Nanocomposites of Pyroxicam with Inorganic Oxides

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Abstract

Nanocomposites of nonsteroid anti-inflammatory preparation pyroxicam with aluminium, magnesium and silicon oxides were obtained with the help of mechanical treatment in activator mills. Except for the composites of pyroxicam with aluminium oxide, the solubility of pyroxicam in all thus obtained mechanocomposites exceeded the solubility of the initial preparation. The changes observed in the IR spectra of mechanically treated mixtures provide evidence of the interaction of pyroxicam with oxides. The interaction of the medicine with the surface of oxides at the interface provides stabilization of the medicine in metastable state thus preventing its crystallization and the transition from zwitter ion into the neutral state.

Key words: nanocomposites, mechanochemical treatment, pyroxicam, aluminium, magnesium and silicon oxides, pyroxicam solubility

INTRODUCTION

For poorly soluble medicines, the limiting stage of absorption is usually dissolution, so much attention in pharmacy is paid to the development of the methods providing an increase in the rate of dissolution and the solubility of medical preparations. One of the promising methods to solve these problems is the joint mechanical treatment of medical preparations with auxiliary carrier substances [1, 2]. As a result of the mechanical treatment of the mixtures containing molecular crystals under definite conditions, X-ray amorphous material may be formed, which is connected either with a decrease in particle size to 100 nm and below or with the formation disordered layer on the surface of larger particles, or with the distribution of one of the components over another and the formation of films thinner than 100 nm on its surface [3].

So, mechanical treatment results in the formation of nanocomposite differing in its properties from the physical mixture of components, in particular, having higher dissolution rate and solubility of the pharmaceutical substance. Water-soluble polymers are most frequently used as carriers, but it is also possible to use insoluble organic and inorganic substances. While insoluble organic substances (microcrystalline cellulose, chitosan, talc and so on) are widely used to prepare solid dispersed systems, the possibility to use inorganic oxides for modification of properties and solubilization of pharmaceutical substances remain poorly studied yet.

The goal of the present work was to obtain nanocomposites of the nonsteroid anti-inflammatory preparation pyroxicam with the oxides of aluminium, magnesium and silicon using the methods of mechanical activation, as well as the investigation of their effect on the solubility of the pharmaceutical substance.

EXPERIMENTAL

Pyroxicam was synthesized at the Institute of Chemistry, SB RAS (Irkutsk) [4, 5]. γ-Oxide of aluminium (S_{sp} = 355 m^2/g) and magnesium oxide (S_{sp} = 209 m^2/g) were obtained at the Institute of Catalysis, SB RAS (Novosibirsk) according to the developed original methods [6, 7]. Silica gel manufactured by Chempack Co., of KSMG grade (S_{sp} = 650 m^2/g, V_{por} = 0.3 cm^3/g, d_{por} = 3.5 nm) was used as silicon oxide.

Mechanical treatment was carried out using two different activator mills: vibratory mill SPEX 8000 (the USA) and planetary centrifugal mill AGO-2 (Russia) with water-cooled cylinders. The conditions of treatment in SPEX 8000 were: steel cylinder 60 mL in volume, ball diameter 6 mm, the ratio of the charge mass to ball mass 1 : 20, load per a ball 8–10*g*. The conditions of treatment in AGO-2 mill: steel cylinders 40 mL in volume, ball diameter 6 mm, the ratio of the charge mass to ball mass 1 : 30, load per a ball 20*g*. Time of sample treatment in the mills was 15 and 30 min, respectively. The mass ratio of components in the mixtures of the pharmaceutical substance with an oxide was 1 : 1 and 1 : 3.

X-ray phase analysis was carried out using D8 DISCOVER GADDS diffractometer with a two-coordinate detector Hi-Star (Bruker), CuK_α radiation, 2θ = 5–65. The infrared absorption spectra were recorded within wavenumber range 4000–550 cm^{-1} with the help of a Fourier transform IR spectrometer Infralum FT-801 (Russia) in tablets with KBr (1 mg of sample per 100 mg of KBr). The IR spectra of disturbed complete internal reflection (DCIR) of the same mixtures within wavenumber range 7500–580 cm^{-1} were recorded with a Fourier transform IR spectrometer Digilab Excalibur 3100 (the USA) using DCIR attachment (Pike Co.) with ZnSe crystal without special sample preparation. Electron spectra of diffusion reflection (ESRD) were recorded with a UV-2501 PC spectrometer (Shimadzu, Japan) with the diffuse reflection attachment ISR-240 A with respect to the reflection reference $BaSO_4$ within the range 11 000–54 000 cm^{-1} and represented in the coordinates Kubelka–Munk function–wavenumber.

Thermoanalytical experiments were carried out using a Netzsch DSC-204 instrument by means of differential scanning calorimetry (DSC) within temperature range from room temperature to 220 °C. Measurements were carried out in aluminium crucibles with caps during heating at a rate of 9 K/min in the atmosphere of argon; blown at a flow rate of 20 mL/min. Sample mass was about 6 mg.

To determine the rate of pyroxicam release, we used the solubility tester Varian 705 DS. A weighed portion of sample with particle size 125–315 μm, containing the pharmaceutical substance in excess with respect to its solubility, was placed in a glass beaker thermostated at (37±0.5) °C and equipped with a mechanical mixer; the beaker contained 200–250 mL of water. After definite time intervals, the solution to be analyzed was sampled with a pipette doser and filtered. The optical density of the resulting solution was measured with Cary 50 spectrophotometer on the basis of the intensity of the band at 358–365 nm.

RESULTS AND DISCUSSION

Pyroxicam–aluminium oxide

Mechanical treatment of the mixture of pyroxicam with aluminium oxide (1 : 1) resulted in a substantial decrease in the intensity of X-ray reflections of pyroxicam after treatment in SPEX 8000 mill for only 15 min, but even after grinding for 30 min the peaks did not disappear completely. With the components ratio of 1 : 3 after treatment for 15 min X-ray amorphous product was obtained. A similar situation was observed when the mixtures were treated in AGO-2 mill. The DSC curves of the samples pyroxicam–Al_2O_3 (1 : 1) treated either in SPEX 8000 or in AG)-2 exhibit endoeffect of pyroxicam melting. In this situation, the DSC curve of the sample after treatment for 30 min

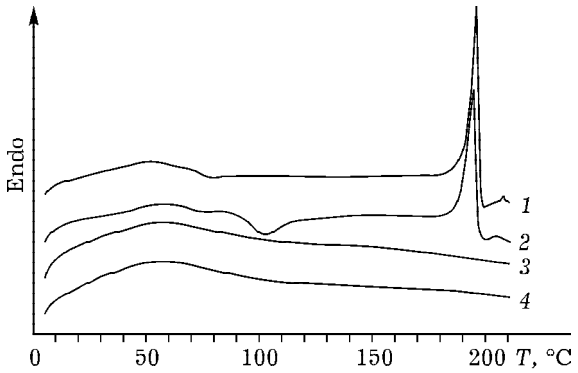

Fig. 1. DSC curves of the samples of pyroxicam–Al_2O_3 mixture at a ratio of 1 : 1 (*1*, *2*) and 1 : 3 (*3*, *4*) obtained after treatment in SPEX 8000 mill for 15 (*1*, *3*) and 30 min (*2*, *4*).

exhibits exoeffect at a temperature of about 100 °C; it may correspond to recrystallization of the pharmaceutical substance. For X-ray amorphous samples with the components ratio of 1 : 3, no endoeffects of pyroxicam melting are observed. This is evidence that the pharmaceutical substance has been finely dispersed in the matrix and thus stable composite was formed.

In the IR spectra of pyroxicam–Al_2O_3 samples (Fig. 2) we observed a decrease in the intensity of the absorption band at 3340 cm^{-1} corresponding to the stretching vibrations of N–H groups with an increase in the time of mechanical activation and in carrier content. These N–H groups are bound through hydrogen bonds with the oxygen atoms of SO_2 groups and form dimmers in β-pyroxicam crystal [8].

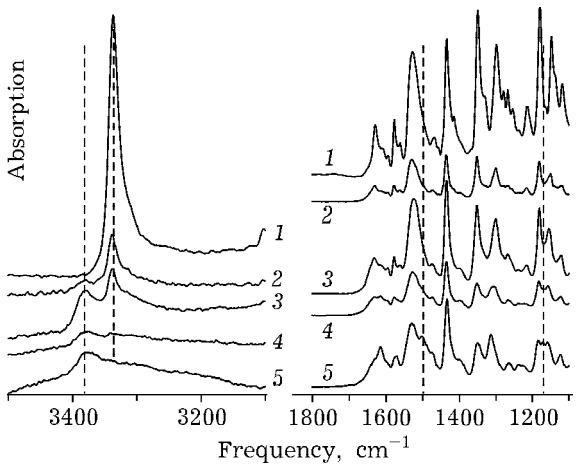

Fig. 2. IR spectra of disturbed complete internal reflection of the initial pyroxicam (*1*) and the samples prepared by treating in SPEX 8000 mill, having the composition pyroxicam–Al_2O_3 1 : 1 (*2*, *3*) and 1 : 3 (*4*, *5*) for 15 (*2*, *4*) and 30 min (*3*, *5*).

Relative intensity of the absorption band at 3385 cm^{-1} increase; this band is present in amorphous pyroxicam [9]. In addition, the frequency of vibrations of the carbonyl group in the IR spectra of the pyroxicam–Al_2O_3 (1 : 3) mixture mechanically activated for 30 min decreases by approximately 15 cm^{-1} in comparison with that for pure pyroxicam. This is an evidence of the interaction of the preparation with the carrier, perhaps due to the formation of the intermolecular hydrogen bonds between C=O groups of pyroxicam and hydroxyl groups on the surface of aluminium oxide [4]. The appearance of new absorption bands in the frequency region lower than 1800 cm^{-1} (broken lines in Fig. 2) points to the interaction of the preparation with the carrier, too. The interaction between the components is likely to lead

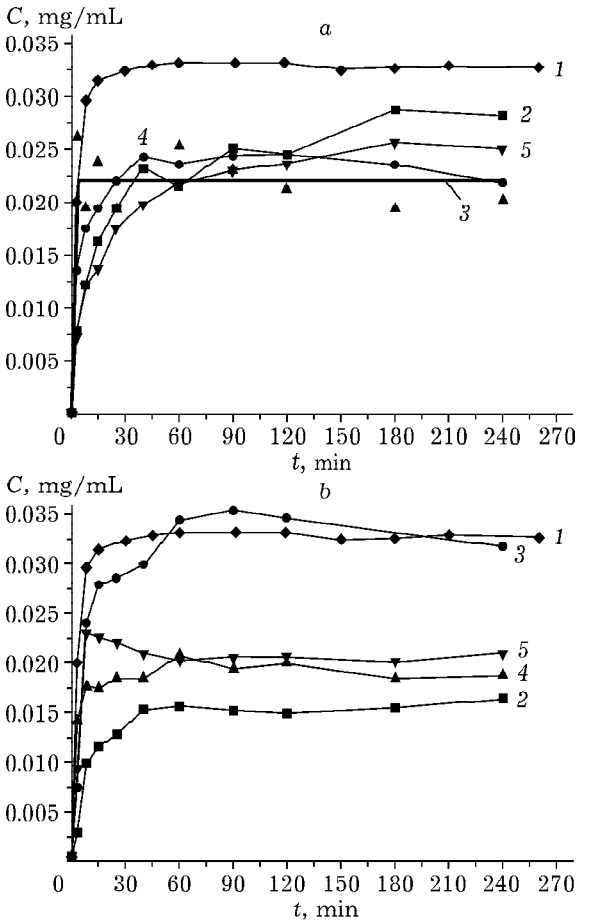

Fig. 3. Curves of dussolution of initial pyroxicam and samples obtained with SPEX 8000 (*a*) and AGO-2 (*b*): *1* – initial pyroxicam; *2*–*5* – composites pyroxicam–Al_2O_3 at a ratio of 1 : 1 (*2*, *3*) and 1 : 3 (*4*, *5*) after treatment for 15 (*2*, *4*) and 30 min (*3*, *5*).

to the formation of a stable composite during the joint dispersing of the pharmaceutical substance with aluminium oxide.

Pyroxicam is present in the samples partially in disordered, amorphous state, so we may speak of the apparent solubility of the pharmaceutical substance [10]. For all the samples, the apparent solubility of pyroxicam turned out to be smaller than the solubility of the initial preparation (Fig. 3), which may be connected with the interaction of pyroxicam with the carrier surface and the formation of strongly bound associates.

Pyroxicam–silicon oxide

Mechanical treatment of the mixtures of pyroxicam with silica gel also is accompanied by a substantial decrease in the intensity of X-ray reflections of the pharmaceutical substance. The DSC curves of the samples with components ratio of 1 : 1, prepared in SPEX 8000 and AGO-2 mills and characterized by the smallest decrease in crystallinity, exhibit exopeaks near 80 °C; they may be related to recrystallization of the pharmaceutical substance [11]. The peaks related to pyroxicam melting are also observed at 190–200 °C (Fig. 4). In the case of pyroxicam–SiO_2 mixtures at a ratio of 1 : 3 that are characterized by lower crystallinity, exopeaks related to recrystallization are absent, while the peaks related to melting are shifted to lower temperatures; the area of the peaks decreases substantially in comparison with that for the samples of pyroxicam–SiO_2 at a ratio of 1 : 1. These results provide evidence that the joint mechanical treatment of pyroxicam with silica gel is accompanied by dispersion of the pharmaceutical substance, its partial amorphization and distribution over the carrier. At the same time, a part of the substance remains in the crystal state, maybe due to the insufficient rigidity of silica gel in comparison with aluminium oxide.

For the mixtures of pyroxicam with SiO_2 after mechanical activation, the intensity of the band of stretching vibrations of N–H band at 3340 cm^{-1} in the IR spectrum decreases (Fig. 5). At the same time, the absorption band at 1640 cm^{-1} corresponding to the stretching vibrations of C=O, for the samples with the components ratio of 1 : 30 after mechanical activation for 30 min gets split into two bands with a distance between them about 35 cm^{-1}. This result in the evidence of the appearance of intramolecular hydrogen bonds of different strength in pyroxicam due to the interaction with silicon oxide. Pyroxicam molecules are likely to be able to form heterobonds similarly to the case of indometacin [12, 13] with silanol groups and siloxane bonds broken as a result of mechanical treatment on the surface of silica gel particles.

The apparent solubility of all the samples of pyroxicam–SiO_2 exceeded that of the initial pharmaceutical substance. The highest dissolution rate and solubility, almost three times

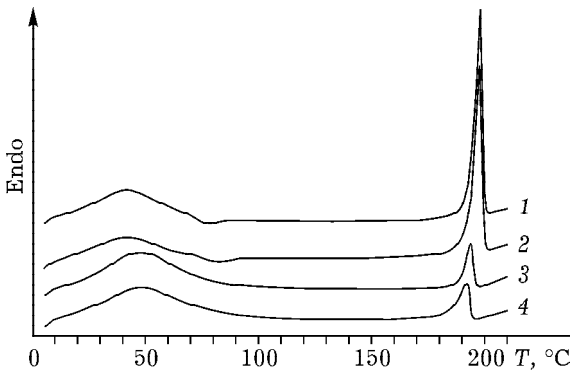

Fig. 4. DSC curves of the samples pyroxicam – SiO_2 at a ratio of 1 : 1 (*1*, *2*) and 1 : 3 (*3*, *4*) obtained by treatment in SPX 8000 mill for 15 (*1*, *3*) and 30 min (*2*, *4*).

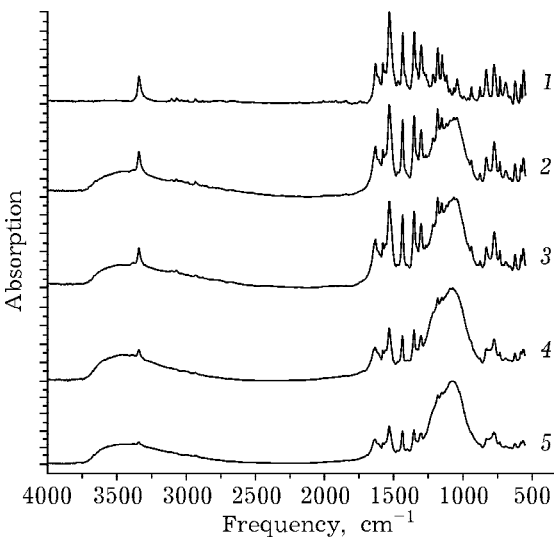

Fig. 5. IR absorption spectra of initial pyroxicam (*1*) and the samples pyroxicam–SiO_2 at a ratio of 1 : 1 (*2*, *3*) and 1 : 3 (*4*, *5*) obtained by treatment in SPEX 8000 mill for 15 (*2*, *4*) and 30 (*3*, *5*) min.

higher than that of initial pyroxicam, is characteristic of the samples with the components ratio of 1 : 1 obtained in SPEX 8000 mill. Slower dissolution is characteristic of the samples treated in AGO-2, however, the achieved apparent solubility is two times higher than the solubility of initial pyroxicam.

Pyroxicam—magnesium oxide

During the treatment of pyroxicam mixtures with magnesium oxide in SPEX 8000 mill, we observed disappearance of the X-ray reflections from the diffraction patterns of all the samples except the sample with the components ratio 1 : 1 treated for 15 min. With AGO-2 mill, the disappearance of X-ray peaks was observed in the samples only after treatment for 30 min. The DSC curves of the samples obtained in SPEX 8000 mill did not exhibit any thermal effects in the region of pyroxicam melting (Fig. 6, *a*). At the same time, for the samples treated in AGO-2 mill, we observed the endoeffect that may be related to pyroxicam melting but with a substantial shift to lower temperature than the initial substance exhibits (see Fig. 5, *b*). The shift increased with an increase in treatment time and carrier content, and the peak area decreased; for the sample with the components ratio of 1 : 3 after treatment for 30 min the melting peak disappeared completely.

In the IR spectra of the mechanically activated mixture pyroxicam–MgO (Fig. 7), the frequency of stretching vibrations of N–H groups is 3388 cm^{-1}, which exceeds the frequency of stretching vibrations of N–H groups for the initial pyroxicam (3340 cm^{-1}). The frequency of stretching vibrations of carbonyl group increases by about 3 cm^{-1}, which points to some weakening of the intramolecular hydrogen bonds. Some most intensive bands in the spectrum in the region 1600–1400 cm^{-1} are observed to split even at the components ratio of 1 : 1. In the case when the ratio is 1 : 3, splitting reaches 20–30 cm^{-1}. This result may be explained as the manifestation of non-equivalence of pyroxicam molecules under the action of surroundings arising as a result of the interaction with magnesium oxide. An increase in the carrier content and activation time causes an increase in transformation degree. This effect is better pronounced when SPEX 8000 mill is used. According to the X-ray data, magnesium oxide used in the work is periclase (MgO) with admixture of brusite ($Mg(OH)_2$). It is known that pyroxicam molecule exhibits weak acidic properties represented by the enol hydroxyl (pK_a = 5.3) [14]. It may be assumed that during mechanical activation, along with grinding, the ineraction of enol hydroxyl of pyroxicam with the hydroxyl groups on the surface of magnesium oxide occurs, resulting in the formation

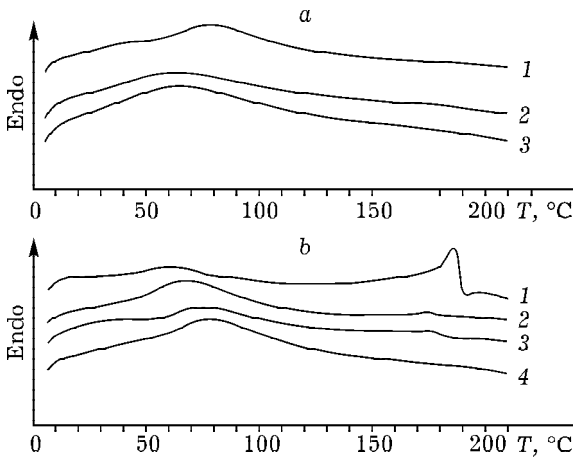

Fig. 6. DSC curves of the samples obtained in SPEX 8000 (*a*) and AGO-2 (*b*): *a* – proxicam–MgO at a ratio of 1 : 1 (*1*) and 1 : 3 (*2*, *3*) after treatment for 15 (*2*) and 30 min (*1*, *3*); *b* – pyroxicam–MgO at a ratio of 1 : 1 (*1*, *2*) and 1 : 3 (*3*, *4*) after treatment for 15 (*1*, *3*) and 30 min (*2*, *4*).

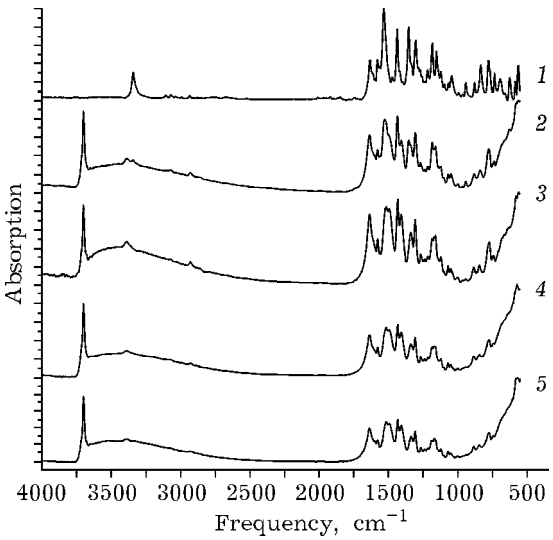

Fig. 7. IR absorption spectra of initial pyroxicam (*1*) and samples pyroxicam–MgO at a ratio of 1 : 1 (*2*, *3*) and 1 : 3 (*4*, *5*) obtained by treating in SPEX 8000 mill for 15 (*2*, *4*) and 30 min (*3*, *5*).

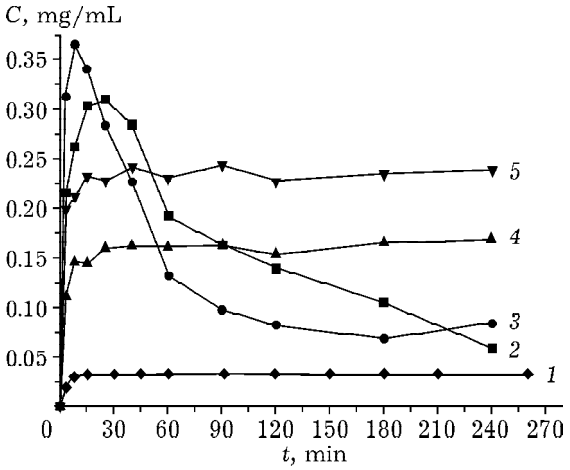

Fig. 8. Curves of dissolution of initial pyroxicam (*1*) and samples pyroxicam–MgO at a ratio of 1 : 1 (*2*, *3*) and 1 : 3 (*4*, *5*) obtained by treating in SPEX 8000 mill for 15 (*2*, *4*) and 30 min (*3*, *5*).

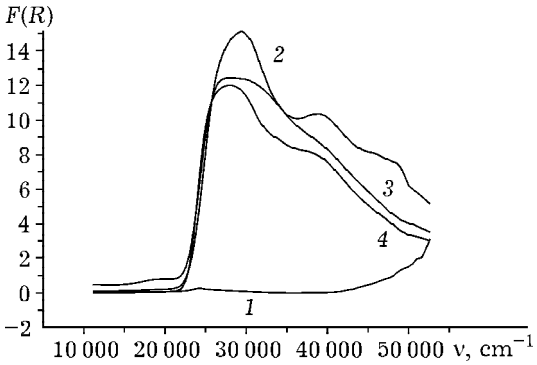

Fig. 9. Electron spectra of diffuse reflection of initial pyroxicam (*1*) and samples pyroxicam–Al_2O_3 (*2*), pyroxicam–SiO_2 (*3*) and pyroxicam–MgO (*4*) at a ratio of 1 : 3, obtained by treating in AGO-2 mill.

of the salt form of pyroxicam. To carry out the interaction, it is more promising to use vibratory mill SPEX 8000 due to the shear strain at the contacts of particles, realized during treatment in this mill.

The solubility of pyroxicam for all the samples of pyroxicam–MgO exceeded the solubility of the initial pharmaceutical substance (Fig. 8). In the case of the sample pyroxicam–MgO (1 : 3) after treatment for 30 min, the concentration of pyroxicam exceeded the solubility of the initial preparation almost by a factor of 8. For some mixtures, the dissolution curves with maximum were obtained. High dissolution rate at the initial moment of time is characteristic of them. Such a behaviour of the kinetic curves of dissolution is likely to be connected with the nonhomogeneity of the system, the presence of active metastable states in it, for example amorpous, nanocrystalline ones that are characterized by increased dissolution rate.

Mechanochromism of the mixtures of pyroxicam with inorganic oxides

During mechanical treatment of pure pyroxicam and its mixtures with oxides, the samples got yellow colouring, which is evidenced by the shift of the absorption band edge in the ESDR spectra (Fig. 9). Colour change is likely to be connected with the transition of the molecules to the zwitter ion form [9, 15] due to the transfer of proton to pyroxicam molecule and is likely to proceed in the intermolecular manner. It may be assumed that pharmaceutical substances in the zwitter ion form possess elevated solubility. However, zwitter ion states are unstable, so in the case of pure pharmaceutical substance the molecules turn back to the neutral state during storage or heating. Experiments with heating the mechanically treated mixtures of pyroxicam with oxides showed that yellow colour is conserved in nanocomposites during heating. This is accompanied by crystallization of pure pyroxicam, while in mechanocomposites the pharmaceutical substance remains in X-ray amorphous state.

CONCLUSIONS

Thus, unlike for pure pyroxicam that does not pass completely into X-ray amorphous state during mechanical treatment under the studied conditions, using aluminium, silicon and magnesium oxides we obtained the samples containing the pharmaceutical substance in X-ray amorphous state. The disappearance of peaks in the diffraction patterns and the absence of the peaks related to melting of the pharmaceutical substance in the DSC curves of X-ray amorphous samples with the high concentrations of carrier and/or subjected to long-term mechanical treatment is the evidence of the distribution of finely dispersed pharmaceutical substance over the carrier and the formation of stable composite.

The apparent solubility of pyroxicam in the majority of cases exceeded the solubility of the initial preparation. The highest dissolution rate and solubility were exhibited by the samples

obtained in SPEX 8000 mill. In the case of the system pyroxicam–aluminium oxide, the solubility of the pharmaceutical substance turned out to be not higher but even lower than that of the initial preparation.

Yellow colour, connected with the transition into the zwitter ion state that appeared in mechanically treated samples was conserved during heating. This is the evidence of the fact that the formation of nanocomposites with oxides causes stabilization of pyroxicam in the zwitter ion state. The changes observed in the IR spectra of mechanically treated mixtures provide evidence of the interaction of pyroxicma molecules with hydroxyl groups on the surface of oxides. The interaction of the pharmaceutical substance with the surface of oxides at the interface is likely to ensure stabilization of pyroxicam in metastable state preventing its crystallization and transition from the zwitter ion state to the neutral state.

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