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MECHANOCHEMICAL PREPARATION OF DRUG-CARRIER SOLID DISPERSIONS

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Abstract

The method of mechanical activation was used to obtain solid-state dispersions of some drugs in polyvinylpyrrolidone, polyethylene glycol and talc as carriers. Solid dispersions obtained by mechanical activation were found to have higher apparent solubilities and dissolution rates than mechanically activated drugs or their physical or eutectic mixtures with carriers used. It was shown by IR-spectroscopy and fluorescence measurements that mechanical treatment gave rise to an interaction between components which was apparently responsible for the solubilization effects observed.

Keywords: dissolution rate, drug-carrier solid dispersions, ibuprofen, mechanical activation, piroxicam, sulfathiazole

Introduction

The method of introducing drugs into drug-carrier solid dispersions [1] is one of the ways to increase the rate of dissolution and, as a consequence, bioavailability of medicines. The traditional methods of preparation of solid dispersions, coprecipitation and melting of components, have often proved to be very successful, but these have a number of disadvantages [2]. In the present work the method of mechanical activation is used to obtain solid-state dispersions of some poorly water-soluble medicinal substances (sulfathiazole, ibuprofen, piroxicam) in organic and inorganic carriers. Polyvinylpyrrolidone, polyethylene glycol and talc are used as carriers.

Experimental

Sulfathiazole (Irbitsk Chemical Pharmaceutical Plant, Russia) was recrystallized from dilute ammonium hydroxide before use. Ibuprofen (Sumitra Pharmaceuticals & Chemicals LTD, India) and piroxicam (Irkutsk Institute of Organic Chemistry, Russia) were used without further purification. Polyethylene glycol (molecular weight fraction 4000) (PEG 4000) (Institute of Chemical Technology, Novosibirsk, Russia), low-molecular, medical polyvinylpyrrolidone (PVP) (M= 12600±2700) (Bolkhov Chemical Plant of Synthetic Half Products, Russia) and talc (NPO "Organika", Novokuznetsk, Russia) were used as commercial products.

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The mechanical activation of the mixtures of components taken in definite proportions was conducted in an AGO-2 planetary-centrifugal mill with water-cooled vials. The vial volume was 40 ml, the ball diameter was 6 mm. The ratio of the ball mass to the sample weight was 20:1. The load on a ball was of the order of 60 g.

The powder X-ray diffraction diagrams of the samples were obtained by a DRON-3 apparatus using CuK_α radiation. Infrared spectra of the samples were recorded on a "Specord-75 IR" spectrometer in vaseline oil and KBr tablets. The fluorescence spectra were measured at liquid nitrogen temperature with a microfluorimeter using a high-pressure mercury lamp with exciting wavelength 365 nm. Experiments were performed by a derivatograph at a heating rate of 5°C min^{-1}. The DSC curves were measured by a Setaram DSC 111 in an argon atmosphere at a heating rate of 10°C min^{-1}.

To study the drug release rate, a weighed sample was put in a glass vessel thermostated at 37± 0.5°C, equipped with a mixer, and containing 100 ml of water. The concentration of the solution was determined at intervals on a "Shimadzu UV-240" spectrophotometer from the intensity of the band at 283 nm for sulfathiazole, 222 nm for ibuprofen, and 357 nm for piroxicam with respect to water or, in the case of using PEG as carrier, a PEG solution of appropriate concentration.

Results and discussion

Sulfathiazole–PVP system

Mechanical treatment of sulfathiazole alone brings about the conversion of form III into form I metastable at room temperature, and, in the initial stage of me-

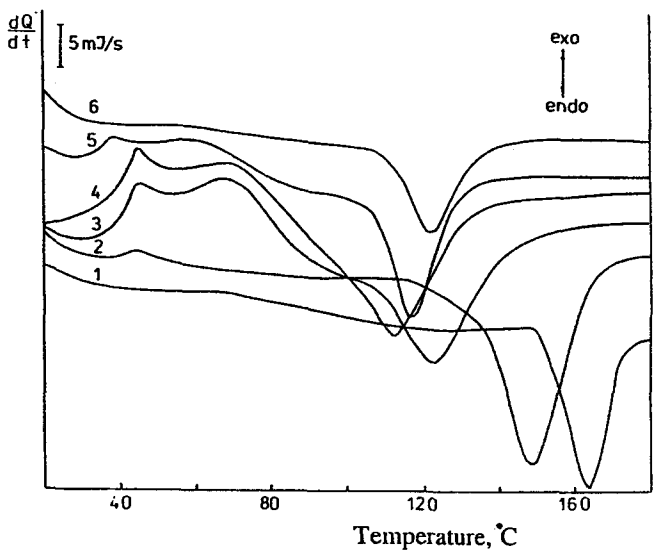

Fig. 1 DSC curves of sulfathiazole intact (sample weight 47 mg) (1) and after mechanical treatment for 1 min (124 mg) (2); 10 min (120 mg) (3); 20 min (107 mg) (4); 30 min (78 mg) (5); 45 min (75 mg) (6)

chanical treatment, a part of the substance (up to 50%) was converted into a noncrystalline solid [3]. This is indicated by a broadening of X-ray diffraction peaks and by a decrease in their intensity. In addition, the DSC curves (Fig. 1) of the samples obtained show two broad exothermic peaks in the range 30–80°C, which is apparently due to crystallization of the substance. These peaks were absent if the mechanically treated samples were annealed at 70°C. Prolonged mechanical treatment or storage of the samples led to recrystallization of the substance. To stabilize the noncrystalline state, the method of introducing the drug into solid dispersion was employed. It is known [4] that the apparent solubility and rate of solution of sulfathiazole were greatly increased if sulfathiazole was previously coprecipitated with PVP. It was of interest to elucidate the potentials of the mechanical activation method in obtaining sulfathiazole solid dispersions.

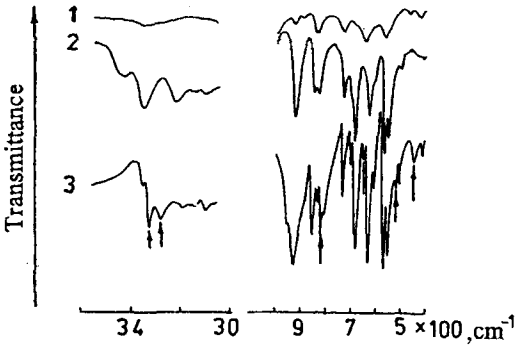

Fig. 2 IR-spectra of PVP (1); sulfathiazole–PVP (1:1) mixture, mechanically activated for 12 min (2); sulfathiazole (3). (Tablets with KBr)

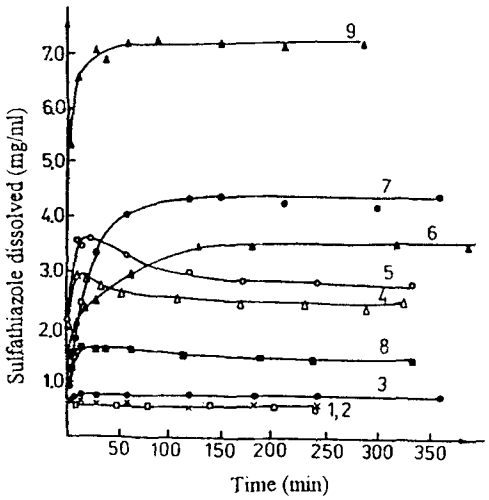

Fig. 3 Dissolution curves of sulfathiazole intact (1) and after mechanical activation (2); sulfathiazole–PVP (1:1) physical mixture (3); sulfathiazole–PVP (1:1) mixture, mechanically activated for 4 min (4); 6 min (5); 8 min (6); 12 min (7); 3:1 (8) and 1:3 (9) sulfathiazole–PVP mixtures mechanically activated for 12 min

As a result of mechanical activation of a sulfathiazole and PVP mixture (1:1, by weight), the X-ray diffraction peaks of sulfathiazole initially broaden and then completely disappear [5]. In the IR spectra of the mechanically activated mixture, a part of bands corresponding to the torsional (520 cm^{-1}), deformation (820–807 cm^{-1}) and stretching (3320–3274 cm^{-1}) vibrations of NH_2 and NH groups disappear (Fig 2) and a new band occurs at 3220 cm^{-1}. It appears that hydrogen bonds are formed between the NH groups of sulfathiazole and the C=O groups of PVP [6] upon mechanical treatment.

Figure 3 shows the dissolution curves for sulfathiazole and its mixtures with PVP before and after mechanical treatment. As is seen, the mechanical treatment of sulfathiazole alone produces no substantial increase in the dissolution rate of the drug. On the contrary, the mechanical treatment of the mixture produces a substantial increase in the rate of dissolution and the solubility of sulfathiazole. The efficiency of mechanical action increases with increased PVP fraction. When the PVP content was low (3:1 sulfathiazole : PVP mixture), a part of sulfathiazole remained crystalline in the mechanically activated mixture whereas it was amorphous in the case of large amounts of PVP.

Thus, the mechanical treatment of the sulfathiazole–PVP mixture produces a substantial increase in the apparent solubility and dissolution rate of sulfathiazole, the formation of a metastable compound between components and stabilization of the activated state of the drug apparently being responsible for these effects.

Ibuprofen–PEG 4000 system

Powder X-ray diffraction studies of mechanically treated mixtures of ibuprofen with PEG have shown that, upon mechanical treatment, the diffraction peaks of ibuprofen disappear. Hence, mechanical treatment appears to result in the distribution of the finely divided drug in the matrix or in the interaction of ibuprofen and PEG with an amorphous product formation.

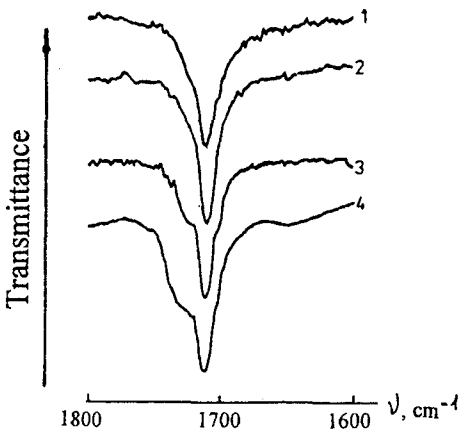

Fig. 4 IR-spectra of ibuprofen (1), ibuprofen–PEG 4000 (1:19) physical mixture (2); ibuprofen–PEG 4000 (1:19) sample, obtained by the melting method (3); mechanically activated ibuprofen–PEG 4000 (1:19) mixture (4). (Vaseline oil)

The samples obtained were studied by IR-spectroscopy in vaseline oil. It is seen from Fig. 4 that in the region of the carboxylic group stretching vibrations, new bands at 1736, 1724 cm^{-1} appear. It should be noted that these bands are also observed for the sample obtained by the melting method. It was shown [7] that the molecules of ibuprofen are bound into dimers via hydrogen bonds. The fact that new absorption bands appear in the IR-spectra upon mechanical activation suggests that hydrogen bonds form between ibuprofen molecules and PEG.

In order to get further evidence on the possible interaction of the drug with PEG, the luminescence analysis method was employed. The studies carried out have shown that, whereas PEG cannot luminesce, ibuprofen exhibits a glow at 450 nm, with the intensity increasing at 77 K. Changes were observed in the vibrational structure in the short-wave region of the luminescence spectra of the ibuprofen–PEG mixtures subjected to mechanical activation (Fig 5): the bands due to the

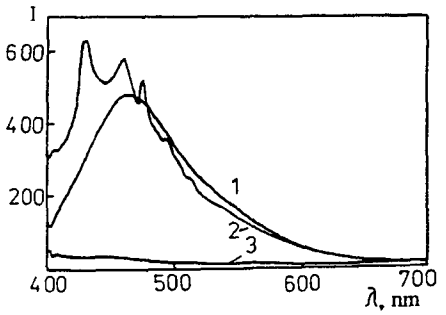

Fig. 5 Luminescence spectra of the mechanically activated ibuprofen–PEG 4000 (1:19) mixture (1); ibuprofen (2); PEG 4000 (3)

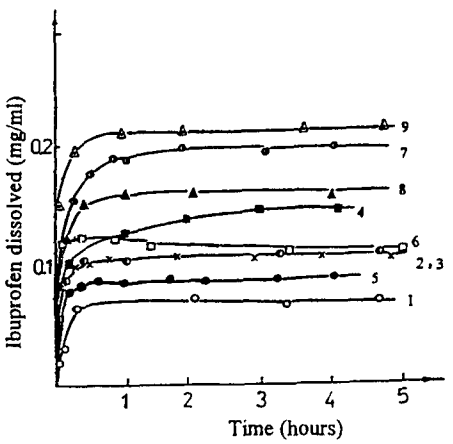

Fig. 6 Dissolution curves of ibuprofen (1); ibuprofen–PEG 4000 (1:19) mixture before (2) and after melting (3); ibuprofen–PEG 4000 eutectic mixture (4); ibuprofen–PEG 4000 mixture, mechanically activated: 1:1 (5); 1:10 (6), 1:19 (7), 1:25 (8); ibuprofen–PEG 4000 mixture (1:19) after prolonged melting (9)

stretching vibrations of benzene in the region 1570–1610 cm^{-1} [8] broadened along with the bands due to the deformational vibrations of the C–C–H groups. This may point to the intermolecular interaction between PEG and the benzene ring of ibuprofen. It appears that the interaction of ibuprofen with PEG proceeds not only with the participation of the carboxyl group of ibuprofen and the hydroxyl or ester group of the polymer but also includes the van der Waals interaction between PEG and the aromatic ring.

Figure 6 presents the dissolution curves of ibuprofen–PEG 4000 solid dispersions obtained. It is seen that the rate of drug release depends on the content of the constituents in the mixture. The equimolar (1:19, by weight) mixture showed the best result. The solubility of ibuprofen in the case of physical mixtures with PEG exceeds the solubility of ibuprofen alone, the effect being larger as the PEG content increases. This is in accordance with the model of solubilization proposed by Goldberg *et al.* [9].

Since data are available [10, 11] on increasing the release of ibuprofen from solid dispersions obtained by the melting method, it was of interest to compare the samples prepared by mechanical treatment with those obtained by the conventional melting technique. For this purpose, the weighed constituents were mixed and heated, with stirring, to complete melting and then cooled. Powder X-ray diffraction analysis has shown that the samples obtained are mixtures of crystalline ibuprofen and PEG. Slow cooling and rapid quenching yield one and the same result. Apart from peaks of starting ibuprofen (*m.p.* 73°C) and PEG 4000 (*m.p.* 54°C), the thermograms of the samples obtained (Fig. 7) show a peak at 45°C associated with melting of an eutectic mixture with the eutectic composition being close to 30wt.% ibuprofen.

The release of ibuprofen from the samples obtained by melting, including those of the eutectic composition, was lower than the release of the drug from the mechanically activated samples. The solubility of the drug in the case of samples prepared by the conventional melting method did not exceed the solubility when the physical mixtures were used. However, for the sample (ibuprofen : PEG ratio of

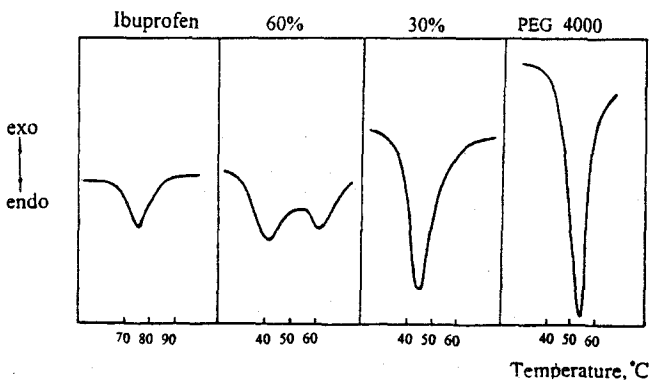

Fig. 7 DTA curves of ibuprofen, PEG 4000 and solid dispersions prepared by the melting method. (Weight of samples 200 mg)

1:19) prepared by holding the melt in a heat chamber at about 80°C for a long time, the solubility of the drug was as high as in the case of mechanically treated samples.

The powder X-ray diffraction analysis shows that, in contrast to the samples prepared by the conventional technique, this sample contains no crystalline ibuprofen. Apparently, as a result of prolonged exposure to a temperature above the melting point, an interaction occurs between the constituents of the mixture, leading to the amorphous product.

Thus, it appears that the interaction between the components is responsible for solubilization of the drug. Since only prolonged exposure to a temperature above the melting point is needed to obtain fast release solid dispersion by the melting technique, the mechanochemical method is a promising and convenient method for the preparation of solid dispersions in the ibuprofen–PEG system.

Ibuprofen–talc system

As a result of mechanical activation of an ibuprofen–talc (1:10, by weight) mixture, the X-ray diffraction peaks of talc broaden and decrease in intensity whereas the peaks of ibuprofen completely disappear. The absense of ibuprofen melting peak on DTA curve (Fig. 8) confirms the amorphous state of the substance.

Figure 9 shows the effect of mechanical activation on the IR-spectra of the ibuprofen–talc mixture. The absorbances at 1722 cm^{-1} disappear, while new peak appears in the 1585–1615 cm^{-1} region. On the basis of literature data [12], it may be suggested that the COOH group is bonded to the Mg^{2+} ions of talc, on mechanical activation. In addition, there were changes in the 400–600 cm^{-1} region, which points to the deformation in the Mg^{2+} ion containing octahedral layers of mechanically activated talc.

To confirm the result obtained, the syntheses of the Mg salt of ibuprofen was conducted. A suspension of MgO in an ethanolic solution of ibuprofen (1:1 molar

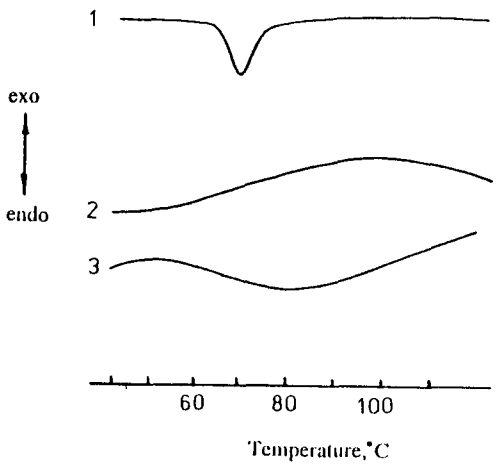

Fig. 8 DTA curves of ibuprofen (weight of sample 50 mg) (1); talc (500 mg) (2); mechanically activated ibuprofen–talc (1:10) mixture (550 mg) (3)

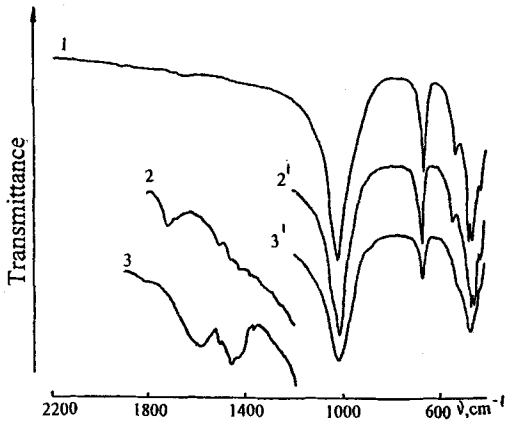

Fig. 9 IR-spectra of talc (1); ibuprofen–talc (1:10) physical mixture (2, 2'); mechanically activated ibuprofen–talc (1:10) mixture (3, 3'). (Tablets with KBr, weight of drug 0.8 mg (1, 2', 3'), 7 mg (2, 3))

ratio) was held for several h at room temperature under stirring. The suspension was then centrifuged, and the precipite was washed and dried. In another method, ibuprofen–MgO pressed tablets were placed into oven and stored at 50–60°C for several hours [11]. Chemical analysis data confirmed that $Mg(ibuprofen)_2$ salt was formed. In the region of the C=O streching vibrations, the IR-spectra of this salt were identical with those of the mechanically activated ibuprofen–talc mixture.

The dissolution curves of ibuprofen–talc samples are shown in Fig. 10. Due to the ibuprofen–talc interaction, the solubility of the drug increased significantly.

Piroxicam–PVP system

It is known [14] that piroxicam exists in at least four polymorphic modifications. According to X-ray diffraction and IR-spectroscopy data [15], the starting pi-

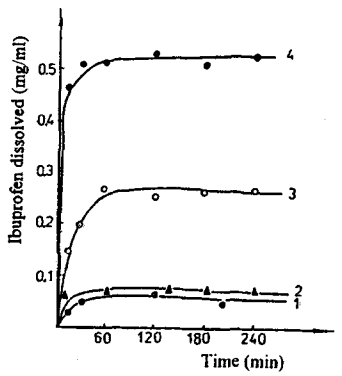

Fig. 10 Dissolution curves of ibuprofen before (1) and after mechanical activation (2); ibuprofen–talc (1:10) physical mixture (3); mechanically activated ibuprofen–talc (1:10) mixture (4)

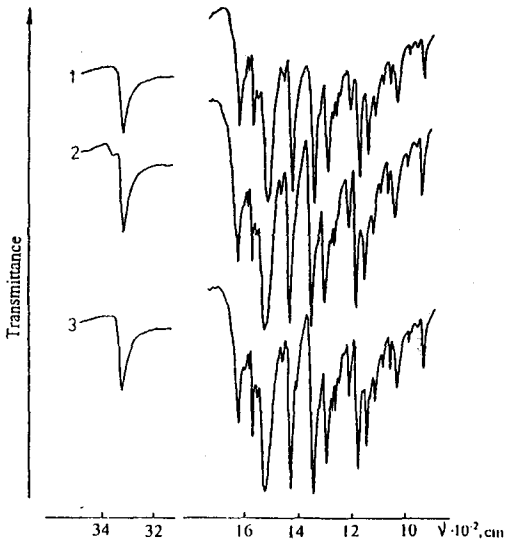

Fig. 11 IR-spectra of piroxicam (1); mechanically activated piroxicam before (2) and after annealing (3)

roxicam was a β-modification. The mechanical treatment leads to a broadening of X-ray diffraction peaks and decrease in their intensity. This suggests that part of the drug was converted into a noncrystalline solid. No appearance of new diffraction peaks suggesting a polymorphic transformation was observed therewith. A band at 3380 cm^{-1} characteristic of the NH stretching vibrations in the α-modification and piroxicam monohydrate [14, 15] appears in the IR-spectra of mechanically treated piroxicam (Fig.11).

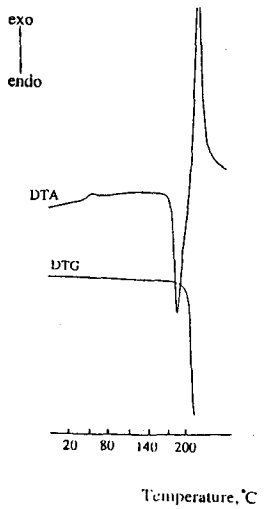

Fig. 12 DTA and DTG curves of mechanically activated piroxicam (weight of sample 400 mg)

In addition, during mechanical activation the substance turned yellow. It can be assumed that mechanical activation brings about changes in the molecular structure of part of the drug molecules. Experiments aimed at clarifying these variations are currently in progress.

DTA data (Fig. 12) show that at 50–70°C an exothermal process, not accompanied by loss of mass, proceeds in the mechanically activated piroxicam as it was observed for amorphous one [12]. As the sample was heated at this temperature for several hours or kept at room temperature for several months, the yellow colour disappeared and the intensity of X-ray diffraction peaks was increased. Thus, during annealing or storage, piroxicam molecules take their initial configuration and, in addition, the ordering of the crystal structure of the substance takes place.

Curves of dissolution of the samples obtained are shown in Fig. 13. The solubility of mechanically activated piroxicam is some times higher than that of the starting drug.

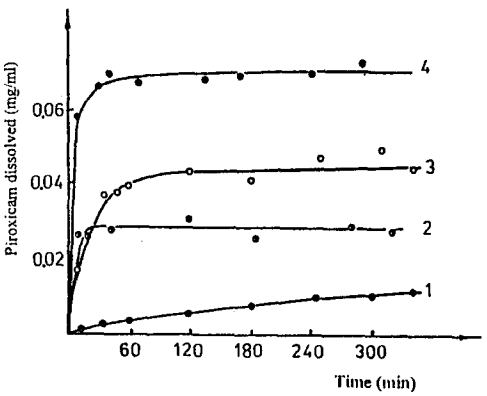

Fig. 13 Dissolution curves of piroxicam (1); mechanically activated piroxicam (2); mechanically activated piroxicam–PVP mixtures: 1:1 (3), 1:10 (4)

To stabilize the active state of the drug the mechanical treatment of piroxicam in mixture with PVP was undertaken. This leads to amorphization of the drug, the process proceeding more completely with a rise in the polymer content. The yellow colour of the mechanically treated mixture does not disappear during annealing, and also in prolonged storage (4–5 months). In the latter case, only a small degree of crystallization was observed.

The samples obtained significantly surpass in solubility the starting piroxicam.

Conclusions

The mechanical activation method was shown to be promising for preparing fast release forms of drugs used. It appears that the interaction of components upon mechanical treatment leading to formation of more soluble complexes and stabilization of active state of medicines is responsible for solubilization of poorly water-soluble drugs.

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References

1 K. Sekiguchi and N. Obi, Chem. Pharm. Bull., 9 (1961) 866.
2 W. L.Chiou and S. Riegelman, J. Pharm. Sci., 60 (1981) 1281.
3 T. P. Shakhtshneider and V. V. Boldyrev, Drug Dev. Ind. Pharm., 19 (1993) 2055.
4 A. P. Simonelli, S. C. Mehta and W. Higuchi, J. Pharm. Soc., 58 (1969) 538.
5 V. V. Boldyrev, T. P. Shakhtshneider, L. P. Burleva and V. A. Severtsev, Drug Dev. Ind. Pharm., 20 (1994) 1103.
6 L. J. Bellamy, The Infra-Red Spectra of Complex Molecules, John Wiley & Sons, New York 1958.
7 J. F. McConnell, Cryst. Struct. Comm., 3 (1974) 73.
8 S. McGlinn, A. Azumi and M. Kinoshita, Molecular Spectroscopy of the Triplet State, Prentice-Hall Inc., New Jersey 1969.
9 A. H. Goldberg, M. Gibaldi and J. L. Kanig, 55 (1966) 482.
10 M. S. Mohamed, F. S. Ghazy and M. A. Mahdy, Pharm. Ind., 47 (1985) 1293.
11 N. M. Najib and M. A. Salem, Drug Dev. Ind. Pharm., 13 (1987) 2263.
12 A.Ikekawa and S. Hayakawa, Bull. Chem. Soc. Jap., 61 (1988) 525.
13 T. T.Kararli, T. E.Needham, C. J.Seul and P. M. Finnegan, Pharm. Res., 6 (1989) 804.
14 F. Vrecer, S. Srcic and J. Smid-Korbar, Int. J. Pharm., 68 (1991) 35.
15 G. Reck, G. Dietz, G. Laban, W. Gunther, Bannier and E. Hohne, Pharmazie, 43 (1988) 477.