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

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The effect of cryogenic grinding on the piroxicam and its mixtures with polyvinylpyrrolidone (PVP) was studied by powder X-ray diffraction and differential scanning calorimetry (DSC). The crystallization of the amorphous piroxicam obtained during cryogrinding showed two events in a DSC curve (noticeable for pure piroxicam, and much more pronounced for the PVP-piroxicam mixtures). For the same measurement conditions, the intensity ratio of the peaks corresponding to the two events differed for the PVP-piroxicam mixtures of different drug-excipient ratios. The temperatures, at which these events were observed, increased with the increase in the PVP-concentration in the mixture. For the mixtures with a high relative content of PVP (≥60%), crystallization was not observed at all. Only one glass transition was revealed for the mixture containing 80% PVP suggesting that a molecular alloy was formed.

Keywords: *cryogrinding, crystallization, glass transition, molecular alloy, piroxicam, polyvinylpyrrolidone*

Introduction

Co-grinding is one of the efficient methods to prepare solid dispersions, in order to enhance the rate of dissolution and bioavailability of poorly water-soluble drugs [1]. A nanocrystalline material can be formed after the mechanical treatment in a mill [2], and obtaining amorphous mixtures is also possible. The formation of amorphous pharmaceutical mixtures is more attractive in the context of enhancing the rate of dissolution of the drugs [3]. Recently, the advantages of ball milling for obtaining glassy molecular alloys were demonstrated in [4–6]. Cryogenic grinding is often more efficient, to prepare the amorphous states of drugs, than grinding at room temperatures [7, 8].

In this work, the cryogenic grinding of the piroxicam–polyvinylpyrrolidone mixtures was studied. Piroxicam is one of the most potent non-steroidal anti-inflammatory drugs. The effect of grinding on pure piroxicam was studied earlier [7, 9]. It was shown, that piroxicam does not undergo any chemical degradation upon grinding [7], but it changes color from white to yellow due to the formation of zwitter-ions [7, 9]. Under cryogrinding, crystalline piroxicam was shown to get transformed into the amorphous state [7]. In contrast to cryogrinding, amorphization on ball milling at room temperature was never complete [9, 10].

Polyvinylpyrrolidone (PVP) is an excipient, which is commonly used to form solid dispersions with active pharmaceutical ingredients [11]. PVP was shown to inhibit the crystallization in amorphous solid dispersions [12]. One of the suggested interpretations was, that having a high glass transition temperature, T_g, [13] PVP will raise the T_g of the mixture and decrease the mobility of the drug molecules, reducing the tendency to crystallize. The interaction of PVP with a drug can also promote stabilization of the drug in a metastable state [9].

In the piroxicam–PVP system, solid dispersions were obtained by solvent method [14, 15], and also by co-grinding at room temperature [9]. Maximum dissolution was observed for the amorphous solid dispersions with large PVP:piroxicam mass ratios (5:1, 6:1 [15], 10:1 [9]). The amorphization of the drug was accompanied by the formation of zwitter-ions, which manifested itself in the yellow coloring of the dispersion [9]. For solid dispersions obtained by solvent method, red shifts of the NH-stretching vibrations in the IR-spectra were reported [14, 15], which can be

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interpreted as a manifestation of the hydrogen bond formation between the components.

The objective of the present work was to study the amorphization of piroxicam alone and in the mixtures with polyvinylpyrrolidone induced by cryogenic grinding, as well as the subsequent crystallization of the amorphous phases.

Experimental

Piroxicam was specially synthesized and tested for its chemical purity by our colleagues from the Irkutsk Institute of Organic Chemistry SB RAS, and then used as received. X-ray diffraction study has shown, that piroxicam was present as polymorph I [10], and did not reveal the presence of any other crystalline phases in the sample [16]. Polyvinylpyrrolidone (Sigma, P-5288) (M_w=360000) 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.

Grinding was performed using a cryogenic mill (6750 Freezer/Mill, SPEX CertiPrep, Inc., USA) consisting of a vessel from organic glass immersed in liquid nitrogen, within which a stainless steel rod is vibrated by means of a magnetic coil. Grinding of 1 g samples was performed at an impact frequency of 10 impacts per second for 2 min periods separated by 1 min cool-down periods. Thus, grinding was performed by cycles, including milling for 6 min, and cool-down periods. The milling time was 60–78 min. After mechanical treatment the grinding vial was immediately transferred to a glove box (15°C, 5% RH) and allowed to warm to room temperature for sampling. The mixtures containing 5–80 mass/mass% PVP were prepared.

The powder X-ray diffraction experiments were performed with a Pananalytical X'pert pro MPD diffractometer (λ_{CuK_α}=1.540 Å) in Bragg–Brentano θ–θ geometry. The powder samples were put in a spinning flat sample holder.

The behaviour of the samples under heating was observed using Kofler WME Hot Bench (Heizbank Reichert, Austria) calibrated with standard samples. The differential scanning calorimetry (DSC) experiments were performed with the DSC Perkin Elmer 7. Sample mass ranged from 2 to 6 mg, and the pans were opened. DSC measurements were carried out from –5 to 180°C at a heating rate of 5°C min^{-1} with a nitrogen purge gas flow rate of 20 mL min^{-1}. T_g was measured as an onset of a peak. The samples were dried in the calorimeter at 40°C overnight to remove water before measuring T_g.

Modulated temperature DSC (MDSC) was also used to analyse the glass transition temperature in the samples obtained. MDSC experiments were performed using the TA Instruments 2920. A linear heating rate of 5°C min^{-1} with a modulation amplitude of 0.796°C every 60 s was applied. During all the experiments the calorimeter was flushed with pure helium gas. Temperature and enthalpy readings were calibrated using pure indium at the same scan rates as used in the experiments. T_g was taken as the inflection point in the heat capacity increment during heating.

Similarly to the previously published work [10], the temperature of crystallization was estimated as a mean value of three measurements obtained under similar conditions (rate of heating, mass of the sample) with a standard error. These efficient values have no strict physical meaning, since the non-equilibrium crystallization below the melting point, in general, and at scanning heating, in particular, cannot be characterized by an exact temperature. At the same time, they are commonly used for the sake of comparison of different samples, provided the heating rate, and the sample mass are the same.

Results and discussion

Cryogrinding of pure piroxicam

Completely X-ray amorphous piroxicam could be obtained after 78 min of grinding (Fig. 1). The thermogram of cryoground piroxicam (Fig. 2) reveals two exothermic crystallization events at 59.1±0.1°C ($T_{c\ onset}$=51.0±0.9°C, ΔH_c=50±5 J g^{-1}) and 90.7±0.1°C ($T_{c\ onset}$=88.5±0.2°C, ΔH_c=2.2±0.3 J g^{-1}), and a melting endotherm at 200.9°C ($T_{m\ onset}$=199.0°C).

Two X-ray diffraction patterns recorded after heating the amorphous sample at 60 and 91°C (i.e. just above each crystallization event) are presented in Fig. 1. The first diffraction pattern reveals a partial crystallization of the amorphous sample towards the

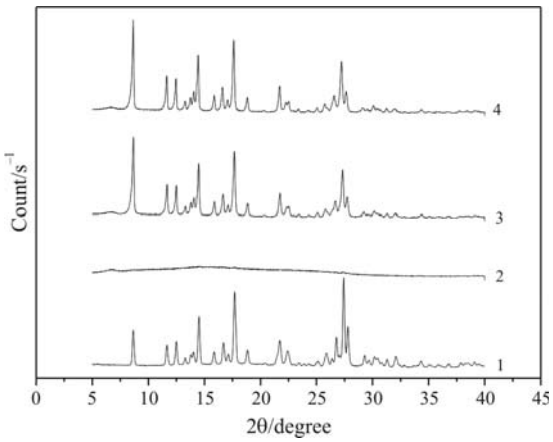

Fig. 1 X-ray diffraction patterns of 1 – piroxicam initial and cryoground for 78 min recorded at 2 – room temperature, at 3 – 60°C after heating for 10 min, at 4 – 91°C after heating for 10 min

form I of piroxicam. The second one is very similar: it shows the same Bragg peaks, some of which are better resolved. The intensity of peaks of recrystallized drug at both plots is slightly redistributed as compared to the diffraction pattern of the starting non-ground sample, possibly due to the effect of preferred orientation. There seems to be no obvious difference in the two diffraction patterns (Fig. 1), which could account for the two-step crystallization process observed by DSC (Fig. 2). Apparently, the final states after the re-crystallization are the same, or similar for the two stages, whereas either there are several (at least, two) starting amorphous states formed on grinding, or there are two different mechanisms dominating the crystallization of the amorphous state at each of the stages. The melting temperature of the cryoground sample was lower at 1°C, than that of the non-treated piroxicam, and was comparable to that for the sample ground at room temperature [17]. During heating in DSC, the glass transition of the cryoground pure piroxicam was not observed (Fig. 2).

Our data on the cryogrinding of pure piroxicam differ somewhat from those reported previously in [10]. According to [10], 'during heating in DSC, the glass transition (T_g) of P_{AII} (amorphous form II) was not observed while that of P_{AI} (amorphous form I) was weak and observed in only two of the three runs (extrapolated T_g onset 0.22±0.94°C)'. As recrystallization temperature, the authors of [10] have reported for modification I: 'onset, 48.01±2.38°C; midpoint, 61.18±0.76°C'. We have observed two crystallization effects, at 59.1 and 90.7°C (the first of which masked a glass transition, see in the next section), both occurring at other temperatures than indicated in [10]).

Cryogrinding of pure PVP

The curves of both initial and the cryoground PVP (Fig. 3) revealed the broad endotherm, due to the removal of absorbed water in the range of 20–90°C. The glass transition temperature for initial PVP was measured by the DSC experiment as 177.3°C and by the MDSC experiment as 181.9°C, what is in a good agreement with earlier reported data [13]. For cryoground PVP, the different values of T_g, 165.4 and 162.6°C, were measured by DSC and MDSC, respectively. Due to changing T_g in a broad range as a function of water content [13], the difference in T_g values for initial and cryoground PVP can be possibly explained by absorbing of water by the ground sample. Another possible reason is the breaking of polymer chains under cryogrinding and the formation of a substance with shorter polymer chains. After cryogrinding, PVP became less stable, than the intact substance, and its chemical degradation occurred just after 190°C as was evidenced from the color changes during heating on the Kofler Hot Bench.

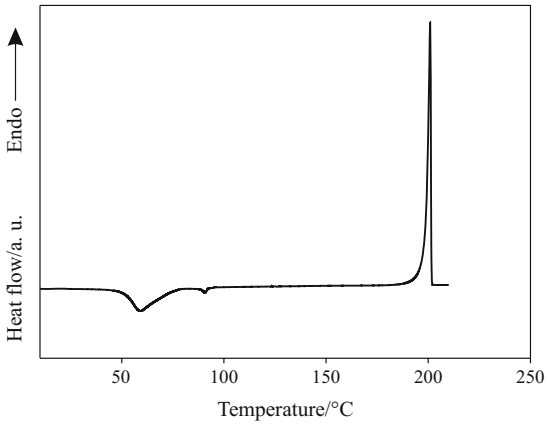

Fig. 2 DSC scan of 78 min cryoground piroxicam alone recorded upon heating

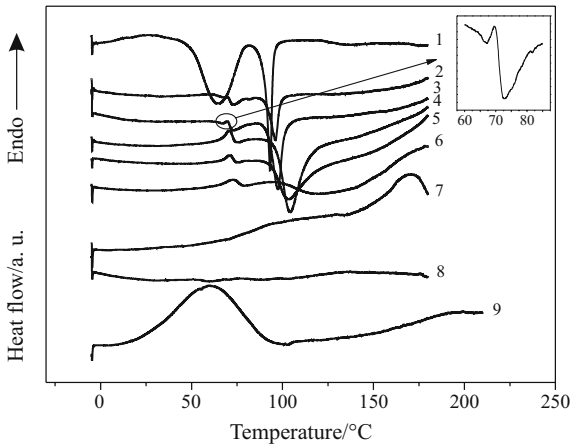

Fig. 3 DSC scans recorded upon heating; 78 min cryoground: 1 – 5/95; 78 min (after drying): 2 – 10/90, 3 – 15/85, 4 – 25/75; 60 min cryoground (after drying): 5 – 35/65, 6 – 50/50, 7 – 60/40, 8 – 80/20% PVP/piroxicam mixture; 9 – 60 min cryoground PVP alone. In the inset, an increased image of DSC scan of 15% PVP–85% piroxicam mixture in the region of glass transition is presented

Cryogrinding of the piroxicam–PVP mixtures

Figure 4 shows the powder X-ray diffraction patterns of the mixtures of piroxicam with PVP. Cryogrinding of piroxicam in the mixtures with the large amounts of PVP gave amorphous samples after a shorter treatment, than that of a pure sample, whereas an opposite effect was observed for the mixtures with a small amount of PVP: All the mixtures containing more than 25% PVP were amorphous after cryogrinding for 60 min. To achieve complete amorphization of the mixtures containing 15 and 25% PVP, cryogrinding for 78 min was needed. Mixtures containing 5 and

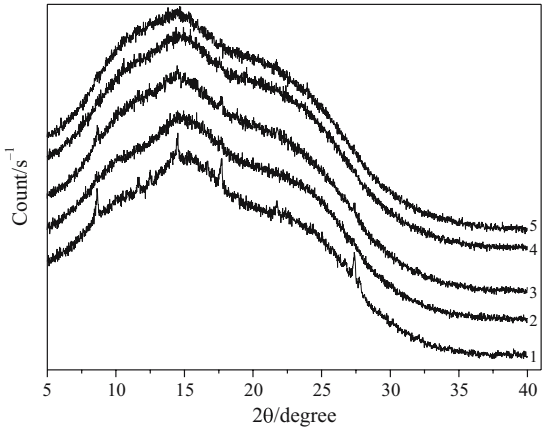

Fig. 4 X-ray diffraction patterns of PVP-piroxicam mixtures; 78 min cryoground: 1 – 5/95, 2 – 10/90, 4 – 25/75% PVP/piroxicam mixture; 60 min cryoground: 3 – 25/75, 5 – 32/68% PVP/piroxicam mixture

10% PVP were not completely amorphous even after cryogrinding for 78 min.

While a simple mixture of PVP and piroxicam was colourless, piroxicam alone and its mixtures with PVP were yellow after cryogrinding, thus confirming that piroxicam was present as zwitter-ions in the cryoground mixtures [7, 9]. This yellow color of the ground piroxicam-PVP mixture was preserved for a very long time (at least one year thus far), whereas the pure cryoground piroxicam lost its yellow color rather quickly at room temperature, and at a slightly longer time at –20°C. The storage of the cryoground samples was accompanied by recrystallization of the drug. Stability of the amorphous state of the drug depended on the content of PVP. Thus, the sample containing 80% PVP was still totally amorphous during storage for two weeks, whereas the 50% PVP–50% piroxicam mixture was partly crystalline.

Figure 3 shows the heating DSC scans of the cryoground piroxicam–PVP samples. Characteristics of the samples, crystallization temperatures, T_c and heat of crystallization, ΔH_c, for piroxicam in cryoground mixtures obtained by DSC experiment are presented in Table 1; the glass transition temperatures, T_g, measured by DSC and MDSC experiments are presented in Table 2.

The crystallization of the cryoground PVP–piroxicam mixtures was very sensitive to the PVP/piroxicam ratio. The curve of the mixture containing 5% PVP revealed two exothermic crystallization events at 64.5°C ($T_{c\ onset}$=51.2°C, ΔH_c= 34 J g^{-1}) and 93.2°C ($T_{c\ onset}$=90.4°C, ΔH_c=14 J g^{-1}). These values are a little bit higher, than that for piroxicam alone. As the content of PVP increased from 5 up to 45%, the temperatures of the crystallization events became higher, as compared with the amorphous piroxicam alone, the enthalpy of the first peak decreased, and that of the second peak – increased (Table 1). After the PVP content reached 50%, only one peak corresponding to the crystallization of piroxicam at higher temperatures was observed, and no crystallization at all could be observed at PVP content ≥60%. For small concentrations of the PVP additive, the crystallization enthalpies correlated well (within the error limit) with the piroxicam content in the mixture. With the increase in the PVP concentration, the enthalpy of crystallization of the mixtures decreased (probably, due to the incomplete crystallization of piroxicam). Unfortunately, it was not possible to measure the enthalpy of melting for the PVP-piroxicam mixtures, to test, if it changed with PVP-content: the cryoground mixtures were noticeably less stable, as compared to the non-treated physical mixtures, and decomposed before melting, at

Table 1 Characteristics of the samples, crystallization temperatures, and heat of crystallization obtained by DSC experiment for piroxicam in cryoground piroxicam–PVP mixtures

N	Content of PVP/*m*/*m*%	Time of grinding/min	X–ray diffraction data	$T_{c\ I\ onset}/T_{c\ I\ max}$/ °C	$T_{c\ II\ onset}/T_{c\ II\ max}$/ °C	$\Delta H_{c\ I}/\Delta H_{c\ II}$/ J g^{-1}
1	0	78	amorph.	50.6±0.9/ 59.1±0.1	88.5±0.2/ 90.7± 0.2	50/2
2	5	78	not totally amorph.	64.5	90.4/93.2	34/14
3	10	78	not totally amorph.	68.7	91.4/96.5	20/27
4	15	78	amorph.	66.1	92.2/97.7	12/36
5	25	60	not totally amorph.	67.1	91.7/98.5	4/35
	25	78	amorph.	66.0	97.0/104.1	5/37
6	32	60	amorph.	69.8	95.6/103.5	1/30
7	35	60	amorph.	69.7	94.0/ 103.0	1/26
8	45	60	amorph.	75.4	101.5/109.3	1/11
9	50	60	amorph.	–	108.1/114.8	3
10	60	60	amorph.	–	–	–
11	80	60	amorph.	–	–	–

Table 2 Glass transition temperatures for piroxicam–PVP cryoground mixtures obtained by DSC and MDSC experiments

N	Content of PVP/ mass/mass%	DSC (after drying)	MDSC (without drying)	
		$T_{g\ I\ onset}$/°C	$T_{g\ I\ midpoint}$/°C	$T_{g\ II\ midpoint}$/°C
1	0	–	–	–
2	5*	–	62.0	
3	10*	67.5	64.8	
4	15	67.6	69.2	
5	25*	65.4	66.1	
	25	66.7	68.5	
6	32	67.4	68.8	
7	35	67.9	68.2	
8	45	68.5	70.8	
9	50	67.5	73.9	165.3
10	60	85.9	84.4	162.6
11	80	116.7	113.3	–
12	100	177.3**	181.9	
	100***	165.5**	162.6	

*not totally amorphous samples, **without drying, ***after cryogrinding

about 170°C, as evidenced by direct observations using the Kofler Hot Bench. Heating of the samples higher than 180°C in the calorimeter lead to the contamination of the device, and was therefore avoided. Experiments with the Kofler Hot Bench confirmed that the 90–100°C exotherm could not be attributed to the degradation of the drug.

The DSC scans of the samples as prepared revealed a broad endotherm in the region of 10–60°C due to the removal of absorbed water, followed by the recrystallization peaks of piroxicam and degradation of the samples before melting. After drying the samples, the glass transition was observed in the region of 67–68°C for the mixtures containing 10–50% PVP. The C_p jump corresponding to the glass transition was followed by the exothermic peak which was larger in the case of 10 and 15% PVP (Fig. 3). For the samples containing 60 % PVP, two glass transitions were observed at about 86 and 160°C, and only one glass transition was revealed for the mixture containing 80% PVP. It was impossible to see the second glass transition event for the mixtures containing less than 50% PVP, probably because the cryoground samples began to degrade at a rather low temperature (near 170°C).

The MDSC scans showed the glass transition for all the samples containing from 5 to 80% PVP in the region of 62–113°C (Table 2). The observed difference between the T_g values measured for dried mixtures (DSC experiments), and for the intact ones (MDSC experiments) can be explained by plasticizing effect of water and by different ways of measuring. Some of the MDSC scans are presented in Fig. 5. Due to the degradation of the samples, the measurements of the spectra were not performed at the temperatures higher than 180°C. Nevertheless, the behavior of a reverse part of the spectrum (characterizing equilibrium processes) in the region near 180°C suggests, that there is a reverse process (probably – a glass transition) in this region in the mixtures containing 5–45% PVP. For the mixtures containing 50 and 60% PVP, we can see the second glass transition in the region of 162–165°C. Only one glass transition was observed for the 80% PVP–20% piroxicam mixture. In Fig. 6 the T_g's of piroxicam–PVP systems were plotted *vs.* the mass fraction of PVP. It is observed that the composition dependence is not monotonic. Only a slight concentration dependence is observed in the range 0–0.5 PVP (*m*/*m*) and then the composition dependence increases rapidly.

The study has revealed several interesting effects characterizing the interaction of piroxicam with PVP in the cryoground mixtures. Interaction obviously manifests itself in the yellow coloring of the samples being preserved for a much longer time, as compared with pure ground piroxicam, as well as in the changes in the behavior of the cryoground mixtures on heating as compared to that of pure samples.

Cryogrinding of piroxicam in the mixtures with the large amounts of PVP gave amorphous samples after a shorter treatment, than that of a pure sample, whereas an opposite effect was observed for the mixtures with a small amount of PVP. The nature of this unusual effect remains unclear and requires further studies. The crystallization of the amorphous piroxicam obtained during cryogrinding showed two

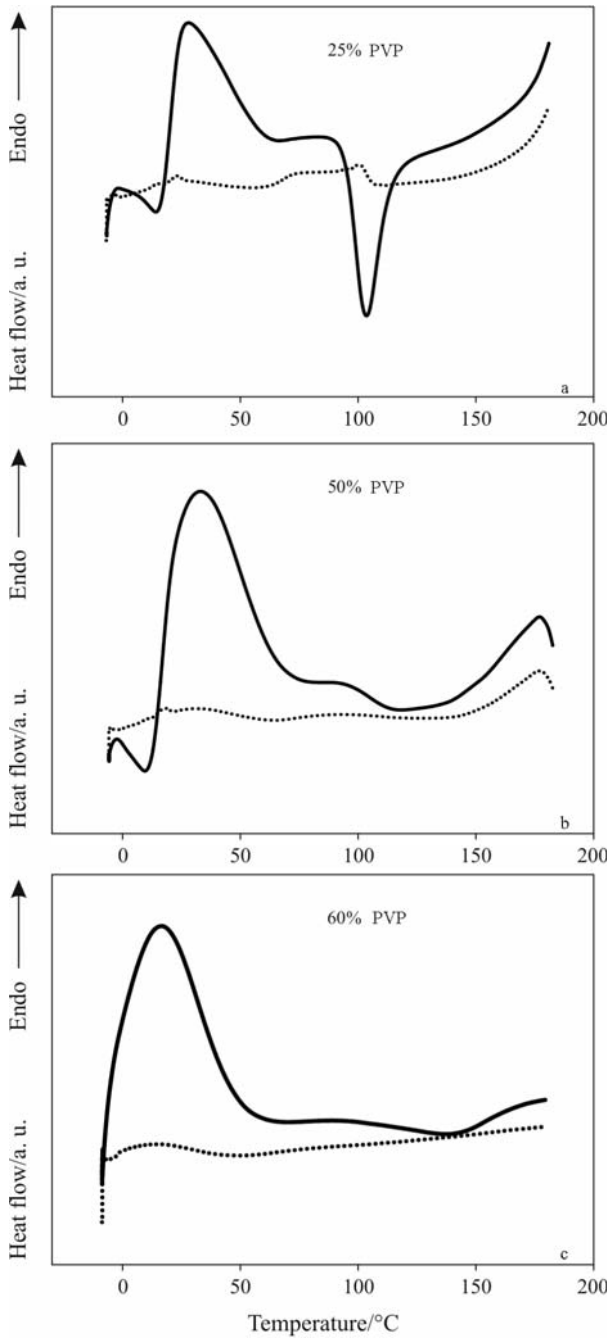

Fig. 5 MDSC scans recorded upon heating; 78 min cryoground: a – 25/75% PVP/piroxicam mixture; 60 min cryoground: b – 50/50, c – 60/40% PVP/piroxicam mixture.
— – Curves for total and · · · – reversing heat flows are presented

events in a DSC curve (noticeable for pure piroxicam, and much more pronounced for the PVP–piroxicam mixtures). For the same measurement conditions, the intensity ratio of the peaks corresponding to the two events differed for the PVP–piroxicam mixtures of different drug-excipient ratios. The temperatures, at which these events were observed, increased with the increase in the PVP-concentration in the mixture. For

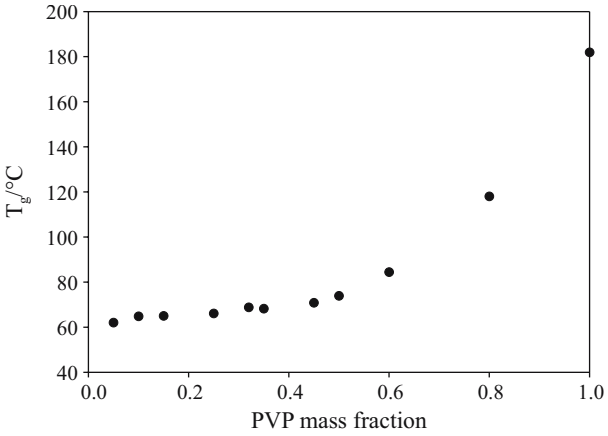

Fig. 6 Glass transition temperatures of piroxicam–PVP cryoground mixtures measured by MDSC experiment plotted *vs.* PVP content

the mixtures with a high relative content of PVP (>60%), crystallization was not observed at all.

We assume that the T_g in the region of 67–68°C represents the T_g of piroxicam. For the mixtures with a small PVP content, the values of T_g were very similar, that is adding PVP modified the system, but did not effect noticeably the mobility of small molecules. According to [3], when a macromolecule is mixed in small amounts with an amorphous small molecule, it introduces 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 theory. The addition of low levels of a small molecule to an amorphous macromolecular system can be expected to be much less disruptive. The presence of very low levels of low molecular mass additives has significant plasticizing effects on pharmaceutical glasses, whereas the addition of low levels of high molecular mass additives often had minimal anti-plasticizing effect [3]. As the PVP concentration increased, the values of piroxicam T_g started growing.

In the MDSC experiment, we can actually see the second C_p jump characteristic of a glass transition located at T_g=170–160°C, i.e. in the region of the PVP glass transition. This C_p jump is better seen when the content of piroxicam increases and glass transition shifts to the lower temperature. We can conclude, that the samples containing 10–60% PVP are not molecular alloys, but the mixtures of amorphous components. It appears that the structure of such a system contains clusters of amorphous drug in the net formed by polymer molecules. For the 80% PVP–20% piroxicam mixture, only one glass transition located between those for pure piroxicam and PVP was observed. This single glass transition indicates, that the amorphous mixed sample obtained is characterized by a single relaxation process. The mixing of the two kinds of molecules, one of which is a polymer, has

thus really been performed at the molecular level, giving rise to a real molecular alloy formed under non-equilibrium conditions.

It should be noted, that when prepared by a solvent method, piroxicam–PVP solid dispersions revealed amorphous character for the mixtures containing more than 60% polymer for PVP K-90 (M_w~1100000), and more than 75% polymer for PVP K-17 (M_w~9000) [15]. The inhibitory effect of PVP on crystallization thus was associated with molecular mass and proportion of PVP. According to the opinion of the authors of [15], a suitable molecular length and a proper amount of PVP may be required to form a net upon the crystal surface or among the drug molecules, resulting in the optimum orientation of the proton-donating and receiving groups and strong interaction between drug and polymer. Taking into account these results, we may assume, that the formation of PVP–piroxicam molecular alloy by mechanochemical method for large quantities of polymer only is characteristic for PVP–piroxicam system, and can be probably explained by molecular size effects.

It is seen from the Fig. 3, that for the mixtures containing 10–50% PVP, crystallization of piroxicam was observed in the temperature region of the glass transition. It is an interesting fact because the mobility of molecules below glass transition temperature is very low, and usually crystallization takes place at the temperatures higher than T_g.

PVP is commonly used to form amorphous pharmaceutical mixtures as a good glass-former. For example, the usage of PVP in amorphous dry co-precipitates with indomethacin significantly inhibits drug crystallization at levels as low as 5% PVP [12]. It is remarkable, that for the piroxicam–PVP system, the content of PVP should be more than 50%, to achieve an essential shift of the crystallization event. The 5% PVP–95% piroxicam mixture does not contain enough polymer to form a totally amorphous sample.

One of the most interesting effects observed in this work is the two-step crystallization of the cryoground amorphous samples in the piroxicam–PVP system. Two-step (and any multi-step) crystallization of amorphous molecular crystals was observed earlier for other systems – for example, for the quench-cooled amorphous paracetamol [18, 19], or for the ground lactose-mannitol mixtures [6]. Several explanations can be suggested for this phenomenon, considering the existence either of the two (or more) states of the starting amorphous form, or of the two different mechanisms dominating the crystallization of the amorphous state at each of the stages. In the literature, the two-step crystallization of quench-cooled paracetamol was interpreted by the presence of some impurities in the starting sample [18], or by a solid-solid phase transformation [19]. The possibility of the existence of several amorphous states is now commonly accepted [20–25]; several amorphous states obtained by different techniques and from different starting crystalline forms were reported also for piroxicam [10, 26]. We cannot exclude the formation of several amorphous states also in the case of the cryoground piroxicam–PVP mixture. At the same time, the non-trivial effect of the PVP concentration on the two-step crystallization of the mixture, suggests one more possible explanation. One can suppose, that during the preparation of the dispersed systems, PVP accumulates in higher concentration at the particles surface to inhibit nucleation and nuclei growth initiated at these areas [27]. The large molecular size of PVP relative to crystallizing molecule promotes a tendency to act as a very efficient steric barrier for small molecules crystal nucleation and growth. This would stabilize the amorphous state of piroxicam, what is actually observed. One can also suppose, that due to the large molecular size of PVP relative to piroxicam, the polymer can inhibit the nuclei formation during grinding much more, than the growth of already formed nuclei. This would increase the contribution of the nuclei growth stage on crystallization at the cost of the nucleation at new sites. If the first crystallization event at a lower temperature corresponds to the nucleation stage, and the second one (at the temperature higher than T_g) – to nuclei growth, one would observe the same concentration dependence of the re-distribution in the relative size of the two crystallization steps in the DSC curves, as was observed in the experiments.

Sekikawa *et al.* [28] pointed out, that PVP might inhibit the association of the drug molecules to form the crystal nucleus and inhibit the crystal growth. It was proposed also by Yoshioka *et al.* [12], that there are some factors, which might contribute to the inhibitory effect of PVP on the crystallization of the drug from the amorphous state. PVP is able to complex with a drug causing a change in molecular motions for the mixed systems and in this way cause inhibition of crystallization. For the PVP–piroxicam system studied in this work, the T_g practically does not depend on PVP content in the region of 10–50% PVP (Fig. 6), but the shift of crystallization temperature was still observed (Fig. 3, Table 1). This suggests that increasing T_g is not the only determining factor in controlling the crystallization rate. Further studies by complementary techniques, for example, by electron microscopy, will help to get a better insight into the nature of the two-step crystallization of the cryoground PVP–piroxicam mixtures.

Due to the crystallization of the drug, the glass transition of cryoground piroxicam cannot be measured directly using the standard heating in a calorimeter. Nevertheless, as the T_g does not depend on PVP content in the region of 10–50% and represent the T_g of piroxicam we tried to estimate the T_g of piroxicam as an average of these values. For the values of T_g measured by DSC experiment, the T_g of piroxicam was estimated as 67.3±0.9°C. We obtained the T_g=68.0±3.4°C for glass transition of piroxicam recorded by MDSC experiment. These values are consistent with reported T_g ($T_{g\ half\text{-}ht}$=62.2±0.5°C, $T_{g\ onset}$=60.1±1.3°C) [29] for piroxicam obtained by quench-cooling. Moreover the value of T_g=62°C measured for the 5% PVP–95% piroxicam mixture is extremely close to the T_g reported in [29] suggesting that it can be a slight influence of PVP on the glass transition of piroxicam in cryoground mixtures. In principle, different cooling rates give glasses, which on reheating yield different T_g's [30]. However, due to the high rates of relaxation, the T_g is not significantly affected by the initial cooling rate [28].

The behavior of the cryoground pure amorphous piroxicam differed noticeably not only from that of the piroxicam in the mixtures with PVP, but also from the behavior of the quench-cooled pure piroxicam. For pure cryoground piroxicam, the two crystallization events (at 59.1 and 90.7°C) were observed, the first event masking a glass transition. T_g could be determined, when the crystallization temperature was shifted by adding PVP to the sample. The quench-cooled amorphous piroxicam showed very different effects: a glass transition at T_g=62°C was followed by a recrystallization exotherm at 133°C, and two endothermic transitions, at 180 and 201°C, suggesting recrystallization of the melt to form III converted into form II [29]. This comparison is one more example of the possibility to obtain different amorphous states, depending on the procedure used for the amorphization. Amorphous forms prepared by grinding usually contain seeds or nuclei of the initial compound, corresponding to the memory of the starting polymorph, and are therefore susceptible to recrystallization of this polymorph [10, 26]. Lower stability of amorphous state of the ground piroxicam as compared to that of the quench-cooled amorphous form, is probably explained by the existence of such seeds.

Conclusions

Amorphous piroxicam obtained by cryogrinding re-crystallizes into the initial form I by a two-step process. The first step of piroxicam crystallization is observed in the temperature region of glass transition. Adding PVP results in the increase in the role of the second step of crystallization. Apparently, the final states after the re-crystallization are the same, or similar for the two stages, whereas either there are several (at least, two) starting amorphous states formed on grinding, or there are two different mechanisms dominating the crystallization of the amorphous state at each of the stages (for example, the first peak corresponds mainly to the nucleation, and the second one – to the nuclei growth at the temperature higher T_g). Further studies using additional experimental techniques may be helpful to distinguish between the two possible explanations. The formation of PVP-piroxicam amorphous molecular alloy is possible for large quantities of polymer.

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