Preparation and studies of the co-crystals of meloxicam with carboxylic acids

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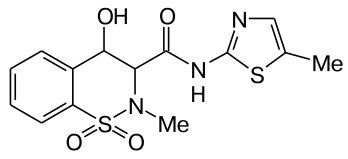
Mechanical treatment with addition of some liquid, crystallization from solutions, and heating of the mixture components preliminary subjected to mechanical treatment were the methods used for the preparation of the co-crystals of 4-hydroxy-2-methyl-*N*-(5-methylthiazol-2-yl)-2*H*-1,2-benzothiazin-3-carboxamide 1,1-dioxide (meloxicam) with carboxylic acids. It was shown that preliminary mechanical treatment plays significant role for the synthesis, whereas the addition of small amounts of solvents accelerates the process. The co-crystals were obtained for 17 mixtures of meloxicam—carboxylic acid. The use of the co-crystals of meloxicam in the compositions of improved pharmaceutical forms was found promising, which was attributable to the fact that the dissolution rate and the solubility of the co-crystals of meloxicam with the carboxylic acids under study are higher than those for meloxicam itself.

Key words: co-crystals, meloxicam, carboxylic acids, mechanochemical synthesis, solubilization of medicines.

Lately, co-crystals of medicines, in which together with molecules of active pharmaceutical ingredient (API) other molecules are present, attract very much attention. In contrast to solid solutions, the alternation of molecules of different components is strictly regular in them. The formation of co-crystals is not accompanied by such substantial redistribution of charges between molecules as it happens in salts, so one cannot suggest formation of cations and anions. The co-crystals allow one to, first, considerably increase the number of forms existing for a certain API (salts, different polymorphous modifications, amorphous forms, hydrates/solvates), which is of great importance for solving the problems related to the patent protection of a certain medicines based on a certain API, and second, improve clinically important physicochemical properties of drugs, for example, solubility, the dissolution rate, stability on storage. Co-crystals can also have technological advantages: behave better on filtration and crystallization, possess lower hygroscopicity and higher stability on treatment.[1] Mechanochemical method is one of the most widely used approaches to the preparation of co-crystals of organic compounds.[1—20] Mechanochemical method is environmentally friendly, since it does not require the use of organic solvents on a large scale.[4,21,22] This method frequently allow one to avoid formation of solvate forms, as well as gives a possibility to obtain co-crystals, whose formation from solutions or melts is impossible.[1,23] Addition of a small amount of solvent during mechanical treatment can accelerate the process of obtaining co-crystals and keep formation of polymorphous modifications of co-crystals under control.[24,25] It is not quite clear how the liquid added influences the process. One of the possible reasons for this influence can be the fact that the process proceeds through the dissolution of at least one of the reagents in the solvent with subsequent crystallization of the co-crystal from the solution.[26—31]

Meloxicam (MOC), 4-hydroxy-2-methyl-*N*-(5-methyl-2-thiazolyl)-2*H*-1,2-benzothiazine-3-carboxamide 1,1-dioxide, is modern nonsteroid antiinflammatory drug.[32] Depending on conditions, it crystallizes in different tautomeric forms: anionic, enol, cationic, and zwitterionic.



MOC

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Earlier,[33] we have used mechanochemical methods for the first preparation of co-crystals of meloxicam with carboxylic acids: succinic and maleic. In continuation of these works, we obtained the co-crystals of meloxicam with another fifteen carboxylic acids[34,35] (Table 1). The literature described[36] the preparation of co-crystals of meloxicam with a number of carboxylic acids by three methods: crystallization from solution, crystallization from a suspension of reagents in solvent, and mechanochemically with addition of small amounts of liquid. Besides acids given in Table 1, the authors of the work[36] reported preparation of co-crystals of meloxicam with 1-hydroxy-2-naphthoic, L-malic, gentisic, 4-hydroxybenzoic, DL-malic, (+)-camphoric, glycolic, and hydrocinnamic acids. The crystal structures were determined for the co-crystals of meloxicam with succinic, fumaric, glutaric, salicylic, 1-hydroxy-2-naphthoic, and L-malic acids.[36] The structure of the co-crystal of meloxicam with succinic acid given in the work[36] is the same as that independently determined by us,[37–39] CCDC 796926 (Fig. 1). Earlier, we have shown that mechanochemical method for the preparation of co-crystals of carboxylic acids with piroxicam (compound related to meloxicam in the structure and having similar therapeutic effect) was more promising than cocrystallization from solutions or from melts.[1]

The purpose of the present work was to compare a possibility of preparation of co-crystals of meloxicam with carboxylic acids using various methods (crystallization from solutions, heating of the mixture components preliminary subjected to mechanical treatment, as well as mechanochemical method, including that with addition of small amounts of various liquids, differing in the ability to dissolve both meloxicam and carboxylic acids), as well as to study the co-crystals obtained by a combination of physicochemical methods.

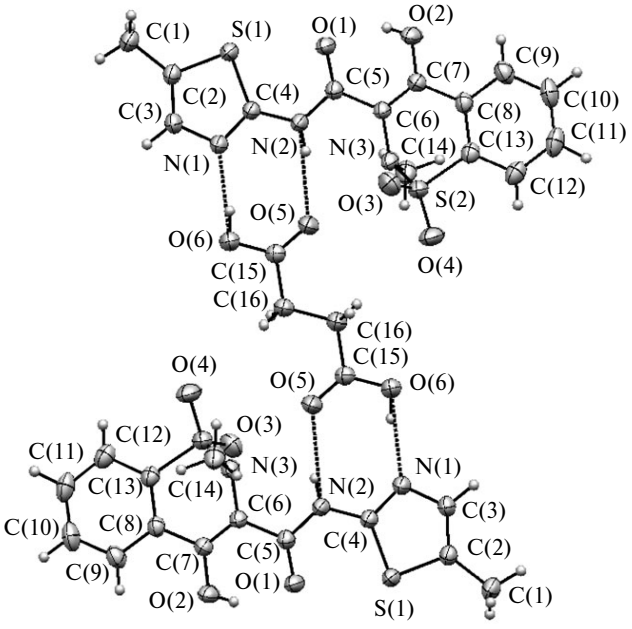

Fig. 1. The structure-forming fragment in the co-crystal of meloxicam with succinic acid (typical of the co-crystals of meloxicam).

Results and Discussion

The results of crystallization from solutions, heating of the mixture components preliminary subjected to mechanical treatment, as well as of mechanical treatment of mixtures of meloxicam and carboxylic acids, including that with addition of small amounts of liquids, are summarized in Table 1.

The crystallization from solutions allowed us to obtain crystals with various ratios of meloxicam : carboxylic acid (2 : 1, 1 : 1, 1 : 2, 1 : 3, and 1 : 4). As it was mentioned previously, the structure of MOC—**1** was found to be the same as reported in the work[36] for the structure of co-crystal of the same composition. The structures of MOC—**2** and MOC—**3** have been described by us earlier.[38] A comparison of the powder diffraction motives showed that the co-crystals MOC—**2**, MOC—**6**, MOC—**12**, and MOC—**13** are identical to those obtained in the work.[36] The structure of MOC—**13** was described[36] based on the single crystal studies, whose calculated diffraction motive matched the experimental one (the present work), that indicated the monophase nature of our sample.

Upon isothermal heating of the mixtures (Table 2), three kinds of co-crystals were isolated, whose powder diffraction motives matched the diffraction motives of co-crystals obtained by mechanochemical method and from solutions. We mainly chose temperatures of heating close to the sublimation temperature, but below melting points. It turned out that the synthesis was possible before the acid melted and even at the temperature below the sublimation point, which was, for example, 0.8 subl.t.

Preliminary mechanical treatment of mixtures of reagents without addition of solvent allowed us to increase the efficiency of formation of co-crystals with subsequent heating of the mixtures, though no formation of co-crystals was observed upon direct mechanical treatment of the same mixtures in the absence of solvent. Heating of simple physical mixture of components did not lead to co-crystals, either.

Mechanical treatment of mixtures of meloxicam with carboxylic acids in the absence of liquid leads neither to the polymorphous transitions in separate components, nor to the formation of new phases, however, after addition of small amount of liquid (~0.2 mL of liquid per 0.1 g of the mixture) the mixtures rapidly lose the yellow color, turning colorless. At the same time, new reflections appear on the diffraction motives, which indicate the formation of a new phase with the crystalline structure differing from the structure of the starting components. This can be con-

Table 1. The co-crystals of meloxicam (MOC) with carboxylic acids **1**—**17**

Acid	Methods of the preparation of the co-crystals and their composition		
	Trituration with acetone	Crystallization from solution	Heating after preliminary mechanical activation
Succinic[36] (**1**)[a]	MOC—**1** (2 : 1)	MOC—**1** (2 : 1)[b]	—
Adipic[36] (**2**)[a]	MOC—**2** (2 : 1)[c]	MOC—**2** (2 : 1)[c]	—
Terephthalic (**3**)	MOC—**3** (2 : 1)	MOC—**3** (2 : 1)[b]	—
Oxalic (**4**)	MOC—**4** (1 : 1)	—	—
Malonic[36] (**5**)	MOC—**5** (1 : 3)	—	—
Maleic[36] (**6**)[a]	MOC—**6** (1 : 2)	—	MOC—**6** (1 : 2)
Fumaric[36] (**7**)	MOC—**7** (1 : 1)	—	—
Glutaric[36] (**8**)	MOC—**8** (1 : 2)	MOC—**8** (1 : 2)	MOC—**8** (1 : 2)
Pimelic (**9**)	MOC—**9** (1 : 4)	—	—
Suberic (**10**)	MOC—**10** (1 : 1)	—	—
Sebacic (**11**)	MOC—**11** (1 : 1)	—	—
Benzoic[36] (**12**)[a]	MOC—**12** (1 : 1)	—	—
Salicylic[36] (**13**)[a]	MOC—**13** (1 : 1)	—	—
Isophthalic (**14**)	MOC—**14** (1 : 1)	—	MOC—**4** (1 : 1)
Trimesic (**15**)	MOC—**15** (1 : 1)	—	—
Phenylsuccinic (**16**)	MOC—**16** (1 : 4)	—	—
Citric acid hydrate (**17**)	MOC—**17** (1 : 2)	—	—

[a] The phases of the co-crystals matched with those obtained in the work.[36]
[b] The structure was determined in the present work.
[c] The structure was determined in the present work and different polymorphous modifications were obtained.

sidered as an evidence for the formation of the co-crystal. A procedure of the phase indexing is described in the Experimental. Analysis of the X-ray diffraction data showed that the samples obtained by us by mechanical treatment of mixtures of meloxicam with benzoic, adipic, succinic, maleic, and salicylic acids with addition of acetone are identical to those reported earlier[36] for the co-crystals of meloxicam with these acids. In the case of benzoic, adipic, and maleic acids, the comparison was performed using X-ray powder diffraction motives, for succinic and salicylic, using the data of the single crystals analysis. It should be noted that in the work,[36] other solvents were used: THF for the preparation of the co-crystals with benzoic, adipic, succinic, maleic acids and ethyl acetate in the case of salicylic acid. At the same time, the X-ray powder diffraction motives of the samples obtained by mechanical treatment of the mixtures of meloxicam with malonic, fumaric, and glutaric acids considerably differed from the diffraction motives given in the work,[36] that indicated that different phases were formed in these systems upon mechanical treatment in our experiments and in experiments described earlier.[36] One of the possible reasons for such discrepancies is the use of additives of different liquids, which, as it is known, can influence the composition, stoichiometry, and crystalline structure of the products of mechanical synthesis.[40] When the same liquids were used, the phases coincided with those described earlier.[36] More in detail discussion on the influence of liquids on the results of mechanosynthesis in the mixtures of meloxicam with carboxylic acids will follow below. In the present work, we for the first time obtained the co-crystals of meloxicam with pimelic, suberic, sebacic, oxalic, isophthalic, terephthalic, trimesic, and phenylsuccinic acids. Despite the fact that no co-crystals were obtained upon mechanical treatment of dry mixtures of

Table 2. Melting points and sublimation temperatures of carboxylic acids and temperatures of heating of mixtures of acids with meloxicam

Acid*	M.p./subl.t.	Temperature of heating
	°C	
Oxalic (**4**)	166/125	130, 160
Malonic (**5**)	135.6/—	90
Succinic (**1**)	185/130—140	130, 180
Maleic* (**6**)	139/—	120
Fumaric (**7**)	296/165	170
Glutaric* (**8**)	98/—	90
Adipic (**2**)	153/130	140
Adipic(**9**)	105.5/—	90
Benzoic (**12**)	122.4/—	130
Isophthalic* (**14**)	348/160	130
Terephthalic (**3**)	300/165	130
Trimesic (**15**)	380/300	130

* The co-crystals were obtained with this acid upon heating.

meloxicam with citric acid,[33] the co-crystal was obtained by trituration of meloxicam with citric acid monohydrate with addition of acetone. No formation of co-crystals was observed either upon mechanical treatment of mixtures of meloxicam with 3-(4-hydroxyphenyl)propionic and 3-(3,4-dihydroxyphenyl)propionic acids. Like in the works,[33,36] no co-crystals of meloxicam with ascorbic or tartaric acid were obtained by the synthetic method chosen.

For the co-crystals with three acids, *viz.*, succinic, adipic, and terephthalic, single crystals were grown from solutions in THF, toluene, and ethanol, respectively, by a slow evaporation in air. Comparison of the powder diffraction motives, which were calculated based on the models obtained by the decoding of the diffractional data for single crystals and the powder diffraction motive measured for the products of mechanochemical synthesis showed that the powders of the products have the monophase nature and the crystalline structures of the single crystals coincide with the crystalline structures of polycrystalline samples.

Thermoanalytical studies of mechanically activated mixtures of meloxicam with acids in those case when the mechanical treatment was interrupted, without the reaction reaching completion, showed the presence of thermal effects characteristic of the melting of the separate components and the product, *i.e.*, the co-crystal. The melting points of the co-crystals can be registered on their DSC-curves. The results of the DSC-measurements of co-crystals of meloxicam with adipic and terephthalic acids are given in Fig. 2. An endothermic thermal effect was detected in both samples, which can be attributed to the melting of the co-crystals, followed by the endo- and exothermic effects apparently related to the sublimation of acids and decomposition of the samples. The co-crystal of meloxicam with adipic acid melts at ~195 °C (m.p. of meloxicam and adipic acid are 260 and 153 °C, respectively). For the co-crystal with terephthalic acid, the endothermic process of melting is observed at 255 °C (m.p.

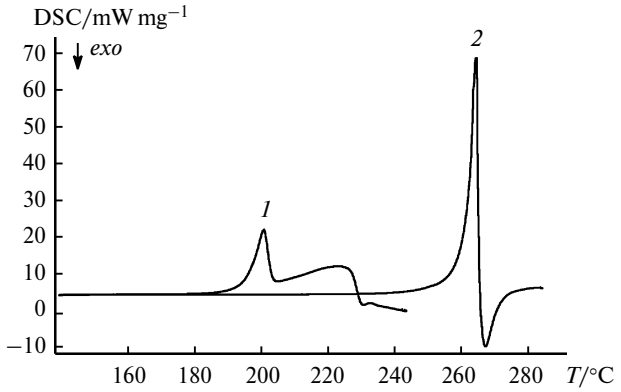

Fig. 2. The DSC curves for the co-crystals of meloxicam with adipic (*1*) and terephthalic (*2*) acids.

of terephthalic acid is 300 °C). It is seen that the co-crystals of meloxicam have different melting points, while formation of the co-crystals suppresses the sublimation and decomposition of carboxylic acids up to the co-crystal melting point.

The mechanochemical method of synthesis has proved more efficient for the preparation of co-crystals of meloxicam with carboxylic acids than crystallization from solutions or heating mixtures. The same behavior was observed for the co-crystals of piroxicam:[1] from the six methods used (co-melting of components, evaporation of solvent, rapid and slow cooling of solution, salting out of solution, and mechanochemical), the mechanochemical method turned out to be the most productive for the crystallization of co-crystals. At the same time, to effect the mechanochemical synthesis of the majority of the systems, the presence in the system of at least a small amount of liquid is still necessary, without which the process does not take place or proceeds so slowly that is not detected within a real duration of the experiment.

The influence of liquid on the process of synthesis of co-crystals upon mechanical treatment was studied more in detail using the systems meloxicam—succinic acid and meloxicam—adipic acid as examples. The results for the system meloxicam—succinic acid are compared in Table 3, where the molar solubility of meloxicam also is given.[41] There is no unambiguous correlation between the solubilities of the starting components in the liquid added and the possibility of the formation of the co-crystals. For example, the co-crystals were formed upon addition of both the liquids dissolving both components (acetone, ethanol, isopropanol) and the liquids, in which one of the components (succinic acid) was virtually insoluble (chloroform, toluene, benzene, ethyl acetate). In the case of solvents, in which neither of the components is soluble (hexane, cyclohexane), no co-crystals were obtained. At the same time, the co-crystals were not formed upon addition of water, though both starting components were soluble in it. In the equilibrium crystallization, a necessary condition for the formation of co-crystals is a lower solubility of the co-crystal obtained as compared to the solubility of separate components in the solvent used. Formation of co-crystals often is a nonequilibrium process and is observed in such cases, when in a certain solvent the crystallization of co-crystals occurs faster than crystallization of the individual phases. We have observed that the mechanochemical synthesis frequently gives products corresponding to the rapid crystallization. Thus, it has been shown earlier for the system glycine—oxalic acid that the mechanical co-treatment of a mixture of glycine and oxalic acid dihydrate initially and very fast led to the formation of bis-glycinium oxalate (the same product as in the rapid spontaneous crystallization from aqueous solutions upon precipitation with acetone), which on further mechanical treatment was transformed to glycinium semi-

Table 3. Solubility of succinic acid and meloxicam in various solvents and the products formed

Solvent	Solubility of succinic acid	Molar solubility of meloxicam[41]	Product of mechanochemical synthesis	Product of synthesis from solution
Chloroform	—	0.001814	MOC—**1** (2 : 1)	MOC—**1** (2 : 1)
Dioxane		0.001796	MOC—**1** (2 : 1)	—
Acetone	+	0.0006055	MOC—**1** (2 : 1)	MOC—**1** (2 : 1)
Toluene	—	0.0001698	MOC—**1** (2 : 1)	MOC—**1** (2 : 1)
Benzene	—	0.0001612	MOC—**1** (2 : 1)	MOC—**1** (2 : 1)
Carbon tetrachloride		$6.166 \cdot 10^{-5}$	—	—
Propan-1-ol		$5.562 \cdot 10^{-5}$	MOC—**1** (2 : 1)	—
Ethanol	+	$4.582 \cdot 10^{-5}$	MOC—**1** (2 : 1)	—
Propan-2-ol	+	$3.93 \cdot 10^{-5}$	MOC—**1** (2 : 1)	MOC—**1** (2 : 1)
Ethyl acetate	—	$3.476 \cdot 10^{-5}$	MOC—**1** (2 : 1)	MOC—**1** (2 : 1)
Water	+	$1.023 \cdot 10^{-5}$	—	—
Hexane	—	$7.701 \cdot 10^{-6}$	—	—
Cyclohexane		$4.474 \cdot 10^{-6}$	—	—

oxalate (*i.e.*, to the product of slow crystallization upon evaporation of the aqueous solution).[42,43] In the present work, in the system of meloxicam—succinic acid the formation of the co-crystals upon crystallization from the solution in acetone, isopropyl alcohol, ethyl acetate also was observed only in such a case, when the solution was subjected to the rapid evaporation, as in the grinding case, whereas the starting components were crystallized upon slow evaporation.

The role of solvents was also demonstrated in the series of experiments, the results of which are shown in Fig. 3. On the X-ray diffraction motive *2*, the reflections related to the co-crystal of meloxicam with succinic acid are marked. It is seen that short-time treatment with addition of the solvent resulted in the incomplete formation of the co-crystal. Mechanical treatment after evaporation of the solvent did not lead to further formation of the co-crystal (X-ray diffraction motive *3*). It can be concluded that the presence of solvent is necessary for the process to take place. After addition of a solvent to a preliminary ground mixture, the product was obtained almost instantly (X-ray diffraction motives *4* and *5*). At the same time, the addition of a solvent to the mixture of components ground separately led to the formation of only insignificant amount of the product (X-ray diffraction motive *6*). To sum up, in the case of meloxicam with succinic acid mechanical co-treatment of the mixture of components plays an important role in the formation of the mixed crystal, whereas addition of solvent, apparently, accelerates the process. The influence of preliminary mechanical activation, possibly, consists in the fact that mechanical treatment leads to the formation of nuclei of the product, which then, upon addition of the solvent, become the centers of its crystallization. This was confirmed, for example, by the fact that meloxicam could react with maleic acid upon heating, if the mixture was preliminary ground when dry.[33] The role of mixing the components during preliminary mechanical treatment of dry mixture should not be underestimated, either.

We compared the preparation of the co-crystals of meloxicam with adipic acid upon mechanical treatment with addition of a small amount of dioxane or toluene, as well as upon slow co-crystallization from solutions of these solvents. The use of different solvents led to the formation of compounds with different crystalline structure by both slow crystallization from solutions and grinding with addition of small amounts of the same solvents (Fig. 4). In this case, the slow crystallization from solution of a certain solvent and mechanical treatment with addition of the same solvent gave the same result. In order to determine whether the compounds obtained were solvates or co-crystals with different stoichiometry, we performed elemental analysis. The results showed that the co-crystals obtained are not solvates but, obviously, different polymorphous modifications of the same co-crystal meloxicam—adipic acid with the ratio of components 2 : 1.

For the practical use of meloxicam as medicinal preparation, it is of importance to develop forms, in which the dissolution rate and solubility would be higher. These properties are characteristic, at least, of some of the co-crystals synthesized in the present work: with succinic, oxalic, isophthalic, benzoic, and terephthalic acids (Fig. 5). Except oxalic acid, all the acids listed have no harmful effects on the organism and are permitted by pharmacopoeia for the introduction in the composition of medicinal forms.[44] Therefore, the co-crystals listed (except the co-crystal with oxalic acid) can be considered as promising for the application in the composition of pharmaceutical forms as alternatives to the individual compound.

The most important characteristics of solid medicinal compound is its crystalline structure. The detailed comparative analysis of the crystalline structures of co-crystals

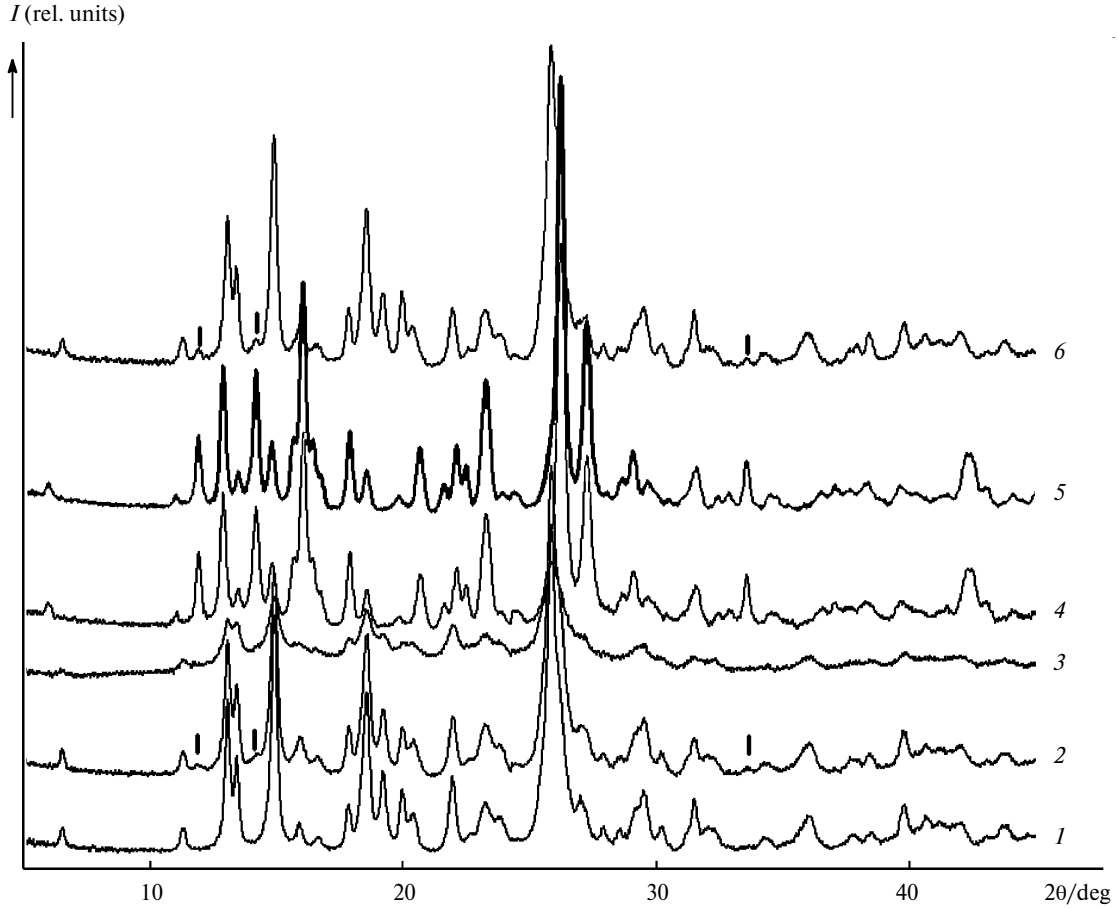

Fig. 3. X-ray diffraction patterns of mixtures of meloxicam with succinic acid (2 : 1): the mixture ground during 3 min without solvent (*1*) or with solvent (*2*), the preceding mixture ground during 15 min after evaporation of the solvent (*3*), the preceding mixture ground for another 20 s with the solvent (*4*); a mixture ground during 9 min without solvent and then 20 s with the solvent (*5*); a mixture of components ground separately during 9 min, which was ground with addition of the solvent during 20 s (*6*).

of meloxicam is given in the work.[38] Meloxicam in the co-crystal exists in the enol prototropic form in such a configuration that the oxygen atoms of the hydroxyl and keto groups are on the same side of the molecule. The O—H...O hydrogen bond is formed between the oxygen atoms of these groups, which stabilizes this conformation. Due to the rigid enough geometry of the molecule, parameters of this intramolecular hydrogen bond cannot considerably vary and lie in the same range as in other structures with meloxicam in similar conformation.

In the known structures of co-crystals of meloxicam with acids, no proton transfer from the carboxyl group of the acid to the thiazole ring of meloxicam takes place, except for the co-crystal with L-malic acid. However, it is obvious that the formation of the hydrogen bond between the nitrogen and the hydrogen atoms leads to the weakening of the conjugation of the lone pair of electron on the nitrogen with the ring and the disappearing of the color of the compound.

Each carboxyl group of dicarboxylic acid is bonded to the NH group and the thiazole group of meloxicam through the hydrogen bonds N—H...O and O—H...N, respectively. This motive was observed in all the known by now structures of the co-crystals of meloxicam with carboxylic acids. Thus, the main structural fragment is formed consisting of one molecule of the corresponding acid and two molecules of meloxicam.[38] These structural fragments form planar layers, as it is shown in Fig. 6, *a*. In the co-crystals with succinic, fumaric, and L-malic acids, the planar layers are formed from similar structural fragments. In the case of adipic and terephthalic acids, the distance between the meloxicam molecules happens to be enough for the meloxicam molecule of one fragment to be placed between two molecules of meloxicam of another fragment, so that the fragments are "hooked" to each other, though forming no dimers (see Fig. 6, *a*). In the co-crystals with succinic, fumaric, and L-malic acids, the distance between the meloxicam molecules in one fragment is smaller and not enough for the meloxicam molecule of the neighboring fragment to be placed between them (Fig. 6, *b* succinic acid was taken as an example). In this case, the structural fragments are arranged in such a way that the formation of

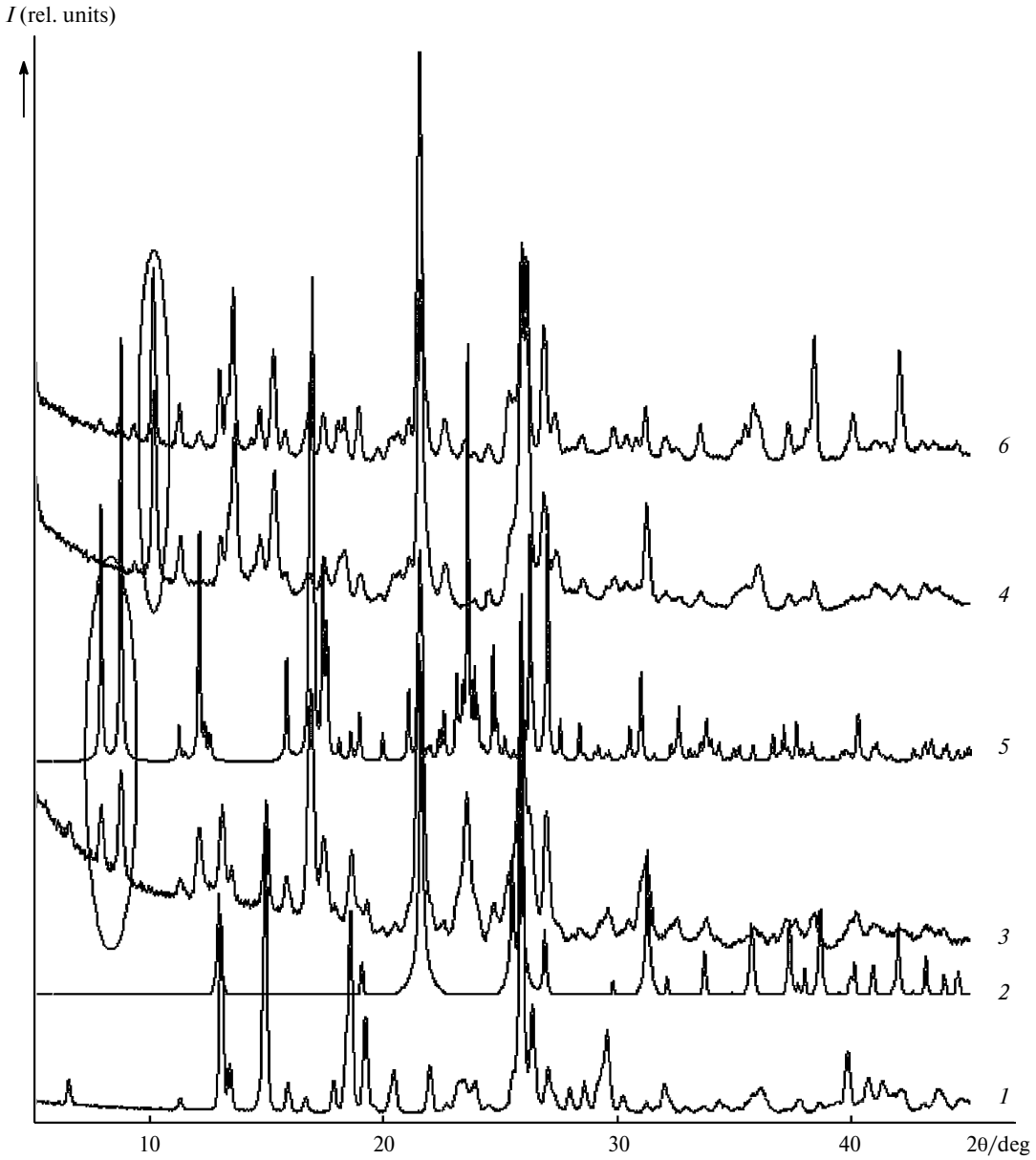

Fig. 4. X-ray diffraction motives of the starting meloxicam (*1*), the starting adipic acid (*2*), the co-crystal obtained by grinding with toluene (*3*) or dioxane (*4*) and obtained from the solution by a slow evaporation from toluene (*5*) or dioxane (*6*).

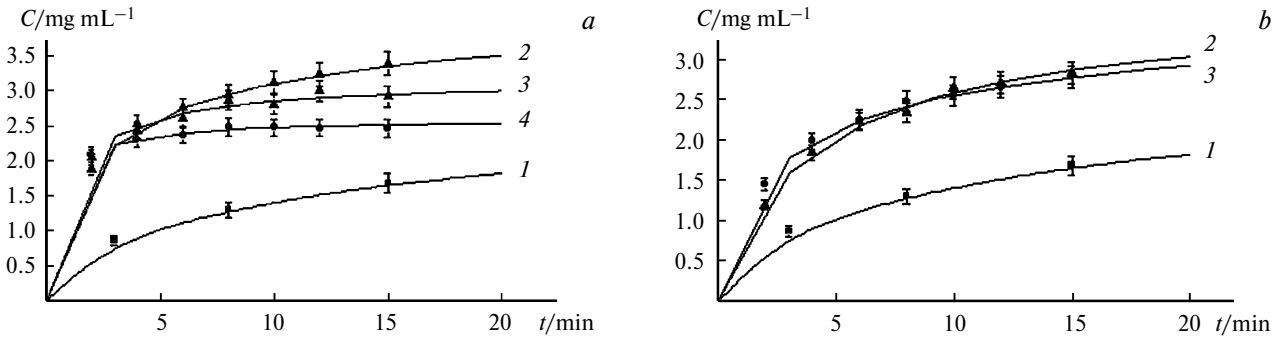

Fig. 5. Curves of dissolution of the co-crystals of meloxicam with carboxylic acids as compared to the individual meloxicam (*1*): (*a*): with succinic (*2*), oxalic (*3*), and isophthalic acid (*4*); (*b*): with benzoic (*2*) and terephthalic acid (*3*).

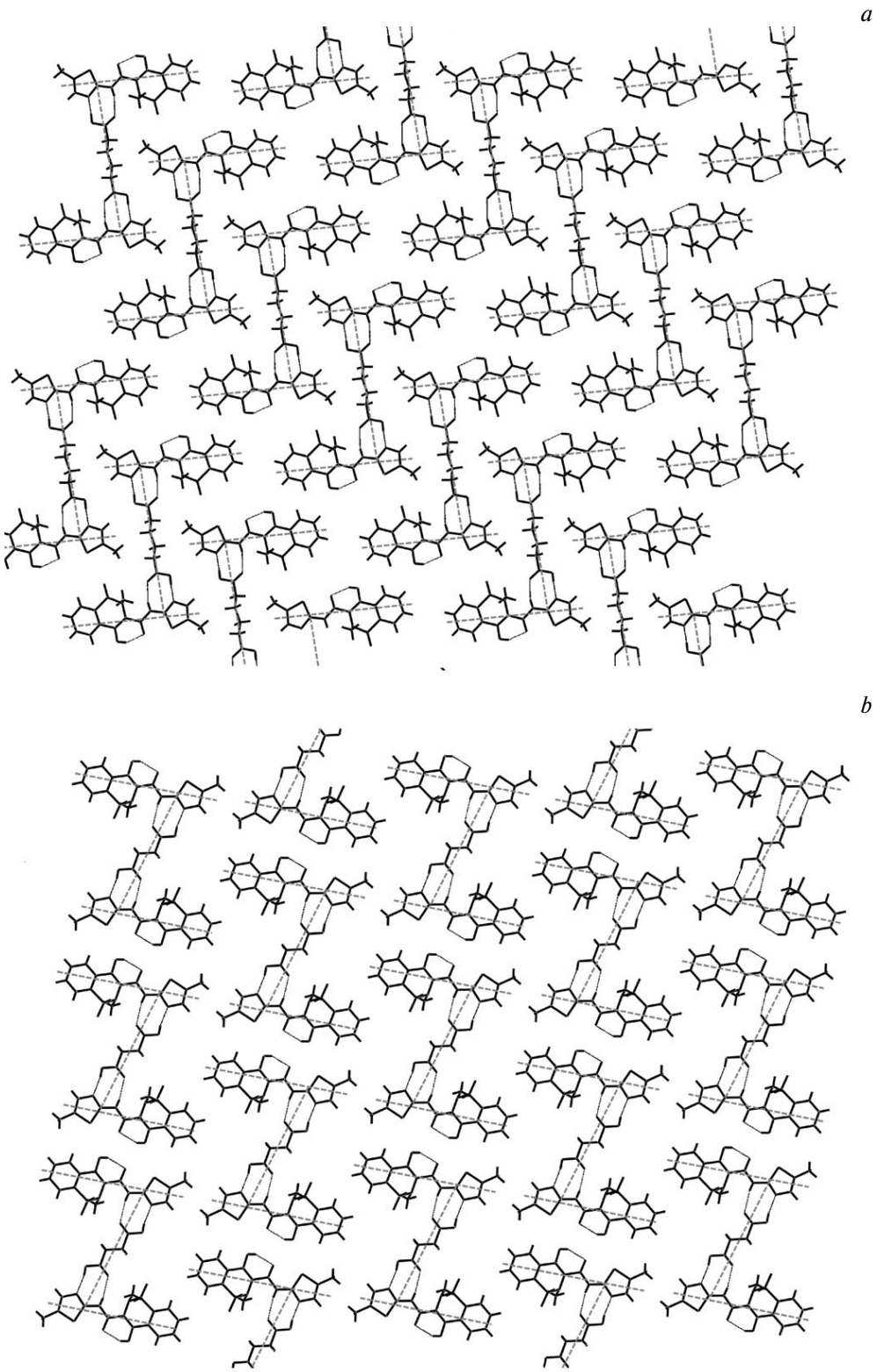

Fig. 6. The motive of planar layers in the structure of the co-crystals of meloxicam with adipic (*a*) and succinic acids (*b*).

molecular pairs (pseudodimers) of meloxicam becomes possible, in which the molecules are situated close to each other, though are not bonded by hydrogen bonds. Such a motive can also be found in the crystalline structures of meloxicam hydrogen sulfate hydrate[32] and benzene solvate of *trans*-dichloro(η^2-ethylene)(meloxicam)platin-

um(II)[45]. For the comparison, in the structure of the individual meloxicam the molecules are bonded by strong hydrogen bonds to true dimers. A suggestion[38] has been made that this is destruction of dimers in the co-crystals based on medicinal compound which can be the reason of the increased rate of their dissolution as compared to the crystals of the individual medicinal compound.

It was of interest to compare the crystalline structures of co-crystals of meloxicam—carboxylic acid with the structures of the co-crystals of piroxicam with the same acids determined in Ref. 46. Piroxicam has molecular structure similar to that of meloxicam, but has a pyridine fragment instead of the thiazolyl group. At least two polymorphous modifications are known for piroxicam, which differ in the molecular packing. In both polymorphous modifications of piroxicam no formation of dimers, analogous to the dimers in compounds of meloxicam, was observed, whereas in the structures of crystals containing piroxicam with such a configuration where the oxygen atoms of the hydroxyl and keto groups are on the same side of the molecule, such dimers are formed. The structures of the co-crystals of piroxicam with 1-hydroxy-2-naphthoic and succinic acids are similar to the structures of the co-crystals of meloxicam with the same acids, whereas the structures of the co-crystals with malonic and fumaric acids in the cases of meloxicam and piroxicam considerably differ, that can be attributed to the influence of the pyridyl group. The motive in the form of planar infinite chains, similar to that present in the structures of the co-crystals of meloxicam with adipic and terephthalic acids, in the co-crystals of piroxicam with carboxylic acids was not observed, that can also be explained by the specifics of the pyridyl group. Conformations of the piroxicam molecule in the co-crystals are distinguished by a greater variety as compared to those of meloxicam. Note that as of the present moment, no formation of the co-crystals of piroxicam with terephthalic acid is described in contrast to meloxicam, but piroxicam is known to form three co-crystals with adipic acid (while meloxicam forms only two co-crystals). Such a difference for the structurally close compounds cannot be explained only from the standpoint of crystallochemical analysis.

Investigation of vibration spectra gives an additional information about the interactions in the structure of co-crystals. The vibration bands of the meloxicam molecule in the IR spectra of co-crystals and an individual pharmaceutical compound have different positions (Fig. 7). A strong peak at 3290 cm^{-1} corresponding to the stretch-

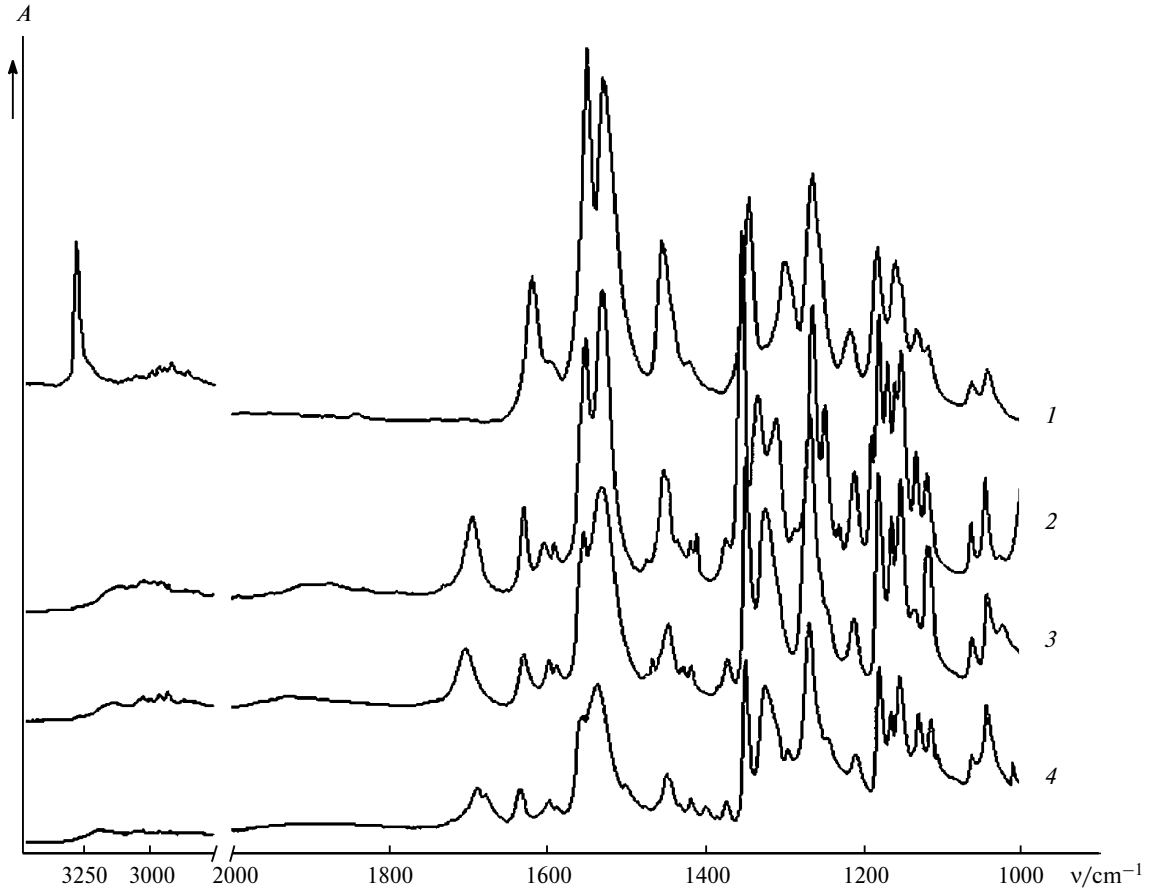

Fig. 7. IR absorption spectra of meloxicam (*1*) and the co-crystals of meloxicam with succinic (*2*), adipic (*3*), and terephthalic acids (*4*).

ing vibration ν(N—H) in the molecule of meloxicam is shifted toward the lower frequencies in the IR spectrum of co-crystals, whereas its intensity decreases. At the same time, the amide II and amide III vibration bands, which are a combination of vibrations ν(C—N) + δ(NH), are displaced toward higher frequencies. These changes correspond to the strengthening of the NH...O hydrogen bonds when the homomolecular dimers in meloxicam are replaced with the heteromolecular clusters meloxicam—carboxylic acid in co-crystals. In the spectra of the co-crystals, the band, which corresponds to the stretching vibration of the C=O group involved in the individual meloxicam in the formation of intramolecular hydrogen bond and short contacts in the molecular pairs (pseudodimers),[38] is slightly shifted toward the high-frequency region, that indicates the "loosening" or the absence (depending on the type of packing) of molecular pairs. The IR spectra of co-crystals with different types of molecular packing also differ. In the spectra of the co-crystals of meloxicam with adipic and terephthalic acids, where a chain-like motive of packing is effected and molecules are bonded through a short contact with participation of the oxygen atom of the SO_2 group, the band corresponding to the stretching vibration $\nu_{as}(SO_2)$ virtually does not change its position, whereas upon formation of the co-crystal with succinic acid, the distruction of the dimers existing in the starting meloxicam bonded by hydrogen bonds with participation of the SO_2 group, leads to the shift of the band toward higher frequencies.

The strengthening of heteromolecular hydrogen bonds in the co-crystals as compared to the homomolecular ones in the individual meloxicam, from the one hand, allows one to explain formation of the co-crystals, rather than the phases of individual components on co-crystallization, but, from the other hand, causes a question about the reasons of the higher dissolution rate of co-crystals as compared to the individual meloxicam. Apparently, as it was suggested in the work,[38] the dissolution rate is influenced not only by the energy of intermolecular interactions in the crystal, but also by the easiness of the attack of the molecule in the crystal by the solvent molecules, which is defined by the crystalline structure. If in the heteromolecular clusters the two molecules of meloxicam are connected by the carboxylic acid bridge, the solvation of the meloxicam molecules can take place easier than if the molecules of meloxicam are bonded to each other in a dimer by hydrogen bonds.

In conclusion, in the present work co-crystals of meloxicam with 17 different carboxylic acids were obtained using various methods. It was shown that preliminary mechanical treatment plays a significant role in effecting the synthesis, whereas addition of small amount of solvent accelerates the process. Varying the liquids, from which crystallization was carried out or which were added to the mixtures of powders during their mechanical co-treatment, allowed us to obtain different polymorphous modifications of the co-crystals of meloxicam. It was shown that the dissolution rate and the solubility of meloxicam in the case of the co-crystals with the carboxylic acids under study was higher than the dissolution rate of the starting medicinal compound, that makes it promising to use the co-crystals of meloxicam for solubilization of medicinal forms based on it.

Experimental

Meloxicam was purchased from Chem-East Ltd. (Hungary). Carboxylic acids (see Table 1) purchased from Hebei Welcome Pharmaceutical Co., Ltd (China) and solvents (see Table 2) purchased from Reakhim (Russia) and Sigma—Aldrich (USA) were used without additional purification.

IR spectra of frustrated total internal reflection (FTIR) in the range of frequencies 4000—580 cm^{-1} with the resolution of 4 cm^{-1} were recorded on a Digilab Excalibur 3100 Fourier-transform IR spectrometer (USA) using an FTIR (Pike) appliance with a ZnSe crystal without special preparation of samples. Elemental analysis was performed on an EA-3000 (HEKAtech GmbH, Germany) elemental analyzer. Thermoanalytical measurements were performed on a DSC-204 (Netzsch) calorimeter, the rate of heating was 6 K min^{-1}, masses of samples were 5.1 and 4.6 mg for the co-crystals of meloxicam with terephthalic and adipic acids, respectively.

X-ray powder analysis. X-ray powder analysis was performed on D8 DISCOVER (Bruker, Germany, Cu-Kα irradiation) and STADI MP (STOE & Cie GmbH, Germany, Cu-$K\alpha_1$ irradiation) diffractometers. The diffraction motives obtained were analyzed using the WinXPOW software.[47] In the cases when only peaks from new phases could be identified, the diffraction motives were indexed. Stoichiometry of a compound obtained was determined proceeding from the volume of a unit cell and approximate volumes of molecules of meloxicam and the corresponding acid. Product was considered as having a monophase nature, when no peaks from the starting reagents remained in its diffraction motive and all the peaks in the diffraction motive of the product were indexed.

Mechanochemical synthesis of co-crystals (general procedure). Mechanical treatment of mixtures of meloxicam with carboxylic acids in different molar ratios was carried out in an agate mortar (the time of treatment 20—30 min) or in a SPEX 8000 roller mill (CertiPrep Inc., USA, 40-mL steel cans, steel balls 6 mm in diameter, the proportion of the compound weight to the weight of the balls 1 : 100, the load on the ball 8—10 g, the time of treatment 15 min). Dry treatment was used initially, then liquid was added (acetone, ~0.2 mL of liquid per 0.1 g of the mixture). Experiments with the variations of liquids were carried out in a mortar, adding solvents (see Table 2) to a preliminary triturated dry mixture of meloxicam with succinic acid in the molar ratio of 2 : 1. Dioxane and toluene were used in the case of adipic acid. For the product of mechanical treatment of the mixture of meloxicam with adipic acid in the presence of dioxane: found (%): C, 48.86; H, 5.23; N, 6.46; S, 9.85. For the mixture triturated with toluene: found (%): C, 48.96; H, 5.20; N, 6.72; S, 10.50. $C_{26}H_{33}N_3S_2O_{12}$. Calculated (%): C, 48.47; H, 5.13; N, 6.52; S, 9.96.

Synthesis of co-crystals by crystallization from solutions. The co-crystals of meloxicam with succinic acid (2 : 1) were obtained

by crystallization from a THF solution. A preliminary triturated mixture of meloxicam with succinic acid (2 : 1) was dissolved at 40 °C in the solvent (15 mL). The solution was subjected to the slow evaporation (using a cap with a small opening) at ~20 °C. The co-crystals of meloxicam—adipic acid were obtained from the solution in toluene saturated at 50 °C with the mixture of meloxicam with adipic acid (2 : 1) by cooling to ~20 °C. The co-crystals of meloxicam with terephthalic acid were obtained from the solution in ethanol saturated at 50 °C with the mixture of meloxicam with terephthalic acid (2 : 1) by cooling to 5 °C. The co-crystals of meloxicam with glutaric acid were obtained from the solution in benzene subjected to a slow evaporation at ~20 °C.

Synthesis of co-crystals upon heating. A preliminary triturated dry mixture of meloxicam with carboxylic acids was placed in an oven (LF-60/350-VS1, Russia) and subjected to the isothermal heating for 2 h at the temperature below the melting point of the acid (see Table 4).

Measurement of the dissolution rate and solubility of samples. The rate of liberation of meloxicam was studied using a Varian 705 DS solubility tester. A weighed sample containing excess of meloxicam was placed into a glass vessel thermostated at 37±0.5 °C and equipped with mechanical stirrer and containing a buffer solution with pH = 9 (200—250 mL) (sodium tetraborate was used as an alkaline buffer solution because meloxicam does not dissolve in acidic solutions). A pipette dispenser was used to collect samples of the solution under analysis after certain periods of time, followed by their filtration. Optical density of the solution obtained was measured on a Cary 50 spectrophotometer using the intensity of the band at 362 nm for meloxicam. Distilled water was used as a comparison solution.

Single crystal X-ray diffraction analysis. X-ray diffraction experiments were carried out on an Oxford Diffraction Gemini Ultra R CCD diffractometer (graphite monochromator, λ(Mo-Kα) = 0.7173 Å, temperature 293 K). The structures were solved by direct methods using the SHELXS-97 program[48] and refined by the least squares method using the SHELXL-97 program.[48] Hydrogen atoms were placed in the calculated positions and refined in the rigid binding with the neighboring nonhydrogen atom. The crystalline structure of MOC—**1** were deposited with the Cambridge Structural Database (CCDC 796926), the structures of MOC—**2** and MOC—**3** were described in detail in the work.[38]

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