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Mechanochemical Preparation of Organic-Inorganic Hybrid Materials of Drugs with Inorganic Oxides

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The nanocomposites of piroxicam and meloxicam with alumina were obtained by ball-milling as a result of distribution of the drugs at the surface of oxide with formation of the stable composites. The observed changes in the IR spectra of the ball-milled mixtures suggested the interaction of the drugs with the alumina active surface sites. The functional groups in molecules of piroxicam and meloxicam involved into formation of bonds between the drugs and the surface of the oxide were determined, they are amide, sulfate, enol groups, and pyridyl / thiazolyl nitrogen atoms. It appears that the formation of the new bonds at the contacts of particles in the composite leads to the stabilization of the drugs in metastable state inhibiting their transformation into initial crystalline form.

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1. Introduction

The attention of many researches has turned to the studies of the systems based on organic-inorganic hybrids. A growing interest is attributed to the diverse properties of such systems [1]. These systems represent hybrid core-shell particles with unique properties and could widely been used in many areas of technologies including pharmacy. Nowadays, the technology provides many approaches to obtain such systems and the mechanochemical methods can be regarded as attractive eco-friendly alternative route, which allows us to decrease the synthesis temperature and avoid or decrease the amount of organic solvent used.

Although mechanical treatment of the systems including two or more solid components is widely used in a wide range of practical applications to prepare new materials with desirable properties (solubility, catalytic activity, etc.), little is known about process mechanisms and phase interactions in solids induced by this treatment [2]. In turn, investigations of chemical reactions in molecular solids that occur during mechanical action, including the interactions between drug and excipient is of great interest for pharmacy [3, 4], because control of these reactions allows to increase stability and bioavailability of drugs. Different methods such as vibration spectroscopic methods, thermal analysis studies, nuclear magnetic resonance spectroscopy and some others are widely used to characterize these interactions [3–7]. To the best of our knowledge, X-ray photoelectron spectroscopy (XPS) has never been used before for characterization of drug-excipient systems.

The present study is aimed at the preparation of hybrid organic-inorganic composites of drugs, piroxicam and meloxicam, with alumina by mechanochemical methods, and at the investigation of the interaction between the components by the IR spectroscopy and high resolution XPS methods.

Piroxicam and meloxicam (Fig. 1) are non-steroidal anti-inflammatory drugs poorly soluble in water. It is well known [8] that mechanical treatment of drugs with excipients is an efficient method to prepare solid dispersions of drugs with controlled drug release and solubility. Usually, water soluble carriers (such as natural and synthetic polymers, salts of metals, etc.) are widely employed for obtaining solid dispersions with enhanced dissolution rate and solubility of the drug by mechanochemical methods, and in case of non-soluble organic or inorganic excipients, for example inorganic oxides, an effective concentration can be maintained over a longer period of time, so controlled release rate could be achieved [9, 10]. This is also important for development of the target drug delivery systems.

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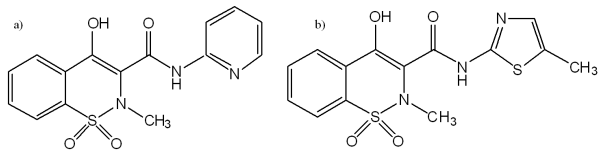

Fig. 1. Piroxicam (a) and meloxicam (b) molecular structures.

Highly dispersed alumina is used as a catalyst carrier and as a sorbent in different fields of technique. It was of great interest to use alumina as a model system for immobilization of organic drugs by mechanochemical methods for further investigation of interaction between drugs and inorganic oxides.

2. Experimental Details

Piroxicam was synthesized at Irkutsk Institute of Chemistry (Irkutsk, Russia) according to an original technology [11]. Meloxicam was purchased from JSC Altaivitaminy (Biisk, Russia). Gamma alumina (S = 355 m^2/g) was prepared at Boreskov Institute of Catalysis (Novosibirsk, Russia) according to an original pilot technology [12].

The drug-oxide mixtures (1:1 and 1:3, w/w) were ball-milled on air in the stainless steel vials using an AGO-2 planetary centrifugal mill with water-cooled vials. A ball diameter of 6 mm and the 1:30 ratio of sample mass to the mass of balls were used. Vial volume of 40 ml, and load per ball of 20 g were employed. Time of treatment was 15 and 30 min.

Electron microscopy photographs of the samples were taken using JEM2000-FX electron microscope (JEOL, Japan) cooling the sample with liquid nitrogen. X-ray powder diffraction patterns were measured with a D8 DISCOVER GADDS diffractometer (Bruker) with CuKα-radiation, $2\theta = 5 \div 45$. Attenuated total reflectance (ATR) infrared spectroscopy was performed with Digilab Excalibur 3100 FTIR spectrometer (Varian) without special preparation of the samples, spectral resolution was better than ± 2 cm^{-1}.

The XPS analyses were performed on a SPECS photoelectron spectrometer (Germany) with MgKα X-ray source (1253.6 eV). The samples were attached to the holder with the help of a double-sided adhesive tape. Prior to the analysis the samples were outgassed under vacuum for 24 h, the spectra were obtained at a pressure of $\sim 5 \times 10^{-9}$ Torr. Each analysis started with a survey scan from 0 to 1100 eV with 1 sweep. For the high resolution analysis the number of sweeps was increased. Pass energy was of 20 eV during recording all the spectra. Voltage in increments was of 0.05 eV. The scale of binding energy of the spectrometer was preliminarily calibrated on the basis of the lines of gold and copper, Au4$f_{7/2}$ (84.0 eV) and Cu2$p_{3/2}$ (932.6 eV). The values of binding energies of photoelectron peaks were determined with the accuracy of ± 0.1 eV. Spectra of non-conducting samples were calibrated on the basis of the C1s line (284.8 eV). The "Flood gun" neutralization system was used to remove the surface charge. The normalization of intensities was performed. Deconvolution of spectral lines into components was made using "XPS Peak" software package.

3. Results and discussion

3.1. Composites of piroxicam with alumina

Piroxicam used in the work is a crystalline modification $I(\beta)$, the NH groups are hydrogen bonded with SO_2 groups forming dimers [13]. Recently [9, 10], upon co-grinding in AGO-2 mill, X-ray amorphous product was obtained for the 1:3 piroxicam - alumina mixture (Fig. 2). It was assumed that the drug was nanodispersed at the surface of the oxide forming the stable composites. Under subsequent heating of the samples obtained the crystallization of the drug was not detected. Also the yellow color of the ball-milled piroxicam-oxide mixtures was preserved on heating, confirming that piroxicam was present as zwitterions in the composites [14, 15].

It is seen from the Fig. 3 that upon ball-milling, alumina particles change their morphology, but their size remains in the nanoscale region. The presence of the drug in the mixture results in less change in the morphology of particles, than in the case of pure oxide. Thus, particles morphology changes into fine rods about 2-5 nm thick and the particles are less aggregated after milling than those in the case of pure oxide.

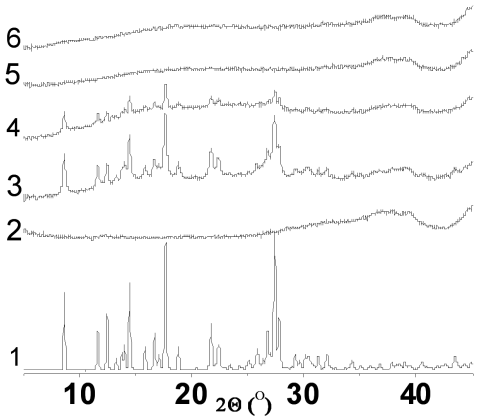

Fig. 2. X-ray powder diffraction patterns of piroxicam and its mixtures with Al_2O_3: 1 – piroxicam initial, 2 - Al_2O_3 initial, 3 – 1:1 piroxicam - Al_2O_3 mixture ball-milled for 15 min, 4 – the same mixture ball-milled for 30 min, 5 - 1:3 piroxicam - Al_2O_3 mixture ball-milled for 15 min, 6 – the same mixture ball-milled for 30 min.

The IR spectra of the ball-milled piroxicam and piroxicam-Al_2O_3 mixtures change in comparison with the spectra of the initial drug (Fig. 4, Table I) [9, 10]. The spectrum of initial piroxicam coincided with that available in Ref. [16]. The bands of piroxicam metal complexes are shown for a comparison in Table I, since it

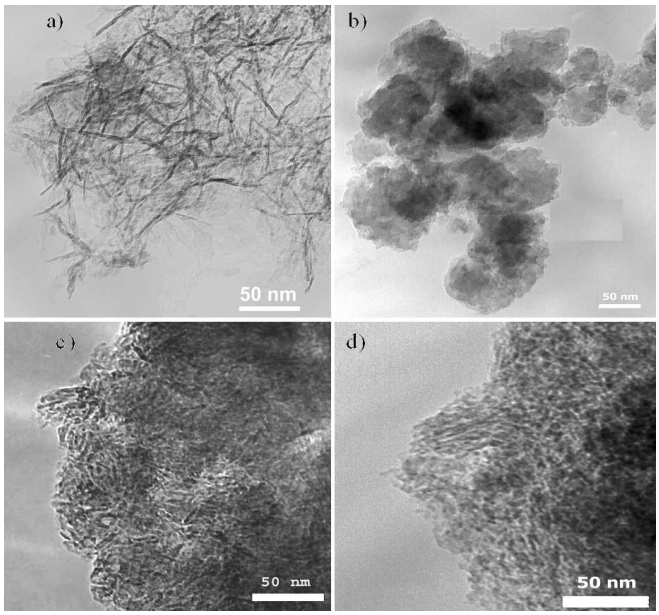

Fig. 3. Electron-microscopy photos of initial (a) and ball-milled (b) alumina, ball-milled mixtures of alumina with piroxicam (c) and meloxicam (d).

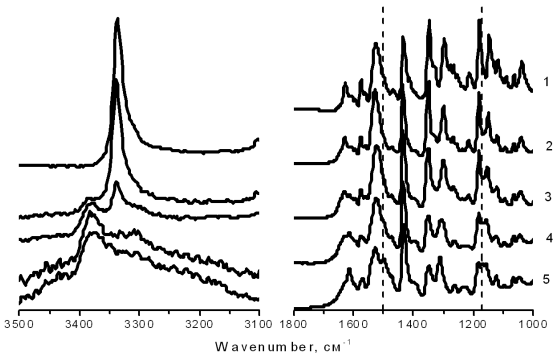

Fig. 4. ATR spectra of initial piroxicam (1), 1:1 piroxicam – Al_2O_3 mixture ball-milled for 15 (2) and 30 (3) min and 1:3 piroxicam – Al_2O_3 mixture ball-milled for 15 (4) and 30 (5) min.

has been demonstrated [16, 17] that for several bivalent metal ions piroxicam is a strong chelator via the amide oxygen atom and nitrogen atom from the pyridyl ring.

In the IR spectra of ball-milled piroxicam, except for 3337 cm^{-1} absorption, a band at 3380 cm^{-1} appears. It has been supposed [15] that this new band in the N-H stretch region corresponds to a second N-H bond, suggesting the formation of piroxicam zwitterion form as a result of proton transfer from enolate O-H group to the basic pyridine N. On the other hand, the well defined peaks at 3396 and 3340 cm^{-1} in the spectrum of piroxicam can be assigned to the ν(N-H) and ν(O-H) vibrations, respectively [16]. In the spectra of piroxicam metal complexes, the strong ν(O-H) peak at 3340 cm^{-1} disappeared supporting the deprotonation of the enol group [16, 17]. In our case, as a carrier content and the time of mechanical treatment increased, the absorption at 3340 cm^{-1} decreased and that at 3380 cm^{-1} increased. Indeed, this may be caused by zwitterion formation, its concentration might be higher when alumina is used as a carrier. Supporting this, the marker bands of zwitterion (1465 and 1400 cm^{-1}) [18] are observed in the spectrum of the composite, a broad band in the region of 3350-3200 cm^{-1} indicated the formation of zwitterion also [19]. Besides, interaction of enol group with hydroxyl groups at the surface of alumina may lead to hydrogen bonding or dehydroxylation that results in a decrease in the ν(O-H) absorption.

In the IR spectra of piroxicam – alumina composites, carbonyl absorption band at 1630 cm^{-1} shifts to lower frequencies in comparison with the spectra of intact and ball-milled piroxicam. It has been proven [16] that the shift of this band in the spectra of piroxicam Cu(II) and Ni(II) complexes results from a strong metal coordination to the amide oxygen atom of the drug. The amide II band, which in secondary amides is a mixed motion involving the N-H in-plane bending and the C-H stretching vibration, is also slightly shifted to lower frequencies in the composite as it was observed in the complexes. The band at 1530 cm^{-1}, which involves C=N stretching vibrations, does not change in the ball-milled piroxicam, whereas in the composite, it is splitted into two bands, similarly to what has been observed in complex compounds. The amide III band involving ν(C-N) and δ(NH) combination is found in practically the same position for ball-milled piroxicam and composite, as well as for intact piroxicam. This band was absent in the spectra of the metal complexes [16]. The bands corresponding to antisymmetric (1350 cm^{-1}) and symmetric (1180 cm^{-1}) stretching vibrations of the SO_2 group are not related to a metal bonding in the complexes, nevertheless, it has been shown [16, 17] that they shifted to lower or higher frequencies, probably due to hydrogen bonding effects. In the piroxicam – alumina composite, these bands lose intensity and 1180 cm^{-1} band is splitted into two ones, at 1184 and 1171 cm^{-1}.

In general, the changes in the IR spectra of piroxicam can be caused by amorphization of the drug, by transformation of piroxicam into zwitterion form, and also by the interaction of the drug with the carrier. The γ-Al_2O_3 used in the work was shown [12] to contain surface Brönsted acid sites representing by terminal and bridged OH groups and strong Lewis acid sites generated by coordinatively unsaturated surface alumina ions. Besides, bridging oxygen atoms (Al-O-Al) and oxygen atoms in OH groups (Al-OH) behave as surface basic sites. These surface active sites can serve as the centers for bonding with the drug functional groups. The similarity of IR spectra of piroxicam – alumina mechanocomposites and piroxicam metal complexes suggests that in the composites, piroxicam carbonyl oxygen and the pyridyl nitrogen atoms can bind to the surface alumina ions. Nevertheless, it is difficult to unambiguously conclude about SO_2

group interactions, because the changes in the spectra can be caused also by some other reasons.

Figure 5, a shows the XPS survey spectra for physical and ball-milled piroxicam – alumina mixtures. The XPS spectrum of piroxicam is, as far as we know, reported here for the first time.

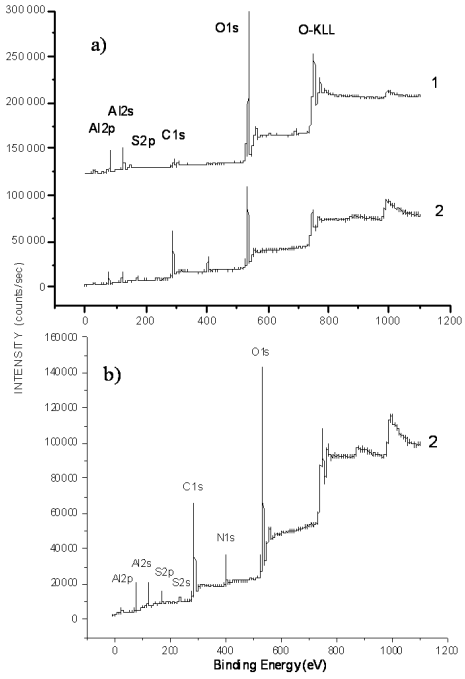

Fig. 5. XPS survey spectra for 1:3 piroxicam (a) – meloxicam, (b) – alumina mixtures: 1 – physical mixture, 2 – ball-milled mixture.

The core lines are assigned according to Ref. [20]. For a physical mixture, the spectrum is a superposition of the core lines of initial components. The intensity of piroxicam lines is not so high compared to alumina, probably due to rather large size of piroxicam particles. In the case of ball-milled mixture, the relative intensity of piroxicam lines increases that can be explained by the formation of core-shell composite resulting in increasing the surface of the organic phase. The C1*s* core-level binding energies of ball-milled piroxicam (Fig. 6a) do not change, suggesting that carbon framework is not destroyed under mechanical treatment. Changes in N1*s* peaks (Fig. 6b) are rather slight. It might be expected, however, that XPS spectra should change in this region as a result of transformation of piroxicam into zwitterion form, but these changes are not strongly pronounced, because of a small content of zwitterion form. Indeed, the content of zwitterion form in cryoground piroxicam is only 8 % [15], and in the piroxicam ball-milled at room temperature, it is obviously even less. The differences in values of the binding energies of the sulfur core lines in the spectra of the piroxicam-Al_2O_3 ball-milled mixtures have been detected (Fig. 6c), which may be rationalized by the formation of bonds between the sulfur of sulfate group of piroxicam and the active sites at the surface of alumina. Thus, the XPS data allow us to conclude that SO_2 group takes part in the interaction with the carrier.

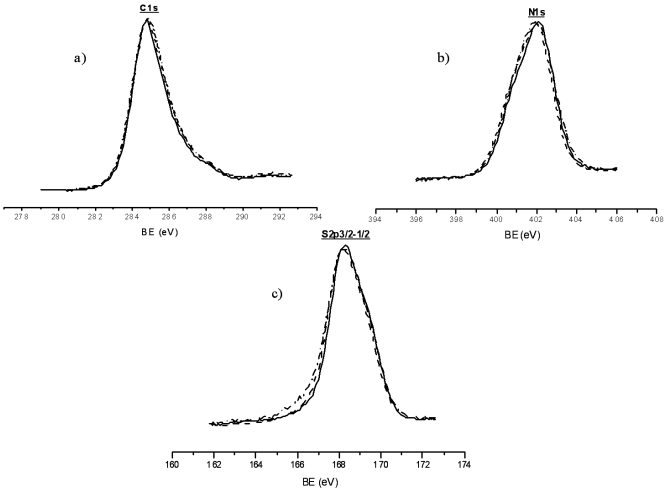

Fig. 6. XPS core lines spectra for piroxicam (solid line), ball-milled piroxicam (dash line) and ball-milled 1:3 piroxicam – alumina mixture (dash dot line): C1*s* a), N1*s* b), S2$p_{3/2-1/2}$ c).

3.2. Composites of meloxicam with alumina

As in the case of piroxicam - alumina mechanocomposites, the presence of meloxicam in the mixture results in the change in the morphology of the particles, but not significantly. It is assumed that the drug is nanodispersed at the surface of oxide, so that a thin layer is formed (Fig. 3). This is confirmed by the absence of alumina lines in the XPS survey spectrum (Fig. 5b). Indeed, as the depth of penetration of radiation into solid in XPS analysis is about 50 Å, we can see only the organic phase in the spectrum.

Initial meloxicam is a crystalline form with enol molecules directly linked into dimers by hydrogen bonds between NH and SO_2 groups, the carbonyl group is involved into the formation of intramolecular hydrogen bonds with hydroxyl group [21]. A significant decrease in the intensities or complete disappearance of the X-ray diffraction peaks of the drug is observed, especially as the duration of mechanical treatment and the content of the oxide increase (Fig. 7).

Figure 8 shows the IR spectra of initial meloxicam and the ball-milled samples. The selected absorption data for the samples obtained and, for a comparison, for the meloxicam Fe(II) metal complex [22], are reported in Table II. The changes in the ball-milled meloxicam spectrum suggested the formation of zwitterion form. In the IR spectrum of 1:3 meloxicam-Al_2O_3 mixture (Fig. 8), the 3290 cm^{-1} band, assigned to N-H stretching vibrations [22], loses intensity. The carbonyl stretching vibration at 1619 cm^{-1} behaves the same way, in contrast to the meloxicam Fe(II) complex, where this band shifts to

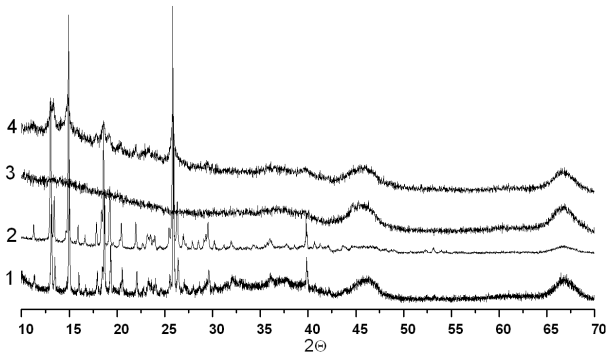

Fig. 7. X-ray powder diffraction patterns of meloxicam - alumina mixtures: 1 – 1:3 physical mixture, 2 – 1:1 physical mixture, 3 – 1:3 meloxicam–Al_2O_3 mixture ball-milled for 30 min, 4 – 1:1 meloxicam–Al_2O_3 mixture ball-milled for 30 min.

higher frequencies [22]. The ν(C=N) absorption practically does not change in the spectrum of the composite. In the CH_3 deformation vibrations region [23] the intensity of the 1458 cm^{-1} band decreases and the new bands appear.

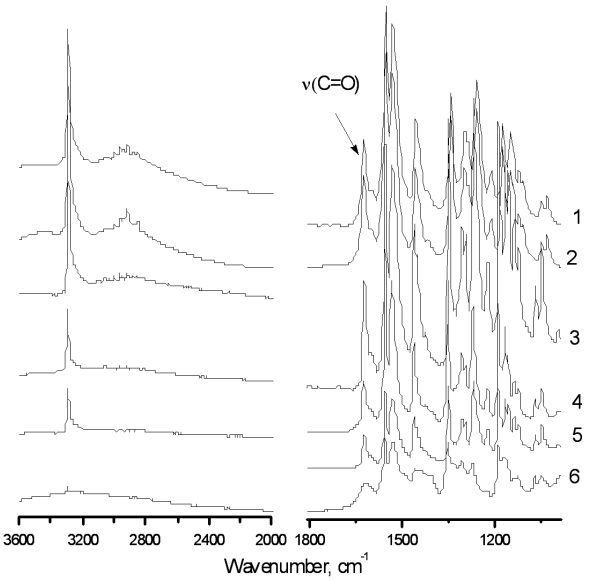

Fig. 8. ATR spectra of meloxicam and meloxicam – alumina mixtures: 1 – initial meloxicam, 2 – ball-milled meloxicam, 3 - 1:1 meloxicam–alumina physical mixture, 4 - 1:1 mixture ball-milled for 15 min, 5 - 1:3 physical mixture, 6 - 1:3 mixture ball-milled for 15 min.

The $\nu_{as}(SO_2)$ (1346 cm^{-1}) and $\nu_s(SO_2)$ (1183 cm^{-1}) bands are broadened in the spectrum of the composite contrary to the meloxicam Fe(II) complex, where these bands significantly shift to lower frequencies [22]. The broadening of the O-H deformation vibration band at 1133 cm^{-1} has been also detected. These changes agree with the expected disordering of the meloxicam crystal structure followed by breaking the hydrogen bonds and with the existence of the interaction between the components in the ball-milled mixture involving amide, sulfate and enol groups of meloxicam and alumina active surface sites such as, for example, hydroxyl groups.

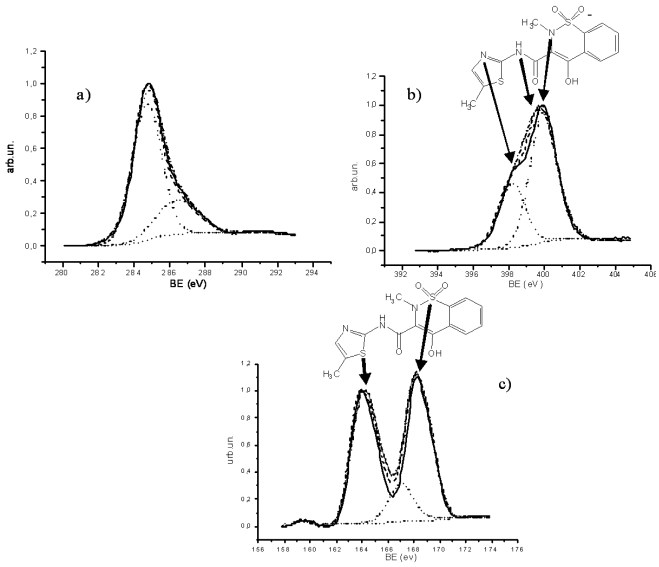

Fig. 9. XPS core lines spectra of meloxicam (solid line), ball-milled meloxicam (dash line) and ball-milled 1:3 meloxicam - alumina mixture (dash dot line): C1s a), N1s b), S2$p_{3/2-1/2}$ c).

The XPS spectra of the initial meloxicam and ball-milled samples are compared in Fig. 9. The XPS spectrum of meloxicam is reported here for the first time. As in the case of piroxicam, no changes in the C1s (Fig. 9a) binding energies under ball milling are observed. After ball-milling meloxicam alone and meloxicam - alumina mixture, a new N1s transition appeared (Fig. 9b) with a binding energy intermediate between those of the initial states. For meloxicam, this can be attributed to formation of zwitterion form and, for the composite, to interaction between meloxicam and active sites at the surface of the oxide. In the XPS spectra of meloxicam, two well-separated S2$p_{3/2-1/2}$ peaks are observed (Fig. 9c). The peak with the lowest binding energy associates with the sulfur in thiazolyl ring, whereas the high binding energy peak is due to the sulfur of sulfate group. The appearance of a new energetic state of sulfur of sulfate group in meloxicam-Al_2O_3 mixtures, intermediate between those of initial states may be considered as a confirmation of the formation of bonds between sulfur of sulfate group in meloxicam and active sites at the surface of alumina. Thus, changes in the S2p and N1s core-level binding energies in ball-milled samples in comparison with the initial ones have been observed, that can be attributed to the presence of hydrogen or donor-acceptor bonding between sulfur- and nitrogen-containing groups of immobilized compound and the surface of the oxide.

TABLE I

IR wavenumbers for selected characteristic bands of piroxicam, ball-milled piroxicam, piroxicam in 1:3 piroxicam – Al_2O_3 composite, and the bands of piroxicam Cu(II) and Ni(II) complexes (cm^{-1}).

Assignments	Piroxicam	Ball milled piroxicam	1:3 Piroxicam – Al_2O_3 ball-milled mixture (AGO-2, 30 min)	$Cu(Pir)_2(H_2O)_2$ [16]	$Ni(Pir)_2(H_2O)_2$ [16]
ν(N-H), or ν(O-H)	3337 vs	3380 s, 3340 vs	3380 m, 3350–3200 m, br	—	—
Amide I, ν(C=O)	1631 s	1631 s	1613 s	1621 vs, br	1625 vs, br
Amide II, ν(C−N) + δ(NH)	1579 m	1579 m	1569 m	1572 vs	1576 vs
ν(C=N)	1530 vs	1530 vs	1531 s, 1500 m	1540 sh, 1527 s, 1512 s	1521 s, br
$\nu_{as}(SO_2)$	1350 vs	1350 vs	1348 s	1330 vs	1328 vs
Amide III, ν(C−N) + δ(NH)	1310 s	1311 s	1313 s, br	-	-
$\nu_s(SO_2)$	1180 vs	1180 vs	1184 s, 1171 s	1166 vs	1162 vs

s = strong, vs = very strong, m = medium, br = broad, sh =shoulder

TABLE II

IR wavenumbers of selected characteristic bands of the meloxicam, ball-milled meloxicam, meloxicam in 1:3 meloxicam – Al_2O_3 composite, and the bands of Fe(II) meloxicam complex (cm^{-1}).

Assignments	Meloxicam	Ball-milled meloxicam	1:3 Meloxicam – Al_2O_3 ball-milled mixture (AGO-2, 15 min)	$Fe(Hmel)_2{\cdot}4H_2O$ [22]
ν(N-H)	3290 vs	3290 vs	3290 vw	—
Amide I, ν(C=O)	1620 s	1620 s	1620 w, br	1582
ν(C=N)	1531 vs	1531 vs	1531 vs	*)
$\delta(CH_3)$	1458 m, 1420 vw	1458 m, 1420 vw	1458 w, 1436 w, 1420 w, 1405 vw	*)
$\nu_{as}(SO_2)$	1346 s	1346 s	1350 s, br	1330
Amide III, ν(C−N) + δ(NH)	1302 m	1302 m	1302 m, br	*)
$\nu_s(SO_2)$	1183 m	1183 m	1183 m, br	1165
δ(OH)	1133 m, 1119 m	1133 m, 1119 m	1127-1122 s, br	*)

s = strong, vs = very strong, m = medium, w = weak, vw = very weak, br = broad, sh = shoulder *) data are not presented

4. Conclusion

The nanocomposites of piroxicam and meloxicam with alumina containing the drug in X-ray amorphous state were obtained by ball-milling as a result of distribution of the drugs in the matrix of oxide with formation of the stable composites. The observed changes in the IR spectra of the ball milled mixtures suggested the interaction of the drugs with the alumina active surface sites. The interaction between the components under ball-milling was also detected by the XPS analysis. In addition to the IR spectroscopy data, the XPS data give information about changes at the surface layers of the samples allowing to evidence core-shell composite formation and estimate the thickness of a drug film on the surface of carrier. The functional groups in molecules of piroxicam and meloxicam involved into formation of bonds between the drugs and surface of the oxide were determined, they are amide, sulfate, enol groups, and pyridyl/thiazolyl nitrogen atoms. It appears that the formation of the new bonds at the contacts of particles in the composite leads to the stabilization of the drugs in the metastable state inhibiting their transformation into the initial crystalline form.

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