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GRINDING OF DRUGS WITH PHARMACEUTICAL EXCIPIENTS AT CRYOGENIC TEMPERATURES
Part II. Cryogenic grinding of indomethacin–polyvinylpyrrolidone mixtures

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The effect of cryogenic grinding on the indomethacin (IMC) and its mixtures with polyvinylpyrrolidone (PVP) was studied by powder X-ray diffraction and differential scanning calorimetry. Cryoground mixtures were shown to form glass solutions. PVP inhibits the crystallization of IMC from the amorphous state: the crystallization temperature of IMC in the mixtures with PVP increases, and the amorphous state is preserved longer on storage. The mixtures were characterized by Raman spectroscopy. Dissolution of the IMC in the cryoground mixtures is higher as compared to the pure form, also after a prolonged storage.

Keywords: *cryogrinding, crystallization, glass solution, glass transition, indomethacin, polyvinylpyrrolidone*

Introduction

Excipients are often added to drugs in pharmaceutical formulations, in order to enhance their compactibility, and/or solubility, and bioavailability [1–8]. Drug-excipient dispersions can be prepared using different procedures, such as co-precipitation from solutions, co-melting and co-grinding.

Co-grinding of drugs with excipients often gives amorphous solid dispersions, which differ in their properties from those obtained by co-precipitation or co-melting [9]. Co-grinding of compounds having very different values of their glass transition temperatures (T_g) is an efficient way to get a homogeneous amorphous sample having one single value of T_g in the range between the two extreme values corresponding to the single pure compounds [10, 11]. In this way, one can control the glassy state, the properties and the stability of the system.

In the last years, cryogenic grinding (as an alternative to room temperature grinding) attracts much attention, as an even more efficient tool of stabilizing metastable and amorphous forms of drugs [12–14]. More generally, grinding a compound far below its T_g often converts the compound to its amorphous state [15]. Still, there are not so many examples so far, when grinding at room temperature was compared with cryogrinding of the same system. In our previous publication [14], we have discussed the results of studying cryogrinding in the piroxicam–PVP system, which were different from those obtained for grinding the same system at room temperature [16, 17]. In the present work we report on the results of the cryogenic grinding of the mixtures of PVP with another drug, which is often used as a model system, to study polymorphous transformations and amorphization of drugs [18–33] – indomethacin (IMC).

Similarly to piroxicam, IMC has functional groups, which can form hydrogen bonds with excipients; IMC can exist in a zwitter-ionic form [13], and can form polymorphs [29]. The effect of grinding on pure IMC was studied at room, and at low temperatures [12, 19, 20, 24, 30–32]. Under cryogrinding, crystalline γ-indomethacin transforms completely to the amorphous state, but this state is unstable, and the sample recrystallizes at faster rates relative to the quenched/ground IMC references, crystallizing to 90% after approximately 13–15 h [12, 30]. On grinding of IMC at room temperature for up to 180 min diffraction peaks of the drug persisted with a mere decrease in their intensity [24]. The same was observed in the case of piroxicam: grinding at room temperature never resulted in a complete amorphization of piroxicam [16].

Polyvinylpyrrolidone (PVP) is commonly used to form solid dispersions [1, 4, 8, 25]; it inhibits crystallization of amorphous drugs, as was shown in several papers [21, 23, 26].

In the IMC–PVP system, solid dispersions were obtained previously by solvent evaporation method

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[21–23, 26], by melt extrusion [27], and also by room temperature co-grinding in a vibration mill [4, 25]. In the dispersions prepared by co-precipitation, IMC was present as an amorphous phase over all the composition range. The usage of PVP in amorphous dry coprecipitates with IMC significantly inhibits drug crystallization at levels as low as 1-5% PVP [21, 23, 26]. Using melt extrusion, IMC was prepared as glass solution with PVP at a 1:1 mass ratio [27]. Grinding of the IMC–PVP mixtures at room temperatures resulted in the amorphization of the IMC, which was complete, if grinding was long enough; only one composition, 1:1, by mol, was studied [4, 25].

The structure of the amorphous state of IMC was reported to be very sensitive to the prehistory of the sample: the starting crystalline form, the details of the experimental procedure [30–33]. The same can be expected for IMC–PVP solid dispersions.

Experimental

Indomethacin (Fluka) was used as received. Polyvinylpyrrolidone P-5288 (Sigma) (M_w=360 000) was dried before the experiments at 80–90°C in a vacuum oven for 16–24 h and was stored in the desiccators over phosphorous pentoxide.

Cryogrinding was performed using a cryogenic mill (6750 Freezer/Mill, SPEX CertiPrep, Inc., USA) as described in a previous paper [14]. The mixtures containing 10–80% (*m*/*m*) PVP were prepared. After the freshly prepared cryoground samples were analyzed, they were stored for about a year at ambient conditions, and characterized from time to time by X-ray diffraction.

The powder X-ray diffraction experiments were performed with a Pananalytical X'pert pro MPD diffractometer ($\lambda_{CuK\alpha}$=1.540 Å) in Bragg–Brentano θ–θ geometry. The powder samples were put in a spinning flat sample holder. After storage of the samples at room temperature, the powder X-ray diffraction patterns were measured on a diffractometer D8 GADSS (Bruker), CuK_α–radiation. The degree of crystallization of the drug was estimated roughly based on the area of peak of crystalline IMC at 2θ=11.6° without internal standards. The calibration curve showed good linearity.

The measurement conditions for differential scanning calorimetry (DSC) and temperature modulated DSC (TMDSC) were described in a previous paper [14].

Freshly prepared cryoground samples were used for a Raman spectroscopy study. The Raman spectra were excited with 514.5 nm line of a mixed Argon-Krypton Coherent Laser. Stokes Raman spectra were collected on a XY DILOR spectrometer in backscattering geometry. Spectrometer slits were kept at 300 μm. The spectra were recorded in the 1400–1800 cm^{-1} region in 300 s with a resolution of about 2 cm^{-1}. The size of the sample was approximately 3 μm^2. A total 5 scans were obtained from different places of the sample, thus ensuring the spectra represent information about the whole sample. For a comparison with the cryoground samples, the physical mixtures were prepared by simple mixing of the powders of the amorphous IMC and PVP cryoground separately. Samples were stored at –20°C and brought to ambient conditions just before measurements.

To measure the dissolution, a weighted portion of the sample, containing IMC in excess, was put into a glass vessel containing 50 mL of water, thermostated at 37±0.5°C and equipped with a mixer. After definite time intervals, the concentration of the substance in solution was measured using a Shimadzu UV-240 spectrophotometer.

Results and discussion

Cryogrinding of indomethacin

According to powder X-ray diffraction data, the initial IMC was a pure gamma modification. After cryogrinding for 60 min, a completely X-ray amorphous IMC was obtained (Fig. 1), in accordance with earlier observations described in [12, 30].

The thermogram of the cryoground IMC (Fig. 2) reveals a glass transition at 42.6°C, an exothermic crystallization event at 83.7°C ($T_{c\ onset}$=75.5°C, ΔH_c=36 J g^{-1}), and a melting endotherm at 160.6°C ($T_{m\ onset}$=159.3°C, ΔH_m=103 J g^{-1}). During heating in TMDSC, the glass transition of the cryoground IMC was observed at 45.4°C, which is in a good agreement with earlier reported data [12, 18, 28].

Cryogrinding of indomethacin–PVP mixtures

Figure 1 shows the powder X-ray diffraction pattern of the cryoground 50% IMC–50% PVP mixture.

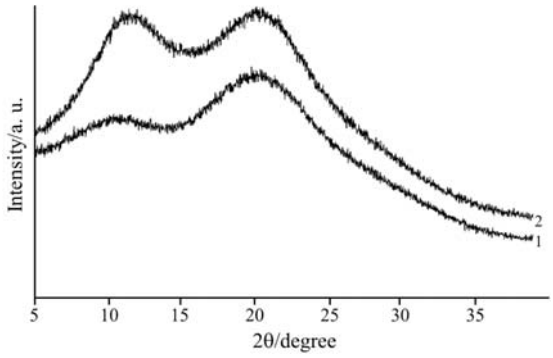

Fig. 1 X-ray diffraction patterns of 1 – cryoground indomethacin and 2 – 50% IMC–50% PVP mixture

The pattern is representative for all the mixtures containing 10–80% PVP, which were amorphous after cryogrinding. For the mixtures containing a large PVP content, less time was needed, to obtain amorphous mixtures; thus, the mixture containing 70% PVP was amorphous after 40 min of cryogrinding. The same was observed for room temperature mechanical treatment (data not shown and will be published elsewhere).

Whereas the simple mixtures of IMC with PVP were colourless, IMC alone and its mixtures with PVP were slightly yellow after cryogrinding, thus suggesting that IMC transformed into zwitter-ions during cryogrinding [13]. This yellow color of the ground IMC–PVP mixture was preserved for a very long time (at least 10 months thus far), whereas the pure cryoground IMC lost its yellow color rather quickly at room temperature. The same was observed during mechanical treatment of IMC at room temperature. X-ray diffraction tests have also shown, that in a cryoground mixture with PVP, IMC is preserved in the amorphous state for up to 10 months thus far, in contrast to pure cryoground IMC. After storage for 2 months the samples containing more than 50% PVP were amorphous as was observed also for the samples prepared by melt extrusion [27]; in contrast, the storage of mixtures containing 10–40% PVP was accompanied by crystallization of the drug into the γ-form identified also by a peak at 1698 cm^{-1} in the Raman spectra. Thus, the crystallinity of the 80% IMC–20% PVP mixture was about 60% after 2 months storage. After 10 months storage, the crystallinity of this sample increased up to 70% whereas the mixtures containing 50-80% PVP were amorphous, diffraction peaks of γ-IMC slightly appearing in the case of 50% PVP (Fig. 3). The samples were of yellow color and the intensity of color correlated with the extent of crystallinity: the less the crystallinity, the more intensive the color. The same was observed for IMC – excipient tablets

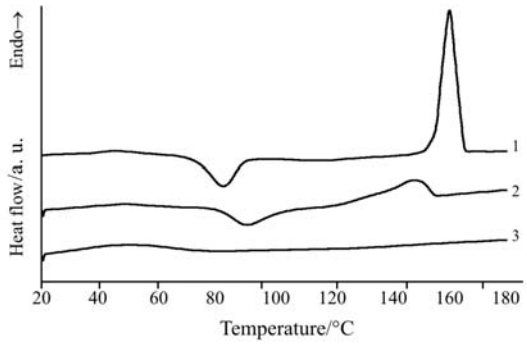

Fig. 2 DSC scans recorded upon heating for cryoground IMC and its mixtures with PVP as prepared: 1 – cryoground IMC; 2 – cryoground 80% IMC–20% PVP mixture; 3 – cryoground 60% IMC–40% PVP mixture

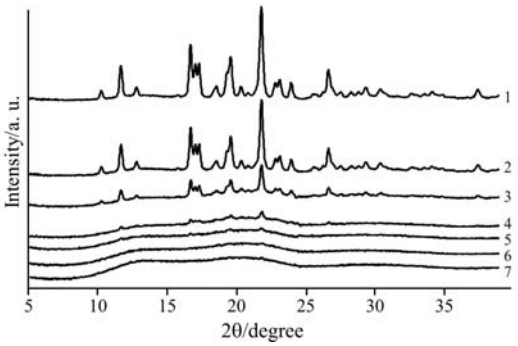

Fig. 3 X-ray diffraction patterns of IMC–PVP cryoground mixtures after storage for 10 months: 1 – 10% PVP; 2 – 20% PVP; 3 – 30% PVP; 4 – 40% PVP; 5 –50% PVP; 6 – 60% PVP, 7 – 70% PVP

compacted with the aid of utrasound [6]. The authors suggested that it is connected with destruction of the crystal lattice of the drug and the formation of an amorphous phase. In the presence of an excipient, re-crystallization was delayed and the color preserved for at least 14 months [6].

In the Fig. 2, the DSC scan 2 corresponds to the heating curve of the freshly prepared 80% IMC–20% PVP cryoground mixture. It is typical for the samples containing small (10–30%) amounts of PVP, and reveals a broad endotherm in the region of 10–60°C due to the removal of the absorbed water, followed by a single recrystallization peak and the melting of IMC. With increasing the concentration of PVP, the melting peak broadened and got smaller, whereas the temperature of the exotherm increased.

The DSC scans for the mixtures containing more than 30% PVP did not reveal any crystallization events (Fig. 2, curve 3). As was shown in [21] for IMC–PVP solid dispersions prepared by the solvent evaporation technique, no crystallization events have been observed at PVP concentrations above 20%. Amorphous forms prepared by grinding usually contain seeds or nuclei of the initial compound, corresponding to the memory of the starting polymorph [12, 16, 32]. This may explain, why a somewhat higher concentration of the PVP was required, to obtain a stable amorphous dispersion by cryogrinding, as compared to solvent-prepared dispersions. This hypothesis is supported by the observation, that the crystallization of the IMC on storage of the cryoground samples at room temperature gave exclusively the γ-indomethacin, whereas the isothermal crystallization of IMC–PVP coprecipitates produced the α-form [21].

Figure 4 shows the heating DSC scans of some of the cryoground IMC–PVP mixtures after drying the samples, which revealed the glass transition in the region of water removal for mixtures containing a low content of PVP. The glass transition temperatures, T_g, obtained by DSC and TMDSC experiments, as well

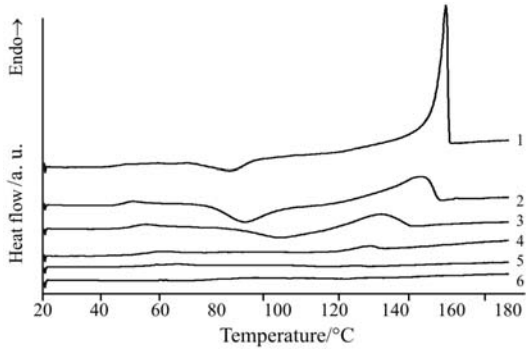

Fig. 4 DSC scans recorded upon heating for IMC–PVP cryoground mixtures after drying: 1 – 10% PVP; 2 – 20% PVP; 3 – 30% PVP; 4 – 40% PVP; 5 – 50% PVP; 6 – 60% PVP

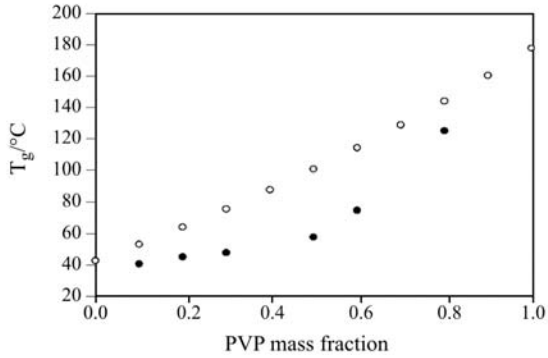

Fig. 5 Glass transition temperatures of IMC–PVP cryoground mixtures plotted *vs.* the mass fraction of PVP: ● – the measured T_g values; ○ – the prediction of the Gordon–Taylor equation

as the crystallization temperatures, T_c, heats of crystallization, ΔH_c, and temperatures of melting, T_m, are summarized in Table 1. The difference between the values of T_g measured for dried mixtures by DSC experiments and for the intact ones measured by TMDSC may be explained by plasticizing effect of water and different ways of measuring.

Only one glass transition located between those for pure IMC and PVP was observed for the cryoground IMC–PVP mixtures, indicating, that the mixing has been performed at the molecular level, giving rise to the glass solutions. In Fig. 5, the T_g's of IMC–PVP mixtures were plotted *vs.* the mass fraction of PVP. Only a slight concentration dependence is observed in the range of 0–0.5 PVP mass fraction, and then the composition dependence increases rapidly. The deviations of the mixtures from ideal mixing were evaluated by a comparison of the experimental T_g values with those predicted by the equation: $T_g=(w_1T_{g1}+Kw_2T_{g2})/(w_1+Kw_2)$, where w_1 and w_2 are the mass fractions of each component, T_{g1} and T_{g2} are the corresponding T_g values of each component. Using the free volume theory, the constant K can be estimated as $K=\rho_1T_{g1}/\rho_2T_{g2}$, where ρ_1 and ρ_2 are the densities of both components (the Gordon–Taylor equation [34]). The densities of the components used in this study were taken from [21]. Figure 5 indicates clearly at the non-ideal mixing of drug with polymer, especially in the region of small contents of PVP. The same effect was observed for piroxicam–PVP system [14]. The system may be not ideal, due to the molecular size effects. When a macromolecule is mixed in small amounts with an amorphous small molecule, it will introduce a considerable excess free volume to the system because of its much larger molecular size. In this situation, the glass transition temperature of the mixture will not be elevated as much as predicted by a simplified theory. Thus, the presence of very low levels of the low-molecular mass additives might have a significant plasticizing effect on the pharmaceutical glasses, whereas adding small amounts of the high-molecular mass additives often had a minimum antiplasticizing effect [35, 36].

IMC-PVP solid dispersions prepared by the solvent evaporation technique exhibited also a single glass transition temperature over all the composition range [21]. In contrast to the results obtained in this study for the cryoground mixtures, the change in the T_g *vs.* the PVP concentration for amorphous IMC–PVP coprecipitates followed the ideal behaviour up to about 50% PVP and above 90% PVP [21]. Mechanical treatment at low temperatures obviously gives samples differing from the ideal mixtures.

Though the T_g practically does not depend on the PVP content in the region of 10–30% PVP, the shift of crystallization temperature was observed (Fig. 4, Table 1). It appears, that the inhibition of drug crystallization by adding small amounts of a higher T_g component cannot be attributed solely to the changes in molecular mobility associated with an increase in T_g. There are several factors, which might contribute to the inhibitory effect of PVP on the crystallization of the drug from the amorphous state [21, 37]. For the drug-polymer coprecipitates, it was shown, that a possible IMC–PVP interaction via the formation of hydrogen bonds may inhibit the nucleation and growth of the γ-form of IMC on crystallization [23]. It is possible also, that other factors, than the formation of hydrogen bonds between the components, might contribute to the inhibitory effect of PVP on the crystallization of the IMC from the amorphous state. For example, during grinding, PVP might accumulate in a high concentration at the surface of the IMC particles, inhibiting the nucleation and the growth of the crystalline phase. Direct scanning electron microscopy observations confirm, that even in simple untreated physical IMC–PVP mixtures the IMC crystals are incorporated into the PVP spheroidal shells [1].

The results obtained by DSC and TMDSC obviously indicate, that an interaction between the PVP and the IMC in the cryoground mixtures does

Table 1 Glass transition temperature, crystallization temperature, heat of crystallization and temperature of melting for IMC–PVP cryoground mixtures obtained by DSC and TMDSC experiments

N	Content of PVP/ *m*/*m*%	Time of grinding/min	DSC					TMDSC
			$T_{g\ onset}$/°C (a.d.)	$T_{c\ onset}$/°C (b.d.)	$T_{c\ max}$/°C (b.d.)	ΔH_c /J g^{-1} (b.d.)	$T_{m\ max}$/°C (b.d.)	T_g/°C (w.d.)
1	0	60	42.6	75.5	83.7	38	160.6	45.4
2	10	60	40.5	78.8	86.5	38	157.7	46.0
3	20	60	45.0	80.5	90.6	33	147.2	46.2
4	30	60	47.6	86.8	101.4	25	101.4	48.4
5	40	60	54.0	–	–	–		55.1
6	50	60	57.5	–	–	–		68.4
7	60	60	74.5	–	–	–		81.0
8	70	42	99.0	–	–	–		86.3
9	80	60	124.7	–	–	–		116.5
10	100	0	177.2 (w.d.)	–	–	–		181.9

a.d. – after drying, b.d. – before drying, w.d. – without drying

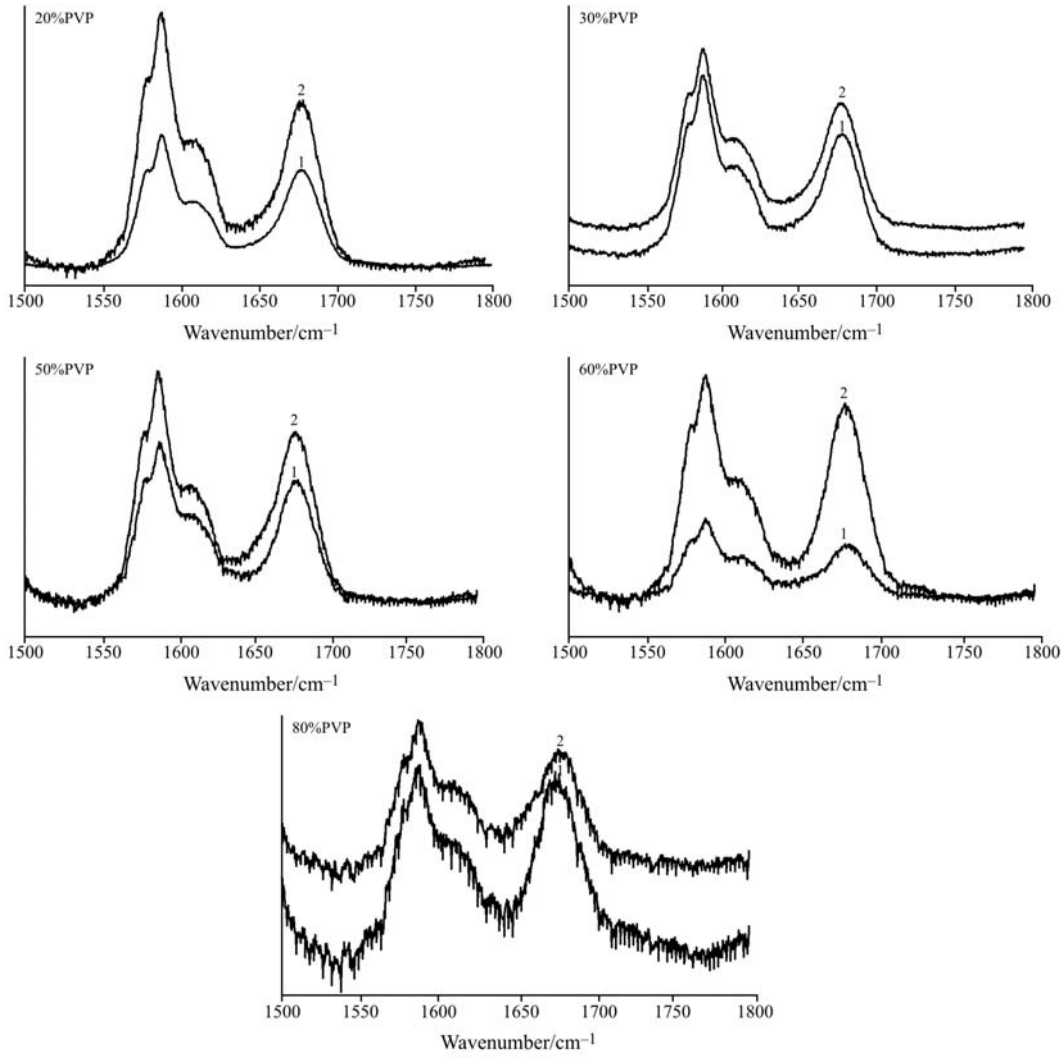

Fig. 6 Raman spectra of IMC–PVP 1 – cryoground and 2 – physical mixtures

exist. This is confirmed also by the X-ray diffraction patterns characteristic for the amorphous state of the IMC, which is being preserved for a much longer time in the cryoground dispersions, than is typical for pure IMC. It is known from the literature, that different experimental techniques are not equally sensitive to the interactions in the drug-excipient systems, and can reveal different types of changes in these systems as compared to pure components [1]. Thus, DSC and color changes can detect signs of interaction at very early stages, already in the untreated physical mixtures, when they are not seen by X-ray powder diffraction, or by vibrational spectroscopy [1]. At the same time, in some publications, the interaction between the IMC and selected excipients was reported to manifest itself also in shifts and broadening of peaks in the IR absorbance spectra [22], or in the NMR-spectra [4, 25], and these changes were interpreted as the formation of the hydrogen bonds between the molecules of drug and of excipient. As examples, one can refer to IR and Raman spectroscopy study of the IMC–PVP dispersions obtained by solvent evaporation [22]; or to a NMR-study of the IMC–PVP and IMC–$Mg(OH)_2$–SiO_2 dispersions obtained by ball milling at room temperature [2, 4, 25].

The Raman spectra measured from powder amorphous samples are characterized by very broad lines [22, 38], and not all the peaks most important for testing the formation of hydrogen bonds between the components are accessible (the IMC acid carbonyl peak is not seen [22, 38] and the PVP carbonyl is coincident with the drug benzoyl carbonyl appearing at 1680 cm^{-1} [22]). Still, it was concluded in [22] based on infrared spectroscopy, that there was no interaction between amorphous IMC and PVP in physical mixtures, but such an interaction could be registered in the solid dispersions prepared by solvent evaporation technique: as the concentration of PVP increased, Raman spectra of the latter dispersions showed a progressive decrease in the peak frequency and peak broadening relative to physical mixtures [22].

We have also measured the Raman spectra of the IMC–PVP mixtures obtained by cryogrinding, to compare our results with those reported in [22]. Figure 6 shows the Raman spectra for IMC–PVP cryoground and physical mixtures in the region of carbonyl vibrations. The spectra of the cryoground samples do not differ from those of physical mixtures of the same composition, despite the fact, that according to the DSC data, the cryoground samples could be characterized as homogeneous glass solutions with a single T_g, different from those of either of the pure components. No peak shifts or broadening could be noticed in the spectra of the cryoground samples, as compared to physical mixtures. Thus, there was no manifestation of the formation of hydrogen bonds between the amorphous indomethacin and the PVP during cryogrinding. One can conclude that Raman spectroscopy is not the technique of choice in this case to detect the interactions in this system.

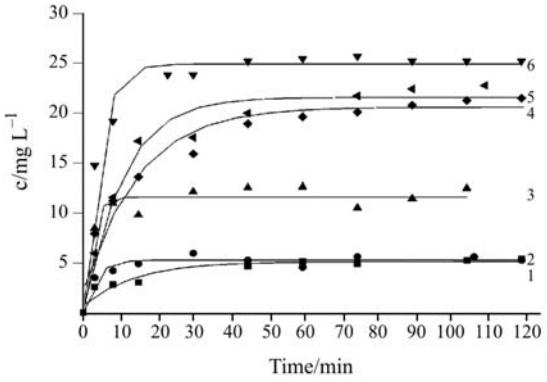

Fig. 7 Dissolution curves of IMC and its mixtures with PVP: 1 – IMC initial; 2 – 50% IMC–50% PVP physical mixture; 3 – 50% IMC–50% PVP mixture ground at room temperature for 15 min (partly amorphous); 4 – cryoground 50% IMC–50% PVP mixture (completely amorphous, after storage for 2 months); 5 – 50% IMC–50% PVP mixture ground at room temperature for 60 min (completely X-ray amorphous); 6 – cryoground 20% IMC–80% PVP mixture (completely amorphous, after storage for 2 months)

Increased dissolution rates and solubility as compared to the pure drug were often observed for the amorphous solid dispersions [25, 27]. We have compared the apparent solubility of pure IMC, with those of the IMC in its physical untreated mixtures with PVP, and in the mixtures prepared by grinding at room and at low temperatures (Fig. 7). The solubility of pure IMC was practically the same as of the IMC in a physical mixture with PVP (compare curves 1 and 2). For the IMC–PVP ground mixtures, the apparent solubility increased both with the duration of grinding, and with the PVP content, and correlated with the amount of the amorphous IMC phase in the sample. The solubility of the cryoground samples after storage for 2 months was comparable with that of the freshly prepared samples of the same composition ground at room temperature (curves 4, 6).

Conclusions

Amorphous samples were obtained during cryogenic grinding of the IMC–PVP mixtures. Cryoground mixtures were shown to form glass solutions. PVP inhibits the crystallization of indomethacin from the amorphous state: the crystallization temperature of IMC in the mixtures with PVP increases, and the amorphous state is preserved longer on storage, as compared to pure IMC. Solubility of the IMC in the cryoground mixtures is higher as compared to the

pure form, or to a physical mixture, also after a prolonged storage. Amorphous state of IMC obtained by cryogrinding is less stable than that obtained by solvent evaporation technique, presumably due to the presence of seeds of the original crystalline form of IMC. The same was observed for piroxicam–PVP system obtained by cryogrinding, suggesting that it is characteristic of mechanical treatment methods. The non-ideal mixing of drug with polymer at cryogrinding, especially in the region of small contents of PVP, was observed for both drug systems. In contrast to the results obtained for indomethacin, for piroxicam, the content of PVP should be more than 50%, to achieve an essential shift of the crystallization event; the cryoground piroxicam–PVP system was less stable than IMC–PVP. It appears that molecular size effect is very important for immiscibility of the drug-polymer systems.

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