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MECHANOCHEMISTRY AND SOLUBILIZATION OF DRUGS

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Abstract

The results on solubilization of poorly water-soluble drugs, indomethacin, piroxicam, and meloxicam, with the help of mechanochemical methods are presented. The mechano-composites of the drugs with various excipients, including soluble polymers and non-soluble fine porous inorganic oxides, were obtained by co-grinding using vibrational and planetary centrifugal mills. The samples obtained revealed higher release rate and apparent solubility of the drugs with respect to the initial ones. Nevertheless, in some cases, e.g. for composites of piroxicam with alumina and ferric oxide, decreasing the release rate and solubility of the drug was observed suggesting the formation of poorly soluble strong drug - carrier associates.

Introduction

Improvement in the extent and rate of dissolution of poorly water-soluble drugs is highly desirable as this can lead to an increased and more reproducible oral bioavailability. During the past four decades, there was a great interest in solid dispersion systems to increase dissolution rate and bioavailability of poorly soluble drugs [1]. Mechanochemical treatment was proposed by Nakai in 1974 [2] as an efficient method to prepare solid dispersions of drugs. Disordering and amorphisation of the drug upon grinding results in enhanced apparent solubility [3]. As a result of co-grinding drug - carrier mixtures, the formation of the particles smaller than 100 nm in diameter, or appearance of the distributed thin layer on the surface of the particles of drugs larger than 100 nm in diameter is possible leading to formation of micro- or nanocomposites [4, 5]. The composites obtained are characterized by special properties such as enhanced dissolution rate and solubility of the drug [6].

The purpose of this work was to study solubilization of poorly water-soluble non-steroidal anti-inflammatory drugs, namely, piroxicam, meloxicam, and indomethacin, with the help of mechanochemical methods. Various excipients including soluble polymers and non-soluble fine porous inorganic oxides were used to prepare mechanocomposites of the drugs.

Experimental

Vibrational [SPEX 8000 (USA)] and planetary centrifugal [AGO-2 (Russia)] mills were used for co-grinding. The 1:1, 1:3 and 1:10 drug-carrier mixtures were prepared. Time of treatment varied from 10 to 30 minutes. The properties of the mechanocomposites obtained were studied by the X-ray diffraction and IR spectroscopy methods. X-ray powder diffraction (XRPD) patterns were measured with a D8 DISCOVER GADDS diffractometer (Bruker, Germany) with CuK_α radiation. IR spectra were recorded with Infralum FT-801 FTIR spectrometer (Russia) in tablet with KBr. Attenuated total reflectance infrared spectroscopy (ATR) was performed with Digilab Excalibur 3100 FTIR spectrometer (Varian, USA).

To measure the dissolution, solubility tester Varian 705 DS was used. A weighed portion of the sample, with the particle size of 125-315 μm, containing the drug in excess, was put into a glass vessel containing distilled water at 37±0.5°C. After definite time intervals, the concentration of the substance in solution was measured with a Carry 50 spectrophotometer.

Results

Solid Dispersion Systems of Piroxicam and Indomethacin with Polymers

The mechanocomposites of piroxicam and indomethacin with polyvinylpyrrolidone (PVP) and polyethylene glycol (PEG) were prepared by co-grinding. In the case of composites with PVP, the X-ray amorphous products were obtained. The changes in IR spectra suggested the interaction between the components due to formation of hydrogen bonds. The piroxicam – PVP mechanocomposites were characterized by increased rate of dissolution and solubility of the drug (Concentration (C) vs. time plots, Fig. 1). In Fig. 2, the dissolution curves for piroxicam – PEG mechanocomposites are presented. As a result of the interaction of the components under co-grinding, the increased rate of dissolution and solubility of piroxicam was observed in comparison with the physical mixture of the components.

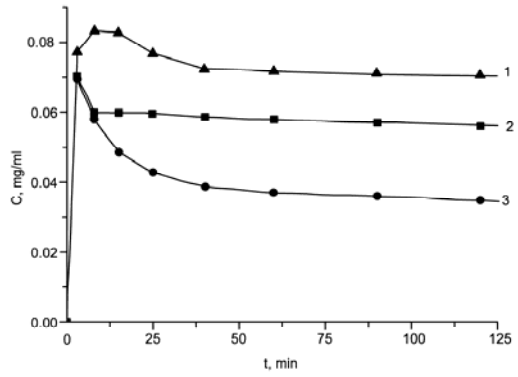

Figure 1. Dissolution curves of ball milled 1:1 (1) and 1:10 (2) (w/w) piroxicam – PVP mixtures, and piroxicam alone (3)

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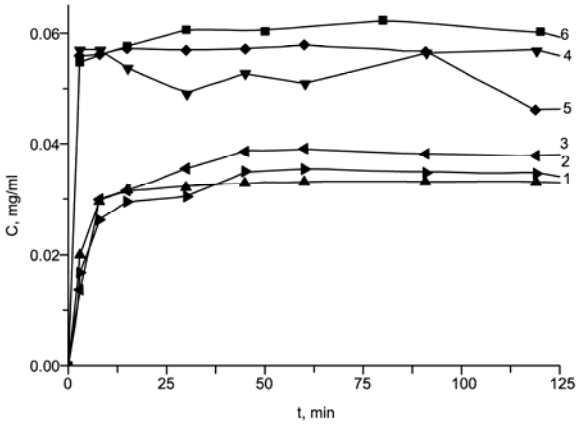


Figure 2. Dissolution curves of initial piroxicam (1); 1:1 (2) and 1:10 (3) piroxicam – PEG physical mixtures; 1:1 (4), 1:3 (5), 1:10 (6) piroxicam – PEG ball milled mixtures

In addition to PVP and PEG, the polypropylene (PP) as an inert additive was used to prepare the mechanocomposites with indomethacin [7]. In Fig. 3, the dissolution curves of indomethacin for co-ground mixtures with PP are presented in comparison with those for indomethacin intact and its co-ground mixtures with PVP and PEG. It is seen that the presence of inert additive influenced on dissolution of the drug. In comparison with initial indomethacin, the higher concentration of the drug in solution was achieved probably due to dispersion of the drug within the carrier.

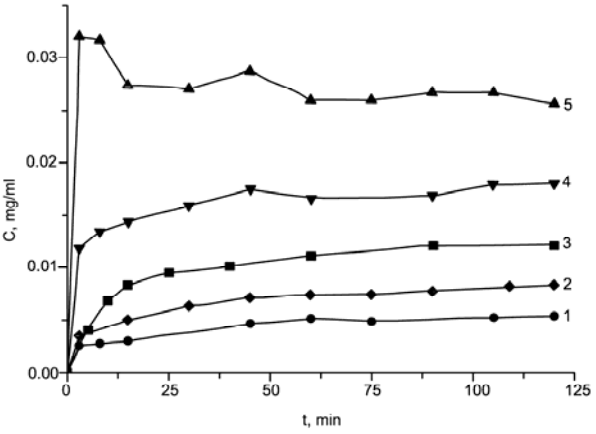


Figure 3. Dissolution curves of indomethacin (1), ground indomethacin (2), mixtures of indomethacin with PP (3), PVP (4) and PEG (5) (1:3, w/w)

The mechanocomposites of piroxicam with microcrystalline cellulose (MCC) revealed increased rate of dissolution of the drug (Fig. 4) [8]. The concentration of piroxicam in solution only slightly increased in comparison with ground piroxicam, nevertheless, the mechanocomposites, in contrast to drug alone, were more stable and preserve piroxicam in active form for a longer time.

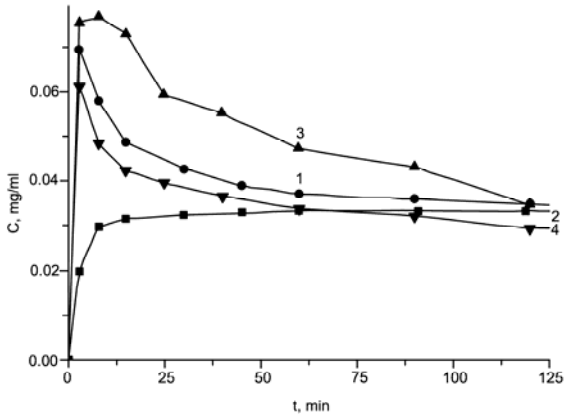


Figure 4. Dissolution curves of mechanically activated piroxicam (1), initial piroxicam (2), 1:1 (3) and 1:10 (4) piroxicam – MCC mixtures ball milled in SPEX mill

Nanocomposites of piroxicam and indomethacin with inorganic oxides

The nanocomposites of piroxicam and indomethacin with fine porous inorganic oxides, alumina, silica, and magnesia, containing the drugs in X-ray amorphous state were obtained by ball milling [9]. The changes in IR spectra suggested the interaction of the components under ball milling that led to stabilization of the drugs in the metastable state.

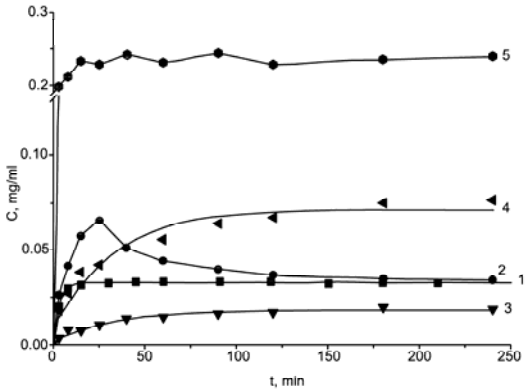
In the case of co-ground mixtures of piroxicam with alumina, the apparent equilibrium solubility of the drug was lower than the solubility of the initial piroxicam (Fig. 5 (a), curve 3). The possible reason for decreasing the concentration of the drug in solution may be the formation of strong water-insoluble drug - carrier complexes at the surface of alumina. At the same time, in the case of indomethacin, all the samples revealed the drug solubility higher than that of the initial drug (Fig. 5(b), curve 3). These facts suggested a stronger interaction of piroxicam with alumina surface, compared to indomethacin. One of the possible reasons may be the formation of complexes of piroxicam employing the pyridyl nitrogen and the amide oxygen atoms of the drug.

Mechanocomposites of piroxicam and indomethacin with silica revealed the higher apparent equilibrium solubility of the drugs than those of the initial ones (Fig. 5). For piroxicam - SiO_2 mixtures, solubility increased by a factor of 2; for 1:3 indomethacin - SiO_2 mixture treated in Spex 8000 mill for 30 min, solubility achieved 0.14 mg/ml, i.e. 28 times higher than that of the initial drug.

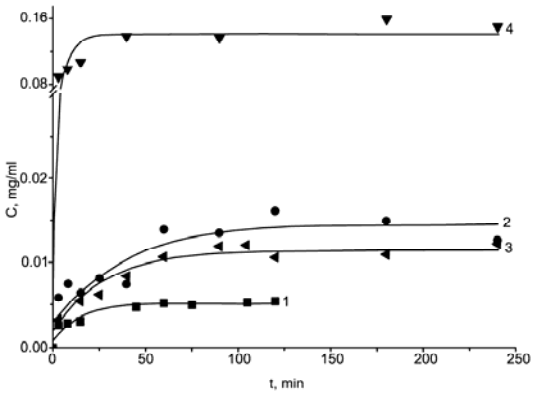
In the case of piroxicam-based mechanocomposites with magnesia, the apparent equilibrium solubility of piroxicam was higher than that of the initial drug (Fig. 5(a), curve 5). As for indomethacin, the salt form of the drug was identified in the solution, the solubility was 80 times higher as compared to the initial drug.

Nanocomposites of piroxicam with ferric oxide presented the particles of the oxide covered by a thin layer of the drug. The rate

of dissolution of the piroxicam was lower than that of the initial drug (Fig. 6) suggesting the formation of strong drug-carrier complexes at the surface of the oxide.



(a)



(b)

Figure 5. Dissolution curves of (a) intact piroxicam (1), ball milled piroxicam alone (2), 1:3 piroxicam – oxide mixtures ground in the SPEX mill for 30 min: with Al_2O_3 (3), with SiO_2 (4), with MgO (5); (b) intact indomethacin (1), ball milled indomethacin alone (2), 1:3 indomethacin – oxide mixtures ground in the SPEX mill for 30 min: with Al_2O_3 (3), with SiO_2 (4)

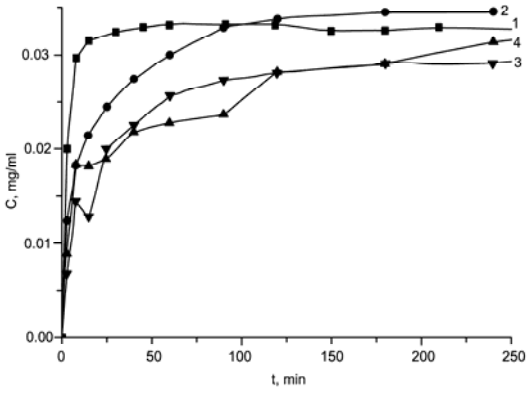


Figure 6. Dissolution curves of initial piroxicam (1); 1:3 piroxicam – ferric oxide mixture ground in SPEX mill for 15 min (2); piroxicam - ferric oxide mixture ground in AGO mill: 1:3, 30 min (3), 1:10, 10 min (4)

Mechanocomposites of Meloxicam with Excipients

Solubilization of meloxicam with the help of mechanochemical methods was studied using excipients which were usually used in tabletted forms of meloxicam, namely, PVP, lactose, starch, magnesium stearate, sodium citrate. Polyethylene oxide (PEO), hydroxypropylmethylcellulose (HPMC), and chitosan were also used as carriers.

In the case of PVP, the X-ray amorphous samples were obtained suggesting distribution of the drug within the polymer or formation of an amorphous product. The use of planetary centrifugal AGO-2 mill and increased content of the carrier were more preferable to obtain amorphous product. Co-grinding the mixtures of meloxicam with PEO, HPMC, MgSt, NaCit resulted in broadening of X-ray diffraction peaks and decreasing their intensity suggesting particle size reduction and partial disordering of crystal structure of meloxicam.

The changes in IR spectra of the mixtures of meloxicam with PVP, HPMC, NaCit, and starch after mechanical treatment suggested the interaction of the components due to hydrogen bonds formation. The absence of changes in IR spectra of ball milled samples with PEO and magnesium stearate confirmed that there were no hydrogen bonding between the drug and excipient in these mixtures.

The data on dissolution of meloxicam for the co-ground mixtures with the excipients are summarized in Table 1. It is seen that the samples obtained revealed the increasing solubility of the meloxicam compared to the initial drug.

Table 1. Dissolution data for meloxicam in co-ground mixtures with excipients

Excipient	Apparent solubility, mg/ml
-	0.03
Starch	0.05
Lactose	0.08
Chitosan	0.08
PEO	0.08
HPMC	0.15
PVP	0.25
Sodium citrate	0.60

For the mixtures with PEO, all the samples obtained revealed the increased dissolution rate of meloxicam, nevertheless, the concentration of the drug in solution only slightly exceeded the solubility of the initial drug (Fig. 7). The curves with maximum were observed for which the high dissolution rate in the initial time was characteristic and then the concentration of the drug in solution decreased. The maximum apparent solubility equal to 0.08 mg/ml was reached for the 1:3 meloxicam – PEO mixture co-ground in AGO-2 mill.

Mechanically activated mixtures of meloxicam with magnesium stearate revealed decreased rate of dissolution and solubility of the drug in comparison with the physical mixtures of the components (Fig. 7) suggesting encapsulating of the drug by carrier.

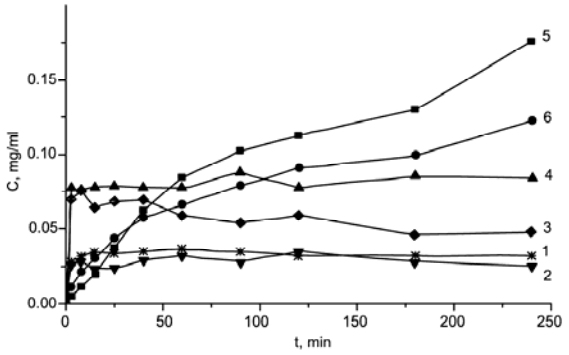


Figure 7. Dissolution curves of meloxicam with PEO and magnesium stearate (1:3, w/w): 1 - meloxicam initial; 2 – meloxicam - PEO physical mixture; 3 – meloxicam - PEO mixture co-ground in SPEX mill; 4 – meloxicam - PEO mixture co-ground in AGO mill; 5 - meloxicam – StMg physical mixture; 6 - meloxicam –MgSt mixture co-ground in AGO mill

As an example, at the Fig. 8 the dissolution curves for the mechanocomposites of meloxicam with sodium citrate are presented. Based on the changes in X-ray diffraction patterns, it can be supposed that mechanical treatment of meloxicam in the mixtures with sodium citrate led to reduction of particle size and, depending on the conditions, to partial or total amorphization of the drug. The changes in IR spectra of the co-ground samples suggested interaction of the components due to intermolecular hydrogen bond formation between C=O groups of excipient and OH- or NH-groups of meloxicam. For X-ray amorphous samples co-ground in AGO-2 mill for 15 min, the maximum was observed at the dissolution curve. The co-ground 1:3 meloxicam – sodium citrate mixture revealed apparent solubility higher than that of the initial drug in 20 times (Fig. 8, curve 5).

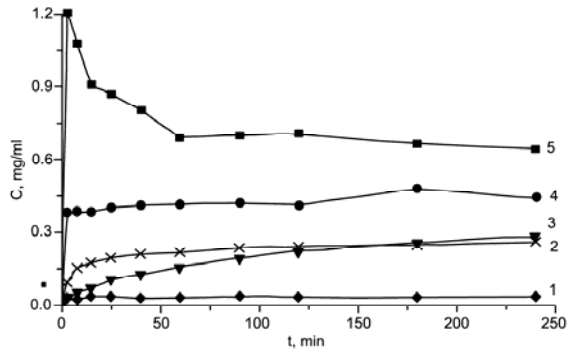


Figure 8. Dissolution curves of the mixtures of meloxicam with sodium citrate (1:3, w/w): 1 – meloxicam initial; 2 – physical mixture; 3 – mixture of the components ball milled in AGO mill separately; 4 - 2:1 (mol.) meloxicam – NaCit mixture ball milled in SPEX mill with addition of ethanol; 5 - meloxicam – NaCit mixture ball milled in AGO mill

Discussion and Conclusions

Thus, it has been shown that ball milling of poorly water-soluble drugs, indomethacin, piroxicam, meloxicam, with different excipients resulted in increasing the rate of dissolution of the drugs and ther concentration in solution that can be possibly used for enhancing oral bioavailability.

It is known that high energy ball milling is both a processing method to reduce particle size and a route to obtaining of metastable materials. Under co-grinding the drugs with excipients, particle size reduction is very effective due to dispersion of the drug within the carrier and, consequently, reduced particle agglomeration. This leads to increasing the release rate of the drug.

Ball milling brings about partial or complete amorphization of the drug. The amorphous pharmaceuticals are markedly more soluble than the crystalline substances, however, during processing or storage the amorphous state may spontaneously convert back to the crystalline state [10,11]. Under co-grinding with excipient, depending on the conditions used, the drug can present as a molecular, a crystalline particulate or an amorphous particulate dispersion. In most cases, co-grinding the drugs with excipients leads to formation of mechanocomposites which are characterized by high surface of contacts between the components and the special properties at the interface. The formation of the drug - carrier complexes at the interface appears to be responsible for the stabilization of metastable state of the drug.

In the case of water-soluble polymers, the particles of the drug can dissolve into the polymer-rich diffusion layer at a sufficiently rapid rate, i.e. carrier-controlled mechanism [12] can be realized, or, following the drug-controlled mechanism [12], the drug is released as solid particles with improving dissolution due to the higher surface area and the possibility of improved wetting and decreased agglomeration. Forming hydrogen bonds with a polymer, the drug can be released as a molecular complex that may be stable in solution or decompose into the components.

When the non-soluble carrier is used, the grafting complexes can be formed at the surface of the carrier. This can lead to increasing the rate of dissolution of the drug. Sometimes, the decreasing rate of dissolution and solubility can be observed probably due to formation of strong drug-carrier associates. This may be interesting for development of medicinal preparations of prolonged action.

In any case, the data obtained showed that ball milling of poorly water-soluble drugs with excipients can be useful for modification of the drugs and obtaining preparations with improved properties.

Acknowledgement

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