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The mechanochemical preparation of solid disperse systems of ibuprofen-polyethylene glycol

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Abstract

The method of mechanical activation is applied to obtain a solid-state dispersion of ibuprofen in polyethylene glycol (PEG). The release rate and solubility of the drug was found to depend on carrier molecular weight and its weight fraction. The highest release rate and solubility were achieved in systems containing equimolar amounts of the drug and PEG 4000 or PEG 6000. It was shown by IR-spectroscopy and fluorescence measurements that the mechanical treatment gives rise to an interaction between ibuprofen and PEG that was a cause of the effects observed.

Keywords: Ibuprofen; Polyethylene glycol; Mechanical treatment; Solid drug dispersion; Luminescence analysis method; Release rate

1. Introduction

The known method of increasing the solubility and hence the bioavailability of poorly soluble drugs involves the preparation of a solid disperse systems drug-carrier (Chiou and Riegelman, 1981). Though the traditional ways of preparation of solid dispersions, i.e., co-precipitation and melting of components have often proved to be very successful, these have a number of disadvantages (Tentsova and Dobrotvorskii, 1981), and need research into new ways of synthesising solid disperse systems. In a previous work, we have used the method of mechanical alloying to obtain solid dispersions in the system sulfathiazole-polyvinylpyrrolidone (Boldyrev et al., 1994). The influence of the mechanical treatment of drugs on their solubility in the presence of various diluents has been shown previously (Kaneniwa and Ikekawa, 1975; Yamamoto et al., 1976; Yagodin et al., 1991). In the present work, an attempt has been undertaken to prepare solid dispersions in the ibuprofen-polyethylene glycol system by the method of mechanical activation.

The non-steroidal anti-inflammatory drug ibuprofen is very slightly soluble in water and has poor wettability properties. With the aim of increasing the solubility of the drug and its bioavailability, solid disperse systems with various diluents such as polyvinylpyrrolidone (Najib et al., 1986), polyethylene glycol (Mohamed et al., 1985; Najib and Salem, 1987), urea (Mura et al., 1986; Asgar and Sharma, 1991) and β-cyclodex-

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trin (Chow and Karara, 1986) have been obtained using conventional co-precipitation and melting methods.

It has been of interest to elucidate the possibilities of the mechanical activation method for modification of ibuprofen to increase its solubility and the dissolution rate. The X-ray diffraction method, IR-spectroscopy and luminescent analysis methods were employed to characterize an effect of mechanical treatment on the substance.

2. Materials and methods

2.1. Materials

Ibuprofen was obtained from Sumitra Pharmaceuticals Chemicals Ltd., India. Polyethylene glycol (PEG) 1500 was purchased from Chemical Pharmaceutical Plant, Kharkov, Ukraine, and PEG 4000 from the Institute of Chemical Technology, Novosibirsk, Russia. PEG 6000 was obtained from Ferak, Berlin, Germany.

2.2. Preparation of drug-PEG dispersions

Solid dispersions were prepared by the mechanical treatment of mixtures of ibuprofen and PEG taken in definite proportions in an AGO-2 planetary-centrifugal mill with water-cooled vials. The vial volume was 40 ml, the ball diameter was 6 mm, and the weight of the ball feed was 60 g. 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. Mixtures were prepared with the following ibuprofen-PEG ratios (by weight): 1:1, 1:10, 1:19, and also 1:7 (PEG 1500), 1:25 (PEG 4000), 1:29, 1:39 (PEG 6000).

Ibuprofen-PEG 4000 samples with different compositions were prepared using the melting method. The weighed constituents were mixed and heated, with stirring, to complete melting. The melt was abruptly cooled.

To compare with solid dispersions obtained, physical mixtures of ibuprofen and PEG 4000 were prepared by a simple mixing of the constituents in the 1:1 and 1:19 ratios.

2.3. X-Ray diffraction

X-Ray phase analysis was conducted on a DRON-3 apparatus using Co K_α radiation.

2.4. Ultraviolet and infrared spectroscopy

The absorption spectra of the equilibrium aqueous solutions of the samples were measured with a 'Shimadzu UV-240' spectrophotometer. Infrared spectra of the samples were recorded on a 'Specord-75 IR' spectrometer in vaseline oil. The amount used in samples was equivalent to 1–2 mg of ibuprofen.

2.5. Luminescence analysis

The fluorescence spectra were measured with a microfluorimeter using a high pressure mercury lamp as a source of excitement, wave length of excited radiation $\lambda = 365$ nm. The powder and compacting tablets of the samples were used. The spectra were measured at room temperature and at liquid nitrogen temperature too.

2.6. Thermal analysis

The thermal analysis of the samples was performed on a 'Paulik, Paulik, Erdey' derivatograph at a heating rate of 5° per min in a 20–300°C temperature range, sample mass 200 mg.

2.7. Dissolution studies

To study the drug release rate a weighed sample containing 120 mg of ibuprofen (with a particle size of 630–400 μm) was placed in 100 ml of water contained in a glass vessel fitted with a mixer thermostated at 37 $\pm$ 0.5°C. The concentration of the solution was determined at intervals by spectrophotometry on a 'Shimadzu UV-240' device according to the intensity of a band at 222 nm. A blank of water solution of PEG of appropriate concentration was employed.

3. Results and discussion

X-Ray phase studies of mechanically treated mixtures of ibuprofen with PEG have shown that, upon mechanical treatment, the peaks of ibuprofen disappear in the diffraction patterns (Fig. 1). The process depends on the content of PEG in a mixture. Thus, in the case of the mixture of ibuprofen and PEG 4000 with a ratio of constituents of 1:19, the reflections of ibuprofen are gone after 4 min, whereas for the mixture with a ratio of 1:1, no complete disappearance was observed, even after 12 min. Hence, mechanical treatment appears to result in the distribution of the finely divided drug in the matrix or the chemical interaction of ibuprofen and PEG with an amorphous product formation, the process occurring incompletely in the case of low PEG contents.

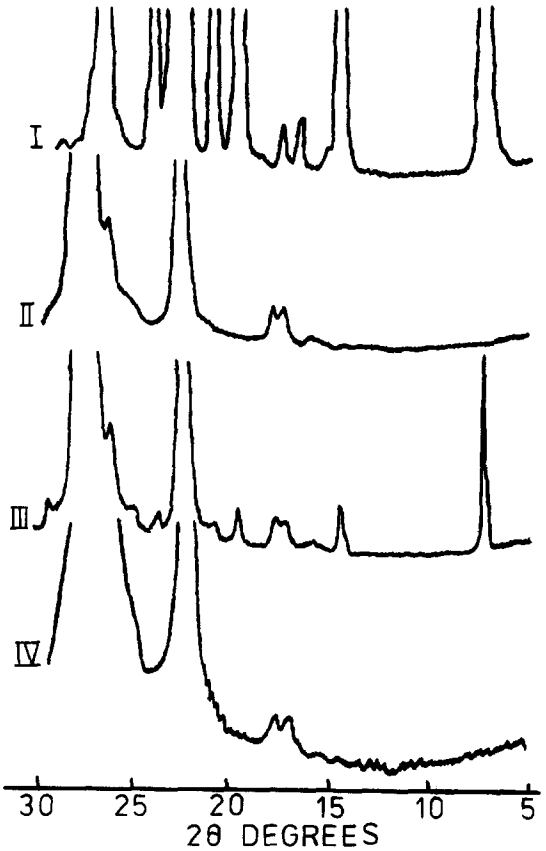

Fig. 1. Powder X-ray diffraction patterns of ibuprofen (1); PEG 4000 (2); the physical mixture of ibuprofen and PEG 4000 (1:19) (3), the mixture of ibuprofen and PEG 4000 (1:19) mechanically activated for 4 min (4).

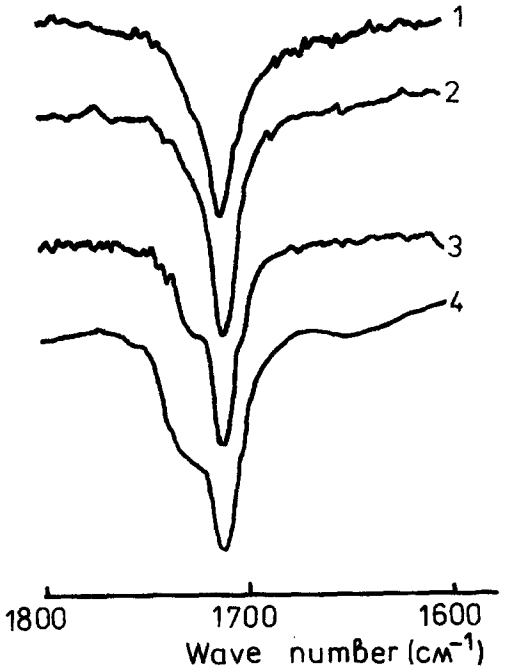

Fig. 2. IR spectra of ibuprofen alone (1), the physical mixture of ibuprofen and PEG 4000 (1:19) (2), the sample of ibuprofen-PEG 4000 (1:19) obtained by the melting method (3), mixture of ibuprofen and PEG 4000 (1:19) mechanically activated (4).

The samples obtained were studied by IR-spectroscopy. In order to prevent the influence of the pressure from compacting, the IR-spectra of the samples were taken in vaseline oil. The excess of PEG in the samples led to the overlapping of the absorption bands of ibuprofen in a large region of the spectrum. However, changes in the absorption due to the stretching vibrations of the C=O group at about 1710 cm^{-1} could be observed since PEG does not absorb in this region. It can be seen from Fig. 2 that the IR-spectra of the mechanically treated mixture differs from the IR-spectra of the physical mixture of the same composition. In the region of vibration of the carboxylic group, bands with higher frequencies (1736 and 1724 cm^{-1}) appear. It should be noted that the appearance of absorption bands is also observed in these regions for the sample obtained by the melting method.

It was shown (McConnell, 1974) 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 new hydrogen bonds form between ibuprofen molecules and PEG. Unfortunately, one cannot infer from the IR-spectroscopy data whether the ester of ibuprofen and PEG, having end hydroxyl groups, form during mechanical activation, since the carbonyl absorption bands of esters lie in the same region (Bellamy, 1957).

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, on exposure to radiation at 313 and 365 nm, ibuprofen exhibits a weak glow in the 450 nm region at room temperature. The glow increases in intensity at 77 K (Fig. 3). The half-width of the band is about 4000 cm^{-1}. The time of decay of luminescence is several seconds. The low temperature spectrum shows a clearly resolved vibrational structure. A detailed interpretation of the vibrational structure of low-temperature luminescence requires additional investigations. However, in a first approximation, the frequencies 1610, 1570 and 780 cm^{-1}, which are associated with vibrations in the skeleton of benzene, can be distinguished.

An analysis of the absorption spectrum of ibuprofen, a derivative of benzene with substituents in the 1 and 4 positions, has shown that

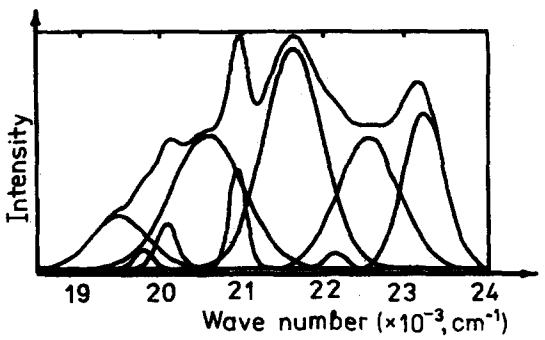

Fig. 3. The luminescence spectrum of ibuprofen at 77 K.

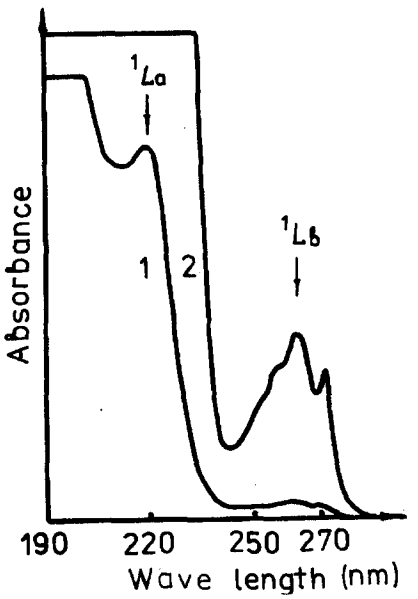

Fig. 4. The absorption spectra of 2.10^{-4} M (1) and 18.10^{-4} M (2) aqueous solutions of ibuprofen.

it is due to the electron transitions in the benzene ring: absorption bands ^1L_a and ^1L_b at 225 and 265 nm, respectively (Fig. 4). In the carboxyl group, the band due to $n-\pi^*$ transition appears to locate in the 210 – 215 nm region and is masked by the more intense band ^1L_a.

In the emission spectra of ibuprofen, both fluorescence and phosphorescence might be expected. If an electron transition occurs at 275 nm, the associated fluorescence is observed in the 275–300 nm region. The position of the observed luminescence band of ibuprofen, its temperature dependence, and the duration of the glow suggests that the emission of ibuprofen is a phosphorescence. The phosphorescence may occur from the triplet ^3L_a level which can be excited in two ways: either as a result of a singlet-singlet transition at $\lambda \approx 230$ nm (corresponding to the ^1L_a absorption band) followed by an intercombinational conversion to the triplet level, or by a singlet → triplet transition. The probability of the last is obviously much less than that of the singlet → singlet transition, nevertheless the $S_0 \rightarrow T_1$ transition in benzene and its derivatives leading to phosphorescence can be observed (McGlinn et al., 1969). The energy of the $S_0 \rightarrow T_1$ transition can be estimated

from the position of the band ^1L_a in ibuprofen (45400 cm^{-1} or 225 nm) and the average value of 18000 cm^{-1} for the splitting ^1L_a-^3L_a in the methyl derivatives of benzene. On the basis of the estimates obtained, the conclusion can be drawn that the transition $S_0 \rightarrow T_1$ occurs at 27400 cm^{-1} or 365 nm. Thus, the observed light emission of ibuprofen at 77 K may be due to the phosphorescence excited at 365 nm as a result of the $S_0 \rightarrow T_1$ transition.

As can be seen from Fig. 5, the mechanical activation with PEG produces not only an increase in the intensity of the absorption spectra due to the increased concentration of ibuprofen in the solution, but also brings about changes in the short-wave region of the band ^1L_b. The change in the short-wave region of the spectrum may be due to the intermolecular interaction of PEG with ibuprofen. An increase in the solubility of ibuprofen in water in the presence of PEG is also indicative of the formation of a complex between these compounds, as suggested earlier (Mohamed et al., 1985).

As in the solution, changes were observed in the vibrational structure in the short-wave region of the luminescence spectra of the ibuprofen-PEG mixtures subjected to compacting (Fig. 6): the bands due to the stretching vibrations of benzene in the 1570–1610 cm^{-1} region broaden alongside the bands due to the deformational vibrations of

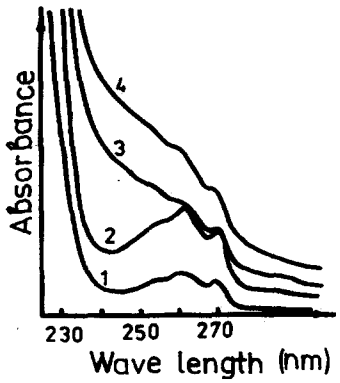

Fig. 5. The absorption spectra of aqueous solutions of ibuprofen intact (1) and mechanically activated (2), of the physical mixture of ibuprofen and PEG 4000 (1:10) (3), and of the mixture of ibuprofen and PEG 4000 (1:10) mechanically activated (4).

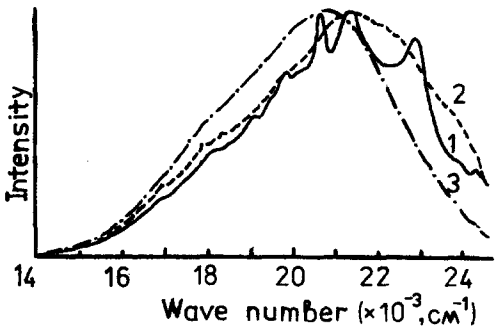

Fig. 6. The luminescence spectra of the ibuprofen-PEG 4000 (1:19) physical mixture as a powder (1), pressed tablet (2), mechanically activated (3).

the C–C–H groups. Besides, the luminescence band shifts to the red region of the spectrum. It should be noted that the preliminary pressing of both the starting ibuprofen and its mechanically treated mixtures with PEG has no effect on their luminescence spectra. Changes in the structure of absorption bands and luminescence, associated with electron transitions in the benzene ring, may point to the intermolecular interaction between PEG and the benzene ring of ibuprofen. It does not seem that the formation of a weak hydrogen bond between the carboxyl group of ibuprofen and the hydroxyl or ester group of PEG results in the changes of electronic structure of benzene ring.

A consideration of the geometry of the ibuprofen molecule shows that the substituents can be *cis* and *trans* located in positions 1 and 4 of the benzene ring with respect to the benzene ring (Fig. 7). Taking into account that the interaction of ibuprofen with PEG proceeds probably not only with the participation of the carboxyl group of ibuprofen and the end hydroxyl group of the polymer, but also includes a van der Waals interaction between PEG and the aromatic ring, one may expect that the intermolecular interaction with PEG is more vigorous for the *trans*-isomer of ibuprofen. Therefore, it is suggested that in the interaction with PEG ibuprofen is predominantly in *trans*-conformation.

Fig. 8, Fig. 9, Fig. 10 show the dissolution curves of the ibuprofen-PEG solid dispersions obtained, with PEG of different molecular

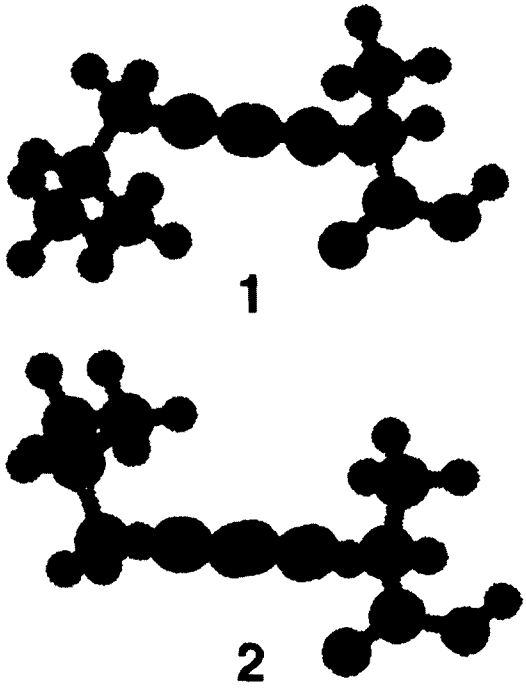

Fig. 7. *Cis*- (1) and *trans*- (2) forms of ibuprofen molecule.

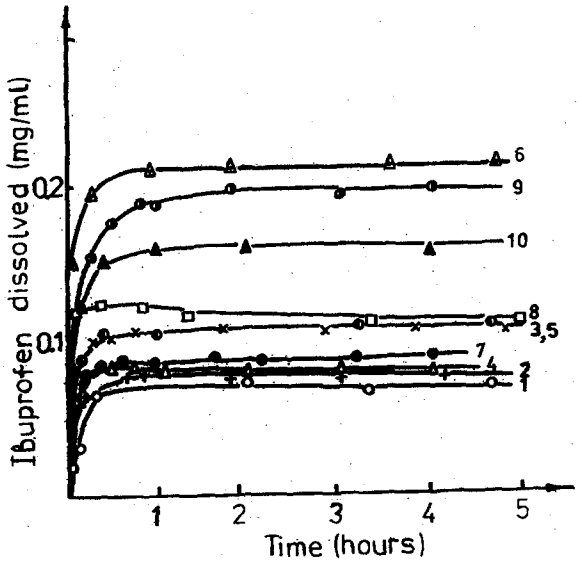

Fig. 9. Dissolution profiles of ibuprofen, pure drug (1); ibuprofen-PEG 4000 physical mixtures, 1:1 (2) and 1:19 (3); ibuprofen-PEG 4000 samples, 1:1 (4) and 1:19 (5) prepared by the conventional melting method and 1:19 (6) prepared by prolonged exposure above the melting point; ibuprofen-PEG 4000 mixtures, 1:1 (7), 1:10 (8), 1:19 (9) and 1:25 (10) mechanically activated for 12, 12, 4 and 4 min, respectively.

weights. It can be seen from the figures that the rate of release of drug depends both on the molecular weight of PEG and on the content of the constituents in the mixture. The best results were obtained for solid dispersions containing PEG 4000 and 6000. It should be noted that samples with a large PEG content (1:25 for PEG 4000 and

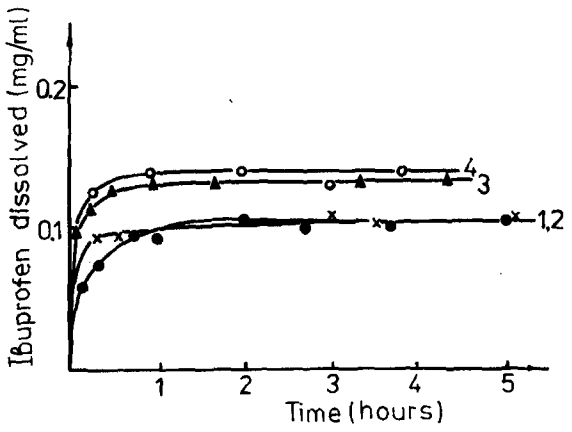

Fig. 8. Dissolution profiles of ibuprofen-PEG 1500 mixtures 1:1 (1), 1:7 (2), 1:10 (3), 1:19 (4) mechanically activated for 12 min.

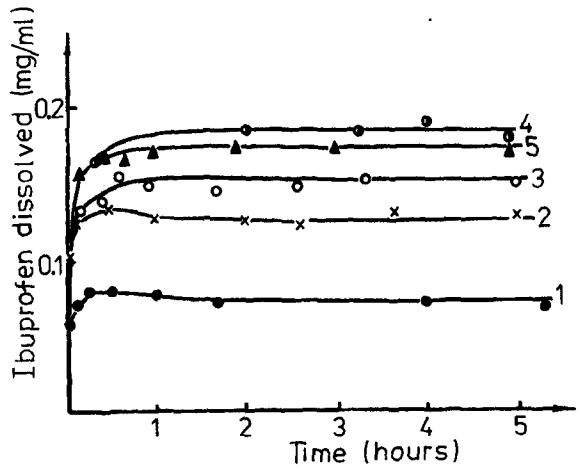

Fig. 10. Dissolution profiles of ibuprofen - PEG 6000 mixtures 1:1 (1); 1:10 (2), 1:19 (3), 1:29 (4), 1:39 (5) mechanically activated for 12, 12, 10, 4, 4 min, respectively.

1:39 for PEG 6000) do not have sufficiently high rate of release of the drug. This appears to be associated with the formation of a solution of high viscosity and diffusion difficulties in solution.

When using PEG 1500, we failed to prepare samples with sufficiently high release rate. This may be attributed to the peculiarities of the mechanical properties of the carriers used. Thus, due to the wax-like nature of PEG with a low molecular mass, the samples prepared by mechanical treatment of the mixtures containing PEG 1500 were a viscous plasticine-like mass.

As can be seen from Fig. 9, the solubility of the physical mixtures ibuprofen:PEG, 1:1 and 1:19, exceeds the solubility of the starting ibuprofen, the effect being larger as the PEG content of the mixture increases. This is in accordance with the model of solubilization proposed Goldberg et al. (1966).

Since in the literature (Mohamed et al., 1985; Najib and Salem, 1987) data are available on increasing the rate of release of ibuprofen from solid dispersions obtained by the melting method, it was of interest to compare samples prepared by mechanical treatment with samples obtained by the melting method. X-Ray phase analysis has shown that the samples obtained are the mixtures of the starting crystalline phases of ibuprofen and PEG. The slow cooling and rapid quenching yield one and the same result. Besides peaks of starting ibuprofen (melting point, 73°C) and PEG (melting point, 54°C), the thermograms of the samples obtained (Fig. 11) show a peak which appears at a constant temperature (45°C) for this system. It is associated with the melting of a eutectic mixture containing 30–35 weight% of ibuprofen.

The rate of release of ibuprofen from the samples obtained by melting, including the sample of the eutectic composition, was lower than the rate of release of the drug from the samples obtained by mechanical activation (Fig. 9). The solubility of the samples prepared by the melting method did not exceed the solubility of the physical mixtures of the same composition. However, for the sample (with an ibuprofen:PEG ratio of 1:19) prepared by holding the melt in a heat chamber at about 80°C for a long time, the rate of release of the drug was as high as in the case of mechanically treated samples (Fig. 9). The X-ray phase analysis data show that, in contrast to the samples prepared by conventional techniques, this sample contains no crystalline ibuprofen phase. Apparently, as a result of prolonged exposure at a temperature above the melting point, an interaction occurs between the constituents of the mixture leading to the amorphous product.

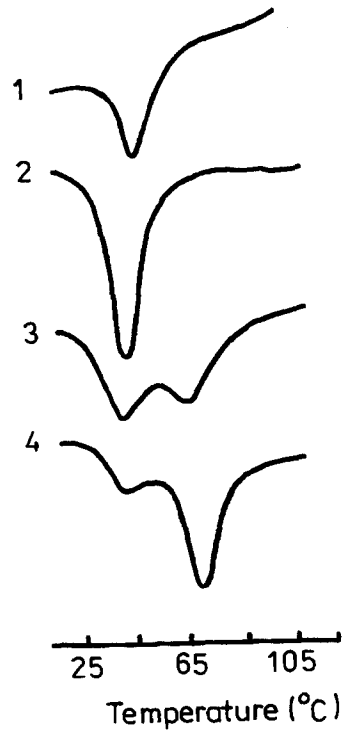

Fig. 11. The DTA thermograms of ibuprofen-PEG 4000 mixtures containing 5 (1), 30 (2), 60 (3) and 93 (4) weight% of ibuprofen (sample masses, 200 mg).

The results obtained suggest that during mechanical activation, an interaction occurs between the carboxyl group and also the aromatic part of the ibuprofen molecule and PEG. As a result of the interaction of the components, the prepared samples show an elevated release rate of the drug comparable with that for the melting mixture observed. Since only prolonged exposure at 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 prepa-

ration of solid dispersions in the ibuprofen-PEG system.

Acknowledgements

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