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Synthesis of co-crystals of meloxicam with carboxylic acids by grinding

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The first co-crystals of meloxicam with succinic and maleic acids were obtained by solvent-drop grinding techniques.

The synthesis of co-crystals representing supramolecular complexes of two or more components is very attractive especially in pharmaceutical chemistry due to the possibility of influencing the stability and dissolution of drugs without changing the molecular structure of the active pharmaceutical ingredient. Co-crystals are generally prepared by solution crystallization, less commonly by growth from the melt.[1–3] An alternative approach is solid-state grinding that eliminates undesired solvate formation and may even produce different adduct crystals compared to those obtained by crystallization from the melt or solution.[4,5] The addition of very small solvent amounts (solvent-drop grinding) speeds up the process significantly and can provide control over the formation of a specific polymorphic form.[6–8]

Meloxicam is a non-steroidal anti-inflammatory drug[9] poorly soluble in water and many organic solvents. Depending on the solvent and the pH of the solution, meloxicam crystallizes in four different prototropic forms: the yellow anion, acidic enol and zwitterion, and the colourless cation. It can be expected that co-crystal formation is accompanied by the transition of meloxicam from one type to another as it was observed for the structurally related compound piroxicam.[10] In this work, the obtaining of co-crystals of meloxicam with carboxylic acids by solid state grinding is studied. Ascorbic, citric, succinic and maleic acids are chosen as co-crystal builders, since all are pharmaceutically acceptable and differ by their structures and the numbers of carboxylic groups (Figure 1).†

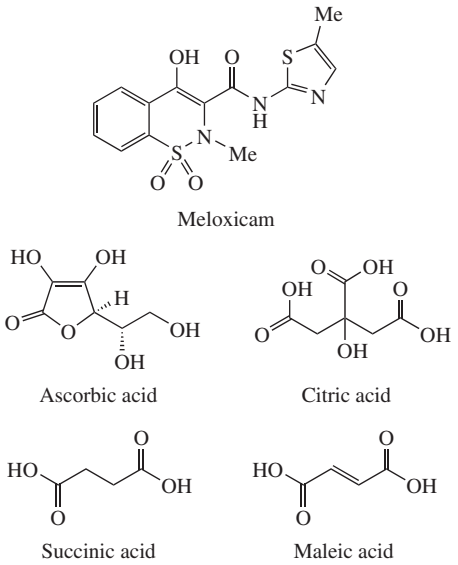

Figure 1 Molecular structures of used compounds.

The mixtures of meloxicam with ascorbic acid showed no new peaks in the XRPD patterns (data not shown) after grinding in the mortar or in the mill; thus, no co-crystal formed. Neither changing the ratio of the compounds nor applying solvent-drop grinding influenced the IR spectra of the ground mixtures. The ground mixtures were yellow as the initial meloxicam. Thus, the data obtained suggested that there was no interaction between meloxicam and ascorbic acid. Probably, the absence of carboxylic groups having a strong tendency to formation of hydrogen bonds and the rather complex network of intermolecular hydrogen bonds in the crystals of ascorbic acid prevents the co-crystallization.

None of the experiments with meloxicam–citric acid mixtures showed new peaks in the XRPD patterns (Figure 2). The peaks were dramatically decreased and rather broadened probably due to comminuting the particles and partial amorphization of the samples. The ground mixtures were yellow as the initial conformation of meloxicam. In the FTIR spectra (Figure 3) of the ground mixture, instead of two bands at 1706 and 1754 cm^{-1}

† Meloxicam was purchased from Altaivitaminy (Russia). Ascorbic, citric, succinic, and maleic acids (Hebei Welcome Pharmaceutical, China) and solvents (Roskhimreaktiv, Russia) of reagent grade were used without further purification.

The meloxicam–acid mixtures (1:1 and 1:2 molar ratio) were ground manually in an agate mortar at room temperature for 20 min in dryness, as well as with the addition of 1 ml of a solvent. The grinding was also performed in a SPEX 8000 vibration ball mill (CertiPrep, USA). Initially, the mixtures were milled without solvent for 30 min; subsequently, 1 ml of solvent was added and milling was continued. The organic solvents listed in Table 1 were used.[11] For co-crystallization from solution, pure solvents (ethanol and THF), and solvent mixtures, such as acetone–THF, ethanol–THF, isopropanol–THF and diethyl ether–THF were employed.

X-ray powder diffraction (XRPD) patterns were recorded using a D8 Discover diffractometer (Bruker, Germany), CuKα radiation. Fourier-transformed infrared (FTIR) spectra were recorded with an Infralum FT-801 spectrometer (Lumex-Siberia, Russia) in KBr pellets. According to XRPD data, the initial meloxicam exists in the yellow enol form.[12] The diffractograms of mill-ground pure meloxicam revealed only peak broadening suggesting reduction of the particle size of the drug and introduction of partial disorder on the structural level.

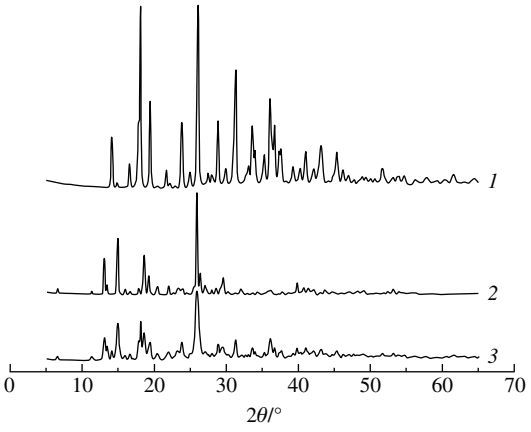

Figure 2 X-ray diffraction patterns of (*1*) citric acid, (*2*) meloxicam and (*3*) 1:1 meloxicam–citric acid mixture ground in the mortar with addition of ethanol.

attributed to acid carbonyl stretching vibrations (for the physical mixture), three bands at 1690, 1728 and 1757 cm^{-1} were observed. In the O–H stretching region, the intensity of the sharp band at 3494 cm^{-1} decreased and the weak band at 3447 cm^{-1} disappeared. In addition, a new band at 3368 cm^{-1} appeared in the spectra of the ground mixture. The IR spectrum of the ground mixture resembled that of citric acid monopotassium salt[13] suggesting the formation of monoester of citric acid with meloxicam during grinding. It has been recently shown that heating a mixture of a solid drug (carvedilol) and citric acid monohydrate at 50 °C for 96 h resulted in the formation of about 3% of a symmetrical ester.[14] In our case, probably, the ground samples were the mixtures of initial components and the citric acid ester with meloxicam, being in an amorphous state.

The extensive dry grinding of meloxicam–succinic acid mixtures did not result in any change in the crystal form, but the addition of 1 ml of ethanol led to a colour change of the mixture from yellow to white indicating a co-crystal formation and a concomitant conversion of the meloxicam molecules into the cationic form. The XRPD patterns showed new peaks (Figure 4) and thus proved the co-crystal formation. The FTIR spectra of the meloxicam–succinic acid mixtures ground in the mortar without solvent showed no significant changes in comparison with the physical mixture (Figure 5). Grinding with the addition of acetone, ethyl acetate, ethanol, isopropanol, chloroform, dioxane or benzene resulted in the above colour change, while hexane, cyclohexane or toluene caused no change. The FTIR spectra of these samples showed significant changes as compared to the physical mixture (Figure 5, curve *4*): the meloxicam carbonyl stretching vibration band (1621 cm^{-1}) decreased in intensity and shifted to 1631 cm^{-1}, while new bands could be detected at 1594 and 1606 cm^{-1}. The shift of the succinic acid OH group deformation vibration band (from 1309 to 1335 cm^{-1}) was observed. Additionally, the meloxicam N–H stretch vibration band at 3291 cm^{-1} decreased in intensity. A new band at 3125 cm^{-1} and a high-frequency wing in the N–H stretching region appeared. The changes observed verify the expected re-construction of hydrogen bond networks in meloxicam, as well as in succinic acid, upon co-crystal formation.

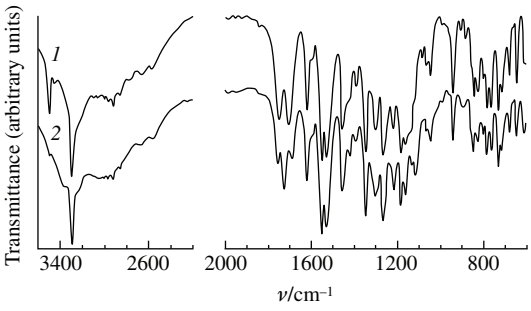

Figure 3 FTIR spectra of 1:1 meloxicam–citric acid (*1*) physical mixture and (*2*) mixture ground without solvent.

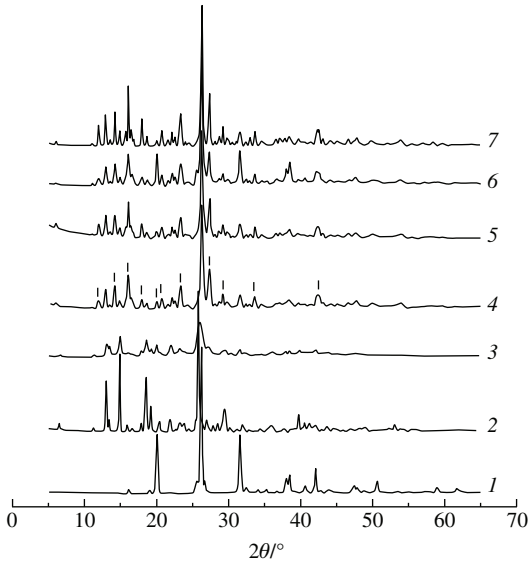

Figure 4 X-ray diffraction patterns of (*1*) succinic acid, (*2*) meloxicam, (*3*) 1:1 meloxicam–succinic acid mixture milled under dry conditions for 30 min, (*4*), (*5*) the mixtures ball milled with addition of ethanol for 2 and 30 min, respectively, (*6*) the mixture ground in the mortar with addition of ethanol and (*7*) the product crystallized from THF–diethyl ether solution.

Although the formation of co-crystals by solvent-drop grinding is attributed to the partial dissolution of the components in the solvent,[6,8] the interaction of meloxicam and succinic acid was also observed using solvents in which compounds show only very low solubility (isopropanol, ethyl acetate) (Table 1); while adding, for instance, toluene, in which meloxicam is soluble, did not result in the formation of co-crystals. It was noted that the usage of polar or water-miscible solvents (Table 1) leads to transition to the co-crystal. One of the possible explanations might be that the addition of water-miscible solvents promoted interaction of the components under grinding due to the stronger attraction of the surface adsorbed water to the solvent molecules and its subsequent removal from the system during evaporation of the solvent. On the other hand, it can be suggested that the addition of water-miscible solvents changed the conditions for

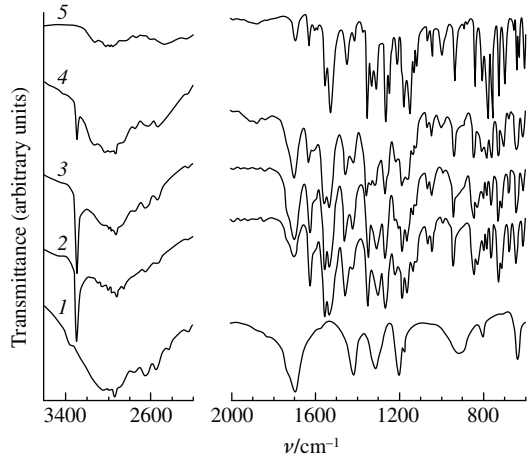

Figure 5 FTIR spectra of (*1*) succinic acid, (*2*) 1:1 meloxicam–succinic acid physical mixture, (*3*) mixture ground without solvent, (*4*) mixture ground with addition of ethanol and (*5*) the product crystallized from THF–diethyl ether solution.

Table 1 The solvents used, their solubility (miscibility) in water and solubility of meloxicam.

Solvent	Solubility of solvent in water (%, w/w)	Mole fraction solubility of meloxicam[11]
Ethanol	miscible	4.582×10^{-5}
Acetone	miscible	6.055×10^{-4}
n-Propanol	miscible	5.562×10^{-5}
Isopropanol	miscible	3.930×10^{-5}
Dioxane	miscible	1.796×10^{-3}
Ethyl acetate	12 (20 °C)	3.476×10^{-5}
Chloroform	0.482 (15 °C)	1.814×10^{-3}
Benzene	0.073 (25 °C)	1.612×10^{-4}
Toluene	0.014 (20 °C)	1.698×10^{-4}
Hexane	0.014 (15 °C)	7.701×10^{-6}
Carbon tetrachloride	0.010 (20 °C)	6.166×10^{-5}
Cyclohexane	insoluble	4.474×10^{-6}

dissolution of the components leading to co-crystal nucleation. The mechanism of co-crystal formation and the role of water in these processes are under study.

For comparison, the co-crystals were prepared by crystallization from solution. Only when a mixture of THF and diethyl ether was used and rapidly evaporated, a colourless product crystallized, which was characterized by an XRPD (Figure 4, curve *7*) and FTIR (Figure 5, curve *5*) spectra identical to those of the sample obtained by solvent-drop grinding. The XRPD pattern was indexed, and the structure was solved from powder data (data will be published elsewhere). The stoichiometry was found to be 2:1 (meloxicam–succinic acid).

The mixtures of meloxicam with maleic acid showed the same behaviour as reported for meloxicam–succinic acid. Dry grinding or using hexane as solvent for solvent-drop grinding resulted in a yellow product with no determinable phase transition. After addition of some drops of acetone or another polar or water-miscible solvent, the colour of the mixture changed from yellow to white. The XRPD pattern (Figure 6) revealed new peaks and thus evidenced the formation of a co-crystal. The FTIR spectra verified these results by showing significant changes in the region of NH and C=O stretching vibrations (Figure 7), indicating the formation of new hydrogen bonds in the product.

To test the influence of water, a physical mixture and a previously dry ground mixture of meloxicam and maleic acid were heated to 120 °C. The latter showed a colour change from yellow to white after 120 min indicating the transition to the co-crystal as verified by FTIR spectra (Figure 7), while the physical mixture did not change upon heating. Since this might result from the preliminary mechanical activation of the ground sample, the grinding experiment was performed at 0% relative humidity (P_2O_5). The initial compounds were equilibrated for 4 h in a dry atmosphere in order to remove surface adsorbed

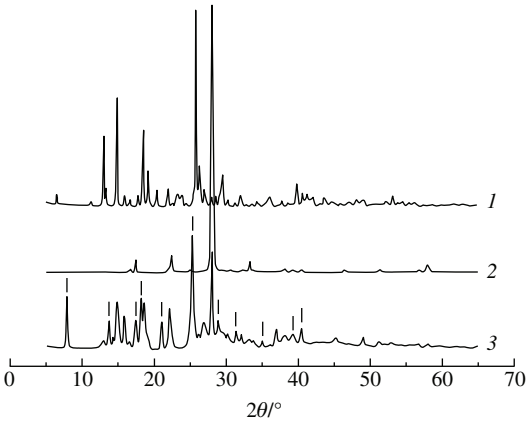

Figure 6 X-ray diffraction patterns of (*1*) maleic acid, (*2*) meloxicam and (*3*) 1:2 meloxicam–maleic acid mixture ground with acetone.

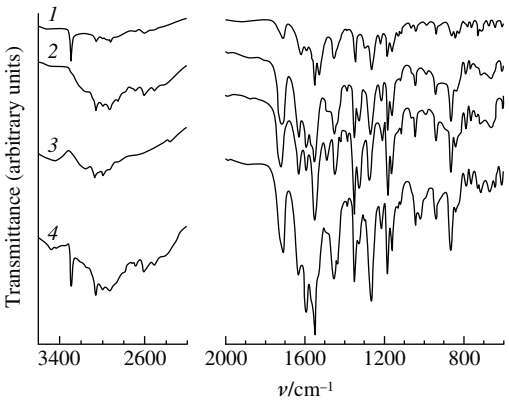

Figure 7 FTIR spectra of 1:2 meloxicam–maleic acid (*1*) physical mixture, (*2*) mixture ground with addition of acetone, (*3*) mixture ground and then heated and (*4*) mixture ground in the dry box.

water and the dry ground product was subsequently monitored for colour change. After two days, the powder turned slightly white indicating the transition to the co-crystal. FTIR spectra taken after seven days of storage verified the transition although traces of the initial compounds can be still detected (Figure 7, curve *4*). It can be assumed that the kinetics of co-crystal formation under dry conditions becomes faster than for the mixtures ground in air without solvent addition; nevertheless, it is slower than that observed for the mixtures ground with the addition of solvents.

To summarize, meloxicam was found to form co-crystals with succinic and maleic acids, which can be easily produced by solvent-drop grinding techniques. Co-grinding with citric and ascorbic acids did not result in co-crystallization. Additionally, it was shown that removing surface adsorbed water by heating or drying before grinding facilitates the co-crystallization and speeds up the reaction kinetics.

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