# Mechanochromism of Indomethacin in Mixtures with Polymers

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## Abstract

Effect of mechanochemical activation on the properties of indomethacin were investigated. The occurrence of the dynamics of indomethacin molecules was revealed by means of NMR. Possible nature of this phenomenon was proposed. Investigation of the mechanochromism of indomethacin in mixtures with different polymers demonstrated that the appearance of colouring is independent of the occurrence of indomethacin interaction with auxiliary components but the colouring is unstable in the absence of interaction.

**Key words:** indomethacin, molecular dynamics, mechanical activation, polymer carriers

## INTRODUCTION

Mechanochromism is known as the change of colour of solids under the action of mechanical strain [1–4]. This phenomenon may have different nature; as a rule, it is connected with polymorphous transformations and changes of molecular configurations. We assumed in our previous works [5, 6] that piroxicam becomes yellow during mechanical treatment as a result of tautomer transition of molecules into the zwitterion form. The authors of [4] proved that piroxicam gets transformed into the zwitterion form during the treatment in the cryogenic mill. It was also stated in the work that indomethacin becomes yellow during grinding, which is likely to be connected with the transition of the molecules of medical substance into the zwitterion state, similarly to the case of piroxicam. Pressing of the mixtures of indomethacin with polyvinylpyrrolidone and polyethylene glycol under the action of ultrasonic treatment also resulted in the appearance of yellow colour of samples [7, 8]. In the opinion of authors, this is connected with the destruction of the crystal structure of medical substance and the formation of amorphous phase as a thin film on the polymer surface.

Investigation of mechanochromism in molecular crystals is interesting from the viewpoint of establishing the effect of mechanical activation on the reactivity of solids. Nonsteroid antiphlogistic preparation indomethacin is widely used at present as a model pharmaceutical substance to study amorphization, solubilization, and interaction with excipients. Investigation of the effect of mechanical strain on indomethacin showed that the treatment in a vibratory mill at room temperature causes only partial amorphization of the preparation [9, 10] while cryogenic comminution causes a complete transformation of indomethacin into the amorphous state [11]. It was discovered that the mechanical treatment of amorphous indomethacin in a ball mill under definite conditions can lead to its crystallization [12].

Mechanical treatment of medical substances with auxiliary compounds allows one to obtain mechanocomposites – solid dispersed systems characterized by increased biological availability and stability of pharmaceutical substances [6]. Polymers – polyvinylpyrrolidone (PVP) and polyethylene glycol (PEG) – are frequently used to obtain solid dispersed systems of pharmaceutical substances, including indomethacin [13]. The antiphlogistic activity of solid dispersions of indomethacin with PVP and PEG is higher and the ulcerogenic effect is lower than for the pure medical substance [14]. It was shown that the treatment of the mixtures of indomethacin with PVP in a ball mill, either at liquid nitrogen temperature or at room temperature, causes the formation of vitreous solutions [15, 16]. In solid dispersions with PVP prepared through solvent evaporation, indomethacin is also present in the amorphous state within the whole concentration range [17–19]; during its interaction with PVP, hydrogen bonds are formed between the hydroxyl group of indomethacin and the carbonyl group of the polymer [20]. In the case of solid dispersions of indomethacin with PEG obtained by means of solvent evaporation, the results of spectroscopic studies provide evidence of the absence of any interaction between the components [21], while increased solubility is due to the solubilising action of the polymer and changes of the surface characteristics of the medical substance.

The goal of the present work was to obtain the composites of indomethacin with polymers using mechanochemical methods and to study mechanochromism in these systems. For comparison between the effects of different polymers on the properties of indomethacin, in addition to the mechanocomposites with PVP and PEG we also obtained the composites with polypropylene (PP).

## EXPERIMENTAL

Indomethacin from Fluka Co. (Switzerland), polyvinylpyrrolidone ($M_r$ = 360 000) from Sigma Co. (USA), polyethylene glycol ($M_r$ = 4000) from Merck Schuchardt OHG (Germany), polypropylene ($M_r$ = 250 000) obtained at the Institute of Catalysis, SB RAS, according to the original technology were used in the work. All the reagents were used without preliminary purification of drying.

Mechanical treatment of initial components and the mixtures of indomethacin with polymers was carried out in a planetary centrifugal mill AGO-2 with water-cooled cylinders. The volume of steel cylinders was 40 mL, the acceleration of milling bodies (steel balls) at the moment of leaving the cylinder walls was 20*g*, ball diameter was 6 mm, the mass ratio of the sample under treatment to the balls was 1 : 30. The ratio of indomethacin to polymer in the mixtures under investigation was 1 : 1 and 1 : 3 (by mass). Treatment time was varied from 15 to 60 min.

The samples of mechanically activated indomethacin for NMR studies were obtained by treatment in the vibratory mill SPEX 8000 (CertiPrep Corp., USA) using the cylinder ($V$ = 40 mL) and milling bodies (2 sp., $d$ = 10 mm) made of tungsten carbide, thus ensuring the absence of microamounts of iron in the sample, which could cause broadening of the lines in NMR spectra.

Analysis of indomethacin after mechanical treatment was carried out by means of high-performance liquid chromatography (HPLC) with a Milikhrom A-02 chromatograph (Ekonova Co., Russia) with UV detector. Chromatographic conditions: ProntoSIL column, 120-5C18 AQ 2.0 × 75 mm, mobile phase $H_2O$(A)–$CH_3CN$(B), gradient mode 0–1000–15000 mL (75–100–100 % B). The solutions of indomethacin in ethanol with the concentration equal to 6 mg/mL, which is close to the level of saturation, were used for investigation, The presence of oxidation products was checked by comparing with the sample subjected to heating at 175 °C for 1 h.

X-ray phase analysis was carried out with a D8 DISCOVERER diffractometer with two-coordinate detector (Bruker Co., Germany) using Cu$K_\alpha$ radiation; 2θ = 5–40°. The degree of crystallinity was determined by comparing the diffraction patterns of completely amorphous and partially amorphous substance according to the method described in [22].

The $^1$H NMR spectra of powdered indomethacin samples were recorded with the help of an automated spectrometer RYa-230 at the Larmor frequency of $\nu_L$ = 23.5 MHz under normal conditions. To increase the signal to

noise ratio, the mode of spectrum accumulation was used.

Optimization of the geometry of indomethacin molecules was carried out using the spin-restricted method of the theory of density functional implemented within the software package LDA (VWN [24]) and the gradient exchange functional GGA [25, 26]. The expanded basis TZ2P without the spanning potentials was used as the basis wave functions for the description of all the atoms of indomethacin.

The IR spectra were recorded by means of the broken complete internal reflection within frequency range 4000–500 $cm^{-1}$ using a Varian Excalibur 3100 FT-IR spectrometer without sample pressing.

The electron spectra of diffuse reflection (ESDR) were recorded with a Shimadzu UV-250IPC spectrometer with the attachment of diffuse reflection ISR-240A with respect to the reflection standard $BaSO_4$. The position of the edge of absorption band of indomethacin was determined after the spectra were normalized with the equation of tangent at the inflection point.

To measure the solubility of the samples, we used the solubility tester DS 705 (Varian). A weighed portion of the sample containing indomethacin in excess was placed into a vessel with water thermostated at (37±0.5) °C. After definite time intervals, samples were taken and indomethacin concentration in solution was determined using a Cary 50 UV-Vis spectrophotometer (Varian Inc., USA).

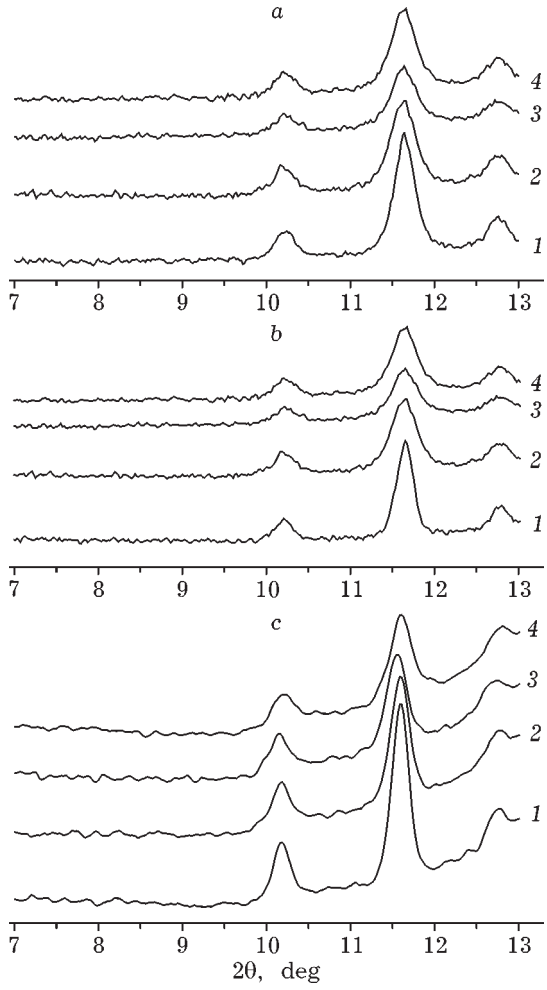



Fig. 1. Diffraction patterns of indomethacin (*a*) and its mixtures at a mass ratio of 1 : 3 with PEG (*b*) and PP (*c*) after mechanochemical activation for 15 (*1*), 30 (*2*), 45 (*3*), 60 min (*4*).

## RESULTS AND DISCUSSION

### *Effect of mechanical treatment on indomethacin*

The HPLC investigation of the stability of medical substance under the action of mechanical treatment showed that indomethacin after treatment in AGO-2 mill is identical to the initial substance (impurity content: less than 0.05 %). Indomethacin was present in the form of γ-modification [27] and did not undergo phase transitions during mechanical activation. Mechanical treatment causes broadening of the X-ray peaks of indomethacin and a decrease in their intensities, which is the evidence of a decrease of crystallite size and partial amorphization of the medical substance. At the initial stage, the degree of sample crystallinity decreases but after 45 min a reverse process is observed (Figs. 1, *a* and 2), which can be connected with annealing of the reaction mixture with the heat released during the treatment.

The $^1H$ NMR spectrum of γ-indomethacin (Fig. 3, *a*) is a superposition of a broad absorption band and a narrow central line the width of which is equal to modulation amplitude, while its intensity is less than 1 % of the total area of the absorption spectrum. Thin line can be attributed to the signal of adsorbed moisture on the surface of γ-indomethacin microcrystals, and we may neglect the contribution from it. The shape of a broad band of NMR absorption is characteristic of the NMR spectra of solids that can be described in the ma-

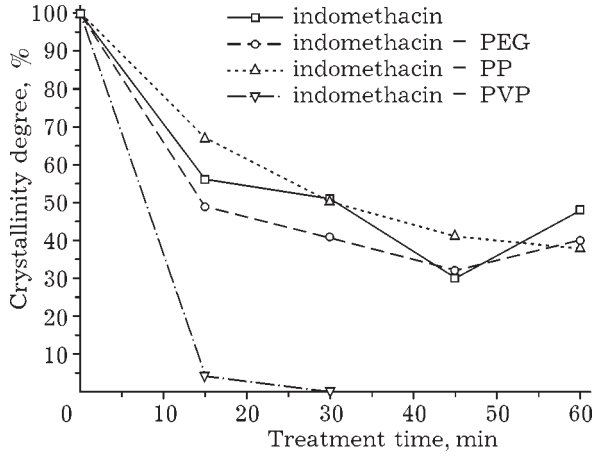



Fig. 2. Changes of the degree of crystallinity during mechanical activation of indomethacin and its mixtures at a ratio of 1 : 3 with PEG, PP and PVP depending on treatment time.

jority of cases by Abraham's function (a convolution of the Gaussian with a triangle) [28]. The shape of $^1$H NMR spectrum of the mechanically activated sample of γ-indomethacin (see Fig. 3, *b*) is essentially different from the $^1$H NMR spectrum of the initial sample. The major parameter characterising the difference between the two spectra is their half-width ($\Delta f$) equal to the distance between the steepness maxima, while the second moments (mean square width) of the spectra differ less substantially (Table 1). It may be assumed that after mechanical treatment changes affected only a part of the sample. The second moment of the Gaussian curve ($M_2$) is linked with the half-width as $\sigma^2$, so the second moment of the spectrum of the affected part of the sample may perhaps be about 3.8 G$^2$. Therefore, the changes affected about 20 % of the sample.

If we assume that a part of the broad absorption band within the frequency range above $\Delta f \approx 25$ kHz relates to the $^1$H NMR signal of γ-indomethacin with non-distorted molecular structure (corresponding to the spectrum shown in Fig. 3, *a*), it is possible to estimate what part of the sample remains unaffected. If we subtract the spectrum shown in Fig. 3, *a*, with the corresponding coefficient, from the spectrum shown in Fig. 3, *b*, it is possible to reveal the difference curve which is to be related to the component of γ-indomethacin spectrum with non-distorted molecular structure (see Fig. 3, *c*).

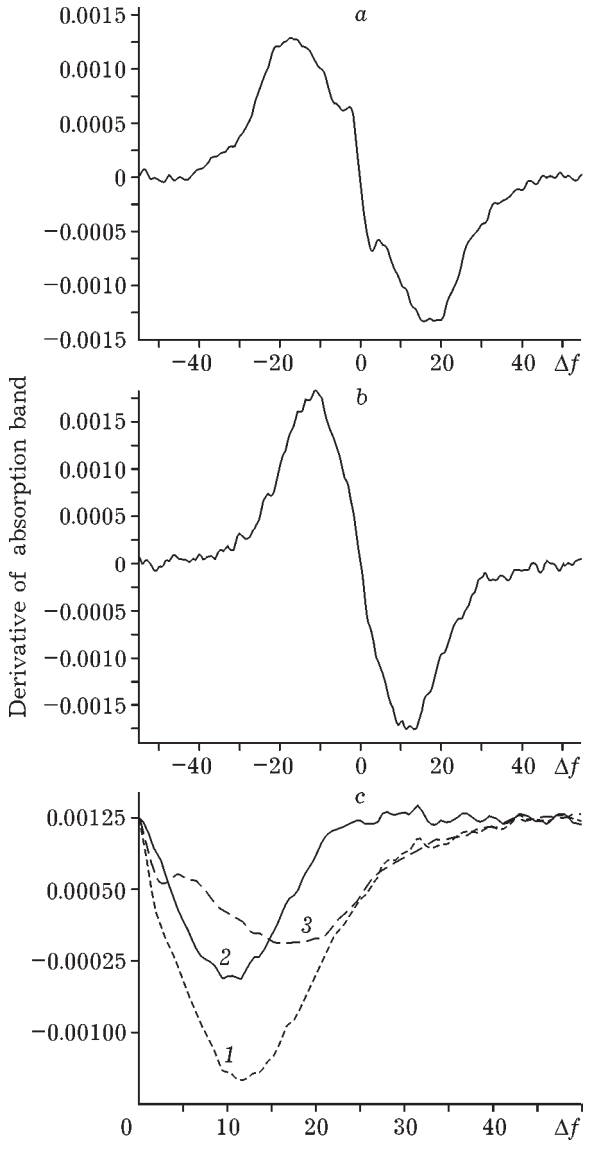



Fig. 3. $^1$H NMR spectra: *a* – initial γ-indomethacin; *b* – treated in the mill for 30 min; *c* – extracted component of the spectrum of mechanically activated indomethacin (*1*), corresponding to the affected (*2*) and non-affected (*3*) parts of the sample.

TABLE 1

Second momentum ($\Delta f$) and half-width ($M_2$) of $^1$H NMR spectra of initial γ-indomethacin and the sample treated in the mill for 30 min

| Sample | $\Delta f$, G | $M_2$, G$^2$ |
|---|---|---|
| Initial | 8.7 | 9.8±0.5 |
| Mechanically activated | 5.4 | 8.5±0.5 |

The square mean width of this component is $M_2 = (3.5 \pm 0.5)\ G^2$, while its fraction in the spectrum is equal to (33±0.5) %, which agrees with the estimated value obtained from the half-widths of the spectrum.

The major contribution into the second moment of the spectrum is made by the most closely located pairs of hydrogen atoms, so the essential changes of the second moment can cause oscillations of the axes of reorientation of $CH_3$ groups and the H–H directions of $CH_2$ groups. The results of the analysis of the resulting NMR spectra and quantum chemical calculations reported in [29] provide evidence of the intramolecular mobility in indomethacin molecules. This mobility is connected with the jump transitions between conformers accompanied by swinging of the $C_3$ axes of methyl groups of indomethacin.

The established dynamics is likely to affect only the surface layers of microcrystals of mechanically activated γ-indomethacin, in which the fraction of molecules increases with grinding, while the internal regions remain unaffected.

The IR spectra of mechanically activated indomethacin samples exhibit changes of absorption bands in the region of bending vibrations of aromatic rings (below 700 $cm^{-1}$) (Fig. 4). At the same time, in the region of the stretching vibrations of functional groups the changes are less clearly pronounced: only broadening of bands is observed, which is connected with a decrease in sample crystallinity. Such behaviour of the bands in the region of bending vibrations is the evidence of distortions of molecular configuration of indomethacin under mechanical treatment.

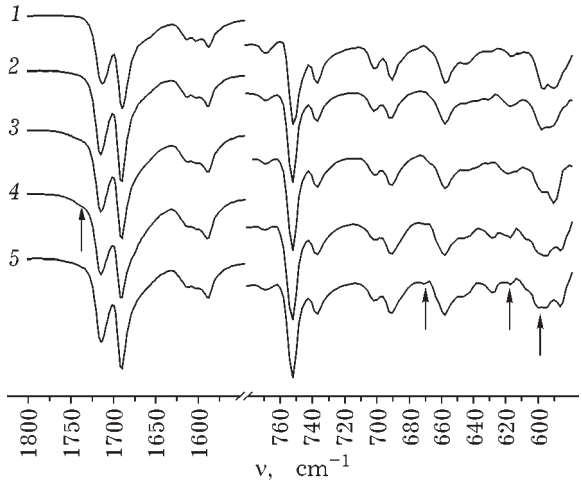



Fig. 4. IR spectra of initial indomethacin (*1*) and after mechanical activation for 15 (*2*), 30 (*3*), 45 (*4*) and 60 min (*5*).

Mechanical treatment causes changes in the colouring of indomethacin samples, exhibited in the ESDR as a batochromic shift of the absorption band edge (Table 2), which is connected with the change of the electronic state of indomethacin molecules and their molecular structure.

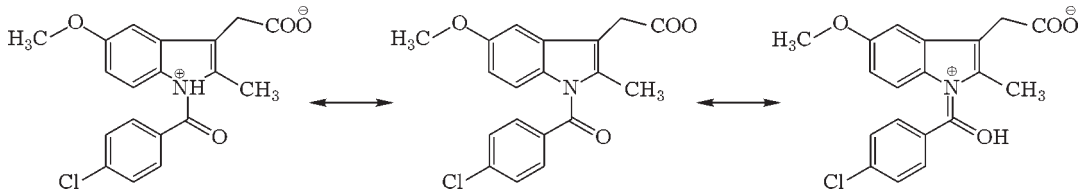
Changes of the molecular structure can lead to changes in the system of conjugated bonds, as it was observed previously for piroxicam [4, 5]. The reason of these changes may be, for example, the formation of the zwitterion form of indomethacin as a consequence of proton transfer from the carboxylic group to nitrogen or oxygen atom (Scheme 1). Quantum chemical calculations showed that both versions of indomethacin zwitterion can occur, but the version with proton transfer to oxygen is more reasonable. Proton transfer may occur through the intermolecular mechanism, similarly to the case

TABLE 2

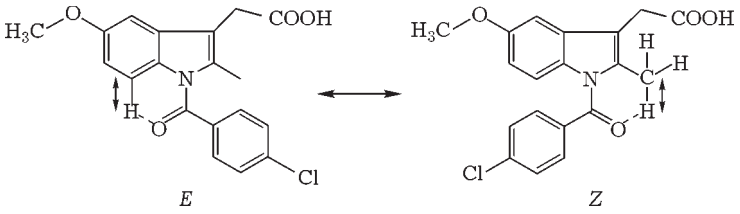
Position of the edge of absorption band in the spectra of indomethacin and its mixtures after mechanical activation, nm

| Sample | Treatment time, min | | | | |
|---|---|---|---|---|---|
| | 10 | 20 | 30 | 40 | 60 |
| Indomethacin (AGO) | 396.7 | 399.6 | – | 421.3 | 421.9 |
| Indomethacin – PVP (1 : 3) (AGO) | – | – | 427.8 | – | 428.3 |
| Indomethacin – PEG (1 : 3) (AGO) | – | – | 396.9 | – | 396.8 |
| Indomethacin (SPEX) | – | – | – | 416.6 | – |
| Indomethacin – PP (1 : 3) (SPEX) | 411.3 | – | – | 408.5 | – |
| Indomethacin – lactose (1 : 3) (SPEX) | 416.5 | – | – | 437.3 | – |

*Note.* dash – not determined.



Scheme 1.



Scheme 2.

previously assumed for piroxicam for which only 8 % of the molecules of medical substance get transformed into the zwitterion form during mechanical treatment [4].

The flat molecular configuration is known to promote the formation of a system of conjugated π-bonds. In γ-indomethacin molecules [27], the chroloobenzoyl and indole groups, each of them having almost flat configuration, are turned with respect to each other by a definite angle. It should be noted that the occurrence of *E*–*Z* configuration transitions (Scheme 2) connected with the rotation of chlorobenzoyl group around the N–C bond is known for the amorphous state of indomethacin (Scheme 3) [30]. In γ-modification, indomethacin molecules are in the stable *Z* configuration, so any rotation is hindered. In the case of mechanically treated indomethacin which is partially in the amorphous state, the molecules may be in the configurations non-typical for the crystal structure. It may be assumed that a part of molecules have the flat configuration, and this will promote the formation of the conjugated system, including the zwitterion state.

The main hypothesis put forward previously to explain the appearance of colouring in indomethacin was the effect of amorphization on the formation of the coloured state of medical substance [7, 8]. Indeed, the rotation of the chlorobenzoyl group would proceed much easier in the amorphous state [30]. However, the shift of the absorption band edge in ESDR of mechanically activated indomethacin does not correlate with the degree of crystallinity (see Figs. 1, 2 and Table 2). This may be connected with the inertia of the system and an increase in the concentration of coloured centres in the amorphous part of the sample after the start of crystallization.

### *Mixtures of indomethacin with PVP*

During the mechanical treatment of the mixtures of indomethacin with PVP, the reflections of indomethacin completely disappear from the diffraction patterns after the action for 30 min (see Fig. 2). This is the evidence of the distribution of the medical substance in the polymer as a result of mechanical treatment.

The IR spectra of the mixtures after mechanical activation exhibit broadening and the hypsochromic shift of absorption bands $\nu_{C\text{-}O}$ and $\nu_{C=O}$ of the carboxylic group of indomethacin, and a bathochromic shift of the maximum of the carbonyl absorption band in PVP in comparison with the spectra of components (Fig. 5, curves *3* and *4*). Similar changes in the IR spectra of dispersed systems of indomethacin with PVP obtained by solvent evaporation were related by the authors of [20] to the formation of hydrogen bonds between the hydroxyl group of indomethacin and the carbonyl group of PVP.

As a result of mechanical treatment, the mixtures of indomethacin with PVP became bright-yellow, which is confirmed by the shift of the edge of absorption band in the ESDR (see Table 2). It should be noted that the carriers used do not have their own absorption in the region above 300 nm and thus they cannot

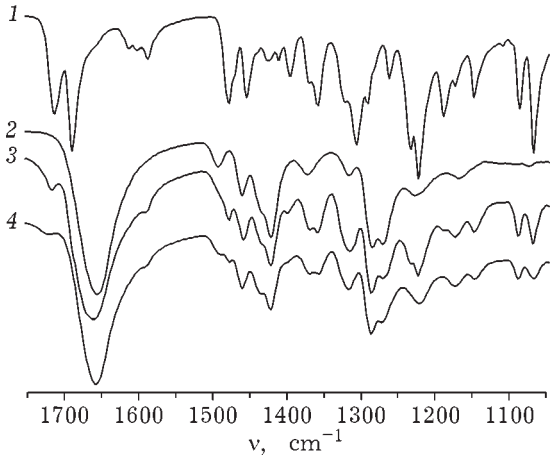



Fig. 5. IR spectra of initial indomethacin (*1*), PVP (*2*) and mixtures of indomethacin with PVP (1 : 3) activated for 15 (*3*) and 30 min (*4*).

affect the position of the absorption band edge. The formation of zwitterions is likely to proceed easier in polar environments with high permittivity. The high hygroscopic ability of PVP is likely to provide the presence of the sufficient amount of water in the matrix, which simplifies the formation of the zwitterion form of indomethacin. The presence of PVP leads to the stabilization of the coloured state of indomethacin, while for pure indomethacin we observe the disappearance of the yellow colour after exposure at 80 °C for 10 min; the colour is more stable when the mechanically activated mixtures of indomethacin with PVP are heated. Crystallization of the medical substance does not occur during this process.

### *Mixtures of indomethacin with PEG*

X-ray phase studies showed that the reflections of indomethacin broaden and their intensity decreases during mechanical treatment of the mixtures of indomethacin with PEG. After activation for 45 min, a reverse process is observed: the degree of indomethacin crystallinity increases (see Figs. 1, *b* and 2). So, amorphization of indomethacin in the presence of PEG proceeds similarly to the amorphization of the pure preparation.

Unlike for the mixtures with PVP, crystallization of indomethacin is observed during the storage of mechanically activated mixtures. For example, after storage for 1 month, the degree of crystallinity of the medical substance reached 70 %. This may be connected with the lower vitrifying point of PEG in comparison with PVP, hence, with the higher mobility of molecules. The IR spectra of mechanically activated mixtures of indomethacin with PEG did not exhibit any changes of the positions of the bands of stretching vibrations of functional groups. On this basis, it may be concluded that chemical interaction – the formation of hydrogen bonds between indomethacin and PEG – does not occur.

Mechancially activated samples exhibited almost no changes of colour; the shift of the absorption band edge in ESDR was smaller than in the case of pure indomethacin (see Table 2). The absence of colour changes in the case of mixtures with PEG can be connected with the low concentration of coloured centres due to the low degree of amorphism of the medical substance and its dilution with the polymer. In addition, it may be assumed that due to the low melting point, PEG may melt during mechanical treatment, which results in coating indomethacin particles with the polymer layer.

### *Mixtures of indomethacin with PP*

To compare the behaviour of indomethacin in mixtures with polymers, we used crystal polymer polypropylene (PP) that has no functional groups for interaction with indomethacin. Investigation of mechanically activated mixtures by means of IR spectroscopy did not reveal any changes in the positions of the absorption bands related to C=O and C–O groups of indomethacin. The mixtures with PP after mechanical activation had bright-yellow colour, which allows us to assume that the occurrence of hydrogen bonds between the components is not a sufficient condition for indomethacin colouring. However, in the case of PP heating of the samples at 80 °C for 10 min causes almost complete disappearance of colouring, which also confirms the assumption concerning the role of hydrogen bonds in the stabilization of disordered state of indomethacin.

The degree of crystallinity of indomethacin at the initial stages of mechanical activation decreases more substantially than in the case of pure indomethacin and its mixtures with PEG. However, no recrystallizaiton effects are

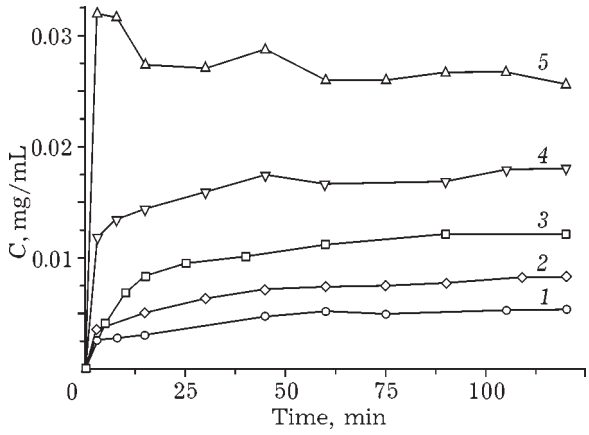



Fig. 6. Dissolution curves for initial (*1*), activated (*2*) indomethacin and its mixtures with PP (*3*), PVP (*4*) and PEG (*5*).

observed in the case when PP is used, and the degree of crystallinity of indomethacin and its mixtures with PEG and PP is approximately the same after the action for 80 min (see Figs. 1, *c* and 2).

The use of PP as the inert additive allows us to establish its effect on the solubility of the medical preparation. For comparison, Fig. 6 shows the curves of indomethacin evolution from mechanically activated mixtures with PP and the curves of indomethacin dissolution in mixtures with PVP and PEG. One can see that the presence of an inert additive affects the solubility of the medical substance. The achievement of higher concentrations (in comparison with indomethacin) at the initial stages of dissolution of the mixtures with PP is likely to be promoted by its distribution over the surface of the carrier. However, polypropylene, unlike PVP and PEG, in insoluble in water, so it cannot increase the solubility of indomethacin through the formation of molecular complexes or due to slowing down the reverse crystallization of the medical substance in solution because of increased viscosity.

## CONCLUSION

The differences between the mechanically activated mixtures of indomethacin with different polymers were established. In the case of mechanical activation of indomethacin with PVP, the medical substance becomes X-ray amorphous rather rapidly, while partial amorphization occurs during the treatment with PEG and PP. No formation of hydrogen bonds between the medical substance and the polymer was established for the case of the mechanical treatment of indomethacin with PEG and PP, and unlike for PVP these polymers during storage do not slow down crystallization of the medical substance. The colour of indomethacin changes during mechanical treatment, which can be connected with the change of the molecular structure of the medical substance. The appearance of colouring is likely to be due to disordering of the crystal structure of indomethacin. The formation of hydrogen bonds with PVP inhibits crystallization of indomethacin and promotes longer conservation of the medical substance in the coloured state. No changes of colour are observed in mechanically activated mixtures of indomethacin with PEG. Experiments with PP as an inert additive showed that the appearance of colour is not connected with the interaction of indomethacin with auxiliary substances, however, colour is unstable in the case when such an interaction is absent.

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