucleation of the M-phase require certain structural transformations of the formed molecular dimers. Probably, the nucleation of the T-phase via the heterogeneous surface mechanism is facilitated in comparison with the nucleation of the M-phase. Favorable conditions for the formation of the M-phase are created only during the nucleation by the homogeneous gas-phase mechanism. The nucleation of the M-phase may be favored by specific intermolecular interactions between carbon dioxide and dioxidine molecules. The increase in the content of the M-phase in the samples with an increase in the CO_2 flow rate from 1.4×10^{16} to 7.0×10^{17} molecules s^{-1} cm^{-2} may be associated with an increased contribution of the homogeneous gas-phase nucleation mechanism to the processes of crystal nucleation and growth. A further increase in the carrier gas flow leads to the formation of a new polymorphic modification of dioxidine. The structure of the latter is difficult to characterize because of the significant broadening of bands in the X-ray diffraction patterns due to the small size of the drug particles.

The dissolution rate of dioxidine was determined using UV/Vis spectrophotometry. For the complete dissolution of the original dioxidine, approximately one hour is required. The dissolution rate of the cryochemically modified dioxidine is much higher. For instance, dioxidine obtained in the absence of a carrier gas flow is completely dissolved after approximately ~60 s, and dioxidine obtained at a maximum carrier gas flow is completely dissolved in ~30 s. At the same time, the curves of solubility of both the cryochemically modified and original dioxidine accurately obey a first-order kinetic law. The kinetic curves of solubility are often described using the Noyes–Whitney equation [43]:

$$dX/dT = (DS/h_D)(C_s - C_t).$$

Here, dX/dt is the dissolution rate; D is the diffusion coefficient; S is the effective surface area of the dissolved substance; h_d is the characteristic diffusion size; C_s is the concentration of the dissolved substance corresponding to saturation; and C_t is the current concentration of the substance in the volume. When the concentration corresponding to the saturated solution is reached and the amount of the substance remaining in the precipitate is much higher than the amount of the dissolved substance, it can be assumed that the effective surface area of the dissolved substance particles remains constant during the dissolution. In this case, the Noyes–Whitney equation for a monodisperse sample is a first-order kinetic equation with a rate constant that is proportional to the S parameter. This indirectly indicates a small dispersion of the particle size distribution. Mathematical processing of the dissolution curves, according to the first-order kinetic law, allowed the determination of the time required to reach the current concentration of an aqueous dioxidine solution, which was equal to half the concentration of its saturated solution. This time was 74 s for the original pharmacopoeial dioxidine and 8.8 s for the cryochemically modified dioxidine obtained in the absence of the carrier gas (CO_2). For cryochemically modified dioxidine obtained at the maximum CO_2 flow under experimental conditions, this time was 5.3 s.

CONCLUSIONS

The method of cryochemical modification, including the sublimation of vapors of the dioxidine medicinal substance and their subsequent joint low-temperature condensation with an excess of an inert carrier (carbon dioxide), allowed obtaining dioxidine nanoforms that were identical to the original pharmacopoeial dioxidine in chemical composition (according to the UV/Vis spectroscopy data). However, these forms differed in molecular packing in the solid-phase nanostructure. Based on the data of powder X-ray diffraction (PXRD) analysis, the phase composition of the obtained samples depended on the rate of the carrier gas flow. The cryomodified dioxidine samples obtained at high values of the flow rate of the inert carrier gas were shown to contain a new crystalline phase of the drug, the structure of which has not been identified yet. An increase in the carrier gas flow resulted in a regular decrease in the average particle size of the cryochemically modified dioxidine antibacterial drug. The dissolution rate of the cryomodified dioxidine nanoform in aqueous media was higher (8–14 times) than that of the original pharmacopoeial drug.

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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