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Effect of physical properties of troglitazone crystal on the molecular interaction with PVP during heating

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Abstract

This study examined the effect of physical properties of troglitazone drug substance on the molecular interaction with polyvinylpyrrolidone K30 (PVP) during preparation by a closed melting method. Milling was conducted using impact and jet mills to change the physical properties of troglitazone, such as particle size, specific surface area, surface free energy and acidic–basic parameters. Solid dispersions (SDs) prepared from milled troglitazone, irrespective of milling method, showed almost 100% dissolution when not less than 7.5% of water was added during heating. SDs prepared from unmilled troglitazone showed almost 100% dissolution when not less than 12.8% of water was added during heating. Physical mixture (PM) containing unmilled troglitazone must be heated above at least 50 °C higher than the glass transition temperature (T_g) of PVP to obtain an SD showing 100% dissolution, while PMs containing milled troglitazone could be heated above only 20 °C higher than the T_g of PVP to obtain an SD showing 100% dissolution. The melting points of troglitazone in PMs containing milled troglitazone, irrespective of milling method, were lower than those in PMs containing unmilled troglitazone. These results indicated that specific interaction could occur more easily during heating between milled troglitazone and PVP during preparation by a closed melting method. In addition, Fourier transform infrared study indicated that hydrogen bonding could occur between the N–H of troglitazone and the C=O of PVP.

Keywords: Troglitazone; PVP; Solid dispersion; Physical property; Interaction

1. Introduction

Troglitazone has characteristic physical changes, depending on thermal change. It has two asymmetric carbons as shown in Fig. 1, and is present as four isomers in equal amounts. These isomers are composed of two crystalline forms: one is the RR/SS form and the other is the RS/SR form. These crystalline forms have different melting points. The RR/SS crystal and the RS/SR crystal of troglitazone (Lot T003) melt at about 120 and 175 °C, respectively (Suzuki et al., 2002; Hasegawa et al., 2004). In this paper, the RR/SS crystal and the RS/SR crystal are abbreviated as L and H form, respectively. On the other hand, the solubility of each isomer of troglitazone is about 10 μg/mL in water, which results in low bioavailability (Suzuki et al., 2002).

The use of solid dispersions (SDs) is an effective method to improve the dissolution properties and bioavailability of poorly water-soluble drugs (Chiou and Riegelman, 1971; Serajuddin, 1999; Leuner and Dressman, 2000). The melting technique is one of the most widely used methods to prepare amorphous solid dispersions, however, drug degradation must be taken into account as high temperature conditions are used (Hancock and Zografi, 1997; Serajuddin, 1999).

Various polymers and saccharides are generally used as carriers for SDs. In the case of using a water-soluble polymer as a carrier for SDs, it is expected that lowering the glass transition temperature (T_g) of the polymer would allow for the preparation of amorphous solid dispersions by heating below the melting temperature of the drug. Therefore, using a plasticizer to act with the polymer is thought to be effective to decrease drug degradation in the SD. Various compounds, such as water, ethanol, triacetin and polyethylene glycol (PEG) are used as plasticizers. It was also revealed that the T_g decreases significantly with

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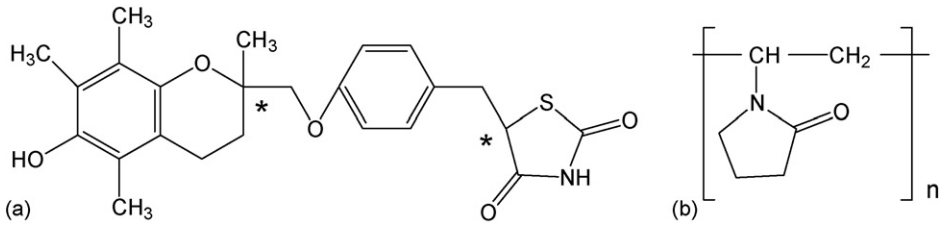

Fig. 1. Chemical structures of (a) troglitazone and (b) polyvinylpyrrolidone. Asterisks represent asymmetric carbons.

increasing weight fractions of water or PEG (Hamaura and Newton, 1999). However, adding a plasticizer lowers the T_g of SDs, and this can thus easily induce drug crystallization. Volatile plasticizers such as water and ethanol can be used to inhibit drug crystallization as they can be evaporated after preparing the SDs. In particular, water has the advantage of being a non-organic solvent from the viewpoint of the environment.

In our previous study, water was selected as a volatile plasticizer, and SDs of troglitazone with polyvinylpyrrolidone K30 were prepared by a closed melting method (Hasegawa et al., 2005); both the water content in the PM and heating temperature affected the dissolution property and apparent crystallinity of troglitazone in SDs via changing the physical state of troglitazone and PVP during heating. By heating at a temperature lower than the melting point of the H form of troglitazone and controlling the water content in the PM at a certain level, a troglitazone SD with an apparent crystallinity of 0% can be obtained.

In this study, we focused our attention on the physical property of troglitazone during the preparation of SDs. Two methods of milling, impact milling and jet milling, were applied to change the physical property of troglitazone drug substance. Then, physical property, including dissolution, of unmilled and milled samples was determined. Moreover, the effect of physical properties of drug substance was investigated on the dissolution properties of SDs prepared by the closed melting method.

2. Materials and methods

2.1. Materials

Troglitazone (Lot T003) was manufactured by Sankyo Co. Ltd. Polyvinylpyrrolidone K30 (PVP) was purchased from BASF Japan Ltd. (Tokyo, Japan).

2.2. Preparation

2.2.1. Milled and amorphous troglitazone

Samples of milled troglitazone were prepared using an impact mill (Centrifugal Mill ZM-100, Retsch Co. Ltd., Germany) and a jet mill (Co-jet, Seishin Enterprize Co. Ltd., Japan). Impact milling conditions were a hammer rotation speed of 14,000 rpm and a feed rate of the drug substance of 1 g/min. Jet milling conditions were air pressure of 0.4 MPa and a feed rate of the drug substance of 1 g/min. Amorphous troglitazone was prepared by the melt (180 °C)-quench method.

2.2.2. Physical mixtures (PMs)

PMs were prepared by mixing troglitazone (unmilled, impact-milled and jet-milled) with PVP in a weight ratio of 1:2 using a high shear mixer (NMG-1, Nara Machinery Co. Ltd., Tokyo, Japan). For the IR study only, PM was prepared by mixing unmilled troglitazone with PVP in a weight ratio of 2:1.

2.2.3. Solid dispersions (SDs)

One gram of the PM was weighed into glass ampoules (20 mL) and the water content was controlled by adding some water directly. The glass ampoules were sealed and heated for 90 min at 130 °C in an oven to prepare the SDs. The caps of the ampoules were opened and then the SDs were dried for 10 min at 130 °C in order to eliminate the water from the SD systems. The resultant SDs were sieved through a 300-μm sieve.

2.3. Characterization

2.3.1. True density

The true densities of powder samples (approximately 1.5 g) were determined with an Ultrapycnometer 1000 (Quantachrome Instruments, Boynton Beach, FL). Calibration was performed using standard stainless steel spheres, and the mean value of triplicate determinations is reported. The true density was calculated using the equation: $\rho_{true} = w/v_p$, where ρ_{true}, w, and v_p are true density, weight of the sample, and true volume of the powder, respectively.

2.3.2. Particle size distribution measurement

The particle size distributions of the unmilled and milled samples were determined using a Sympatec HELOS laser diffraction instrument (Sympatec GmbH, Germany) fitted with a RODOS dry powder dispersion accessory. An air pressure of 1.5 bar and a vacuum of 85 mbar were used to produce a uniform powder dispersion for each sample. These conditions were optimized to achieve a complete dispersion of the primary particles without causing significant particle attrition. The measurement duration was approximately 100 ms. Geometric standard deviation was calculated using the following equation: geometric standard deviation = $d_{86\%}/d_{50\%}$.

2.3.3. Specific surface area

The specific surface area of unmilled and milled samples was measured using Macsorb HM Model-1208 (Mountech Co. Ltd., Japan) on the basis of the BET method.

2.3.4. Inverse gas chromatography

About 200 mg of samples were packed into silanized glass columns of 3 mm in inside diameter and 30 cm in length, and measured by inverse gas chromatography (IGC, Surface Measurement Systems Ltd., UK). After equilibration at 303 K for 3 h, we measured acid–base parameters at a flow rate of 10 cm^3/min and a column temperature of 303 K using helium as the carrier gas. For probes, *n*-heptane, *n*-octane, *n*-nonane, *n*-decane, ethyl acetate, chloroform, and acetone were used.

The adsorption-free energy of a probe molecule, $-\Delta G_0$, is given by the following equation:

$$-\Delta G_0 = RT \ \ln \ V_N + C \quad (1)$$

where R is the gas constant, V_N the net retention volume, and C is a constant. Furthermore, $-\Delta G_0$ is related to the work of adhesion W_A, as shown in the following equation:

$$-\Delta G_0 = N_A a W_A \quad (2)$$

where N_A is Avogadro's number and a is the surface area of the adsorbed probe molecule. Here, the work of adhesion is shown by Eq. (3) as the geometric mean of the dispersive surface energy of a solid and liquid:

$$W_A = 2(\gamma_S^D \gamma_L^D)^{1/2} \quad (3)$$

where γ_S^D and γ_L^D are the dispersive surface energy of the solid and probe, respectively. Eq. (4) is derived from Eqs. (1)–(3) as follows:

$$RT \ \ln \ V_N = 2N_A(\gamma_S^D)^{1/2} a(\gamma_L^D)^{1/2} - C \quad (4)$$

If $RT \ln V_N$ versus $a(\gamma_L^D)^{1/2}$ is plotted, a straight line can be obtained for alkanes. The vertical distance between the data points of a polar probe and the alkane line is the specific energy of adsorption, $-\Delta G_{AB}$. Here, the values of a and γ_L^D were taken from the literature (Schultz et al., 1987; Nardin and Papirer, 1990). According to the acid–base theory of Gutmann, liquids are characterized as electron donors or base number (DN) and electron acceptors or acid number (AN), and AN is corrected to take into account dispersive contributions by Riddle and Fowkes to give AN^*. $-\Delta G^{AB}$ is shown by Eq. (5) using an acid parameter, K_A, and a base parameter, K_D (Newell et al., 2001; Grimsey et al., 2002):

$$-\Delta G^{AB} = K_A DN + K_D AN^* \quad (5)$$

By plotting $-\Delta G^{AB}/AN^*$ versus DN/AN^*, K_A and K_D are calculated and used to describe the acidic or basic nature, respectively.

2.3.5. Scanning electron microscope (SEM)

The SEM images of the samples were collected using a JSM-5310 (JEOL, Japan). A secondary electron beam with 15 kV acceleration voltage was used.

2.3.6. Dissolution

The dissolution of troglitazone was determined using USP Apparatus No. 2 (rotating paddle method). The dissolution media consisting of phosphate buffer (pH 9) was maintained at 37 ± 0.5 °C. About 250 mg of hydroxypropyl methylcellulose (HPMC) was added into the media to inhibit the crystallization of troglitazone. Troglitazone drug substance and SDs containing 100 mg of troglitazone were each added to 500 mL of dissolution medium in a 1000-mL cylindrical beaker. The paddle rotation speed was set to 250 rpm. Samples were withdrawn at 5 min intervals for 60 min. The concentration of troglitazone in the medium was determined using a UV-1600 UV spectrophotometer (Shimadzu, Kyoto, Japan).

2.3.7. Differential scanning calorimetry (DSC)

DSC measurement of troglitazone and PMs was carried out in hermetically sealed aluminum pans using a Thermo plus 8230 L (Rigaku, Tokyo, Japan) calibrated with indium. Troglitazone and PMs were heated under a dry nitrogen gas purge between 40 and 200 °C at a rate of 10 °C/min. As for PMs, in order to eliminate the evaporation heat of the water in the PMs, heating was held at 100 °C for 3 min. The T_g of the PVP was controlled for water content by sealing aluminum pans to prevent water loss during the DSC experiments. The samples were heated under nitrogen atmosphere and heated to 10–25 °C above their T_g. They were subsequently cooled at a rate of 20 °C/min to 0 or −50 °C and then reheated. The first heating run exhibited an enthalpy relaxation endotherm at around the T_g value. Therefore, the T_g value of each sample was determined from the second heating cycle and defined as the midpoint of transition.

2.3.8. Powder X-ray diffraction (PXRD)

PXRD of the samples at various temperatures (30, 100, 120, 130, 150, and 175 °C) was measured by a Geiger Flex Rint-2200 diffractometer (Rigaku Co., Japan) with Cu Kα radiation at 40 kV/40 mA. After the sample was kept at each temperature for 3 min, it was step-scanned at 0.02° intervals from 5.00° to 40.00° (2θ) at the rate of 4.00° min^{-1}.

2.3.9. Fourier transform infrared (FT-IR)

IR spectra of samples were measured by the diffuse reflection method at the resolution of 2 cm^{-1} using a PARAGON 1000-Model Fourier Transform Infrared (FT-IR) Spectrometer (Perkin-Elmer Inc., USA).

2.3.10. Water content (Karl Fischer)

The water content of the samples was determined using a Hiranuma AQ-7 Aquacounter (Hiranuma Sangyo Co. Ltd., Ibaraki, Japan). Hydranal Aqualyte RS and Hydranal Coulomat CG were used as an anolyte and a catholyte, respectively. About 0.1 g of sample was weighed accurately, transferred to the titration vessel quickly, and dissolved in the anolyte.

3. Results and discussion

The SEMs of troglitazone and PVP are shown in Fig. 2. Crystal morphology of the unmilled troglitazone was plate crystal. Both milling methods reduced the particle size of troglitazone. PVP had a spherical shape with some depressions in the surface and its particle size was larger than that of troglitazone. The true

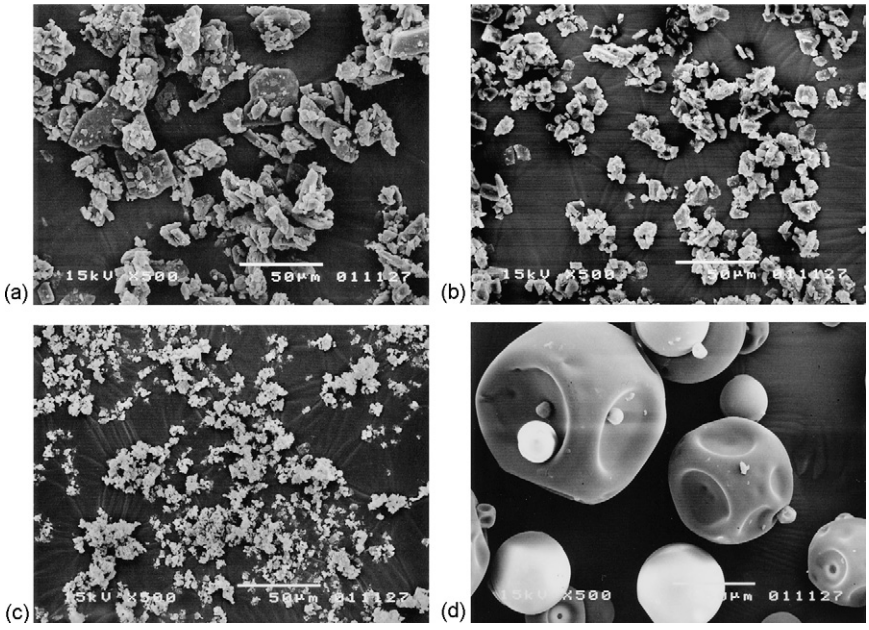

Fig. 2. SEMs of troglitazone. (a) Intact troglitazone, (b) impact-milled troglitazone, (c) jet-milled troglitazone and (d) PVP.

Table 1
True density, particle size and specific surface area of troglitazone (unmilled, impact-milled and jet-milled) and PVP

	True density (g/cm^3)	Particle size (μm)[a]					Specific surface area (m^2/g)
		$d_{10\%}$	$d_{16\%}$	$d_{50\%}$	$d_{84\%}$	$d_{90\%}$	
Unmilled	1.37	2.3	3.4	9.0 (2.7)[b]	24.5	34.1	0.9
Impact-milled	1.37	1.7	2.8	7.1 (2.0)[b]	14.4	17.8	1.4
Jet-milled	1.37	0.9	1.1	2.2 (1.8)[b]	4.0	4.7	4.7
PVP K30	–	22.1	32.0	72.7	110.0	118.6	0.4

[a] Volumetric particle size.
[b] Geometric standard deviation.

density, particle size and specific surface area of troglitazone and PVP are summarized in Table 1. The densities of troglitazone were not changed by milling. The milling process decreased the particle size and increased the specific surface area, which is reflected in the SEM images. Jet-milled troglitazone was the smallest of these samples. The geometric standard deviations of particle size were smaller than unmilled troglitazone. It means that the milled samples had sharp distribution pattern.

DSC thermograms of unmilled and milled troglitazone are shown in Fig. 3. There were two endothermic peaks at about 120 and 175 °C in the unmilled troglitazone. It has been reported from a hot stage microscopic study that these endothermic peaks are attributed to the melting of troglitazone (Hasegawa et al., 2004). Troglitazone has two asymmetric carbons, as shown in Fig. 1, and exists as four isomers in equal amounts. It has been reported that the endothermic peak of the unmilled troglitazone drug substance at about 120 °C (peak temperature) is due to the melting of the L form and the other peak at about 175 °C (peak temperature) is due to the melting of the H form (Suzuki et al., 2002). The melting points of impact-milled troglitazone were almost same as those of unmilled troglitazone. On the contrary, the melting points of jet-milled troglitazone shifted to a lower temperature. Namely, the melting points of the jet-milled L and H forms were 116 and 173 °C, respectively. It was presumed that the reason for this was that the jet milling induced small levels of disorder at the surface of the troglitazone powders.

The PXRD patterns of the unmilled and milled troglitazone at various temperatures (30, 100, 120, 130, 150, and 175 °C) are shown in Fig. 4a–c. The peak positions of the unmilled and

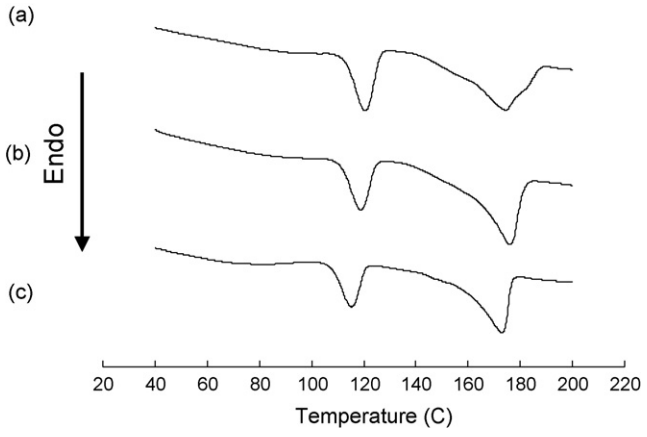

Fig. 3. DSC curves of troglitazone. (a) Intact troglitazone, (b) impact-milled troglitazone and (c) jet-milled troglitazone.

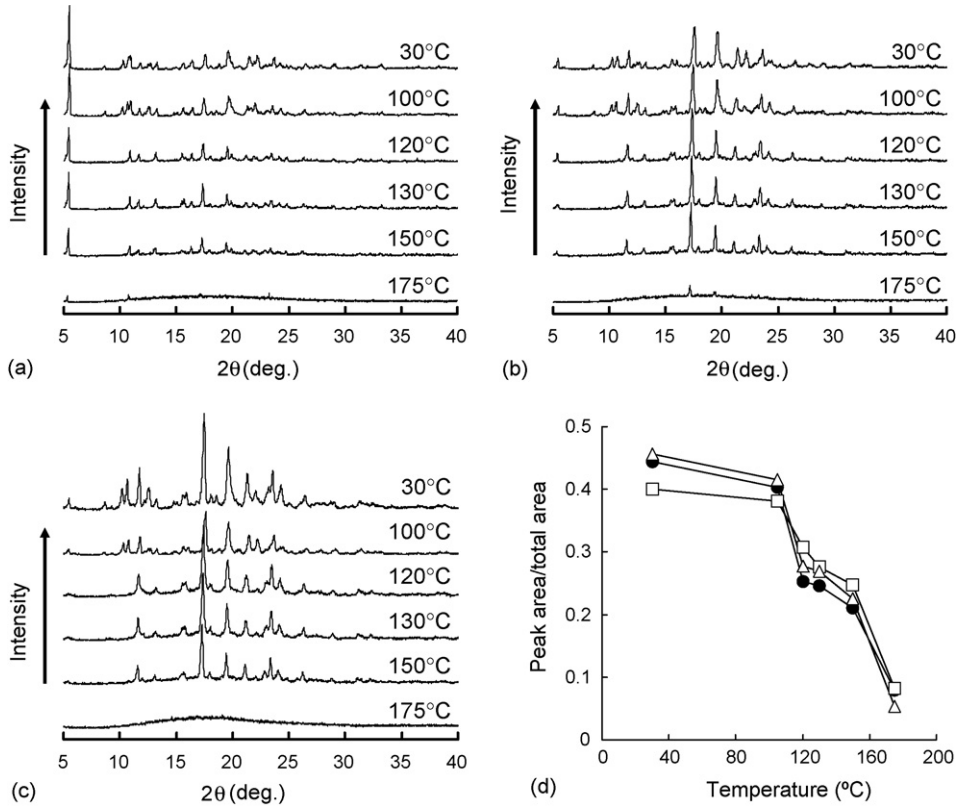

Fig. 4. PXRD data of troglitazone at various temperatures. (a) Intact troglitazone, (b) impact-milled troglitazone, (c) jet-milled troglitazone and (d) relationship between temperature and area ratio (peak area/total area). Circles: unmilled troglitazone; triangles: impact-milled troglitazone; squares: jet-milled troglitazone.

milled troglitazone were the same, indicating that the crystal form was not changed by milling. Impact milling reduced the 2θ at 5.5°, which is the most discriminative peak in the unmilled troglitazone at 30 °C. However, the 2θ peaks at 11.7°, 17.0°, and 19.6° increased. Jet milling had a more pronounced tendency. It is considered that disorder on the crystal surface may be concerned. The L and H forms were separated from each other, and the PXRD of each form was measured (Suzuki et al., 2002). According to this report, the 2θ peaks at 5.5°, 11.7°, 17.0°, 19.6°, 21.5°, and 22.1° were derived from the H form while the 2θ peaks at 5.5°, 8.6°, 10.3°, 10.7°, 12.6°, 19.6°, 21.5°, and 22.1° were derived from the L form. When the samples were heated at 100 °C, there was little change in the PXRD. However, the 2θ peaks at 8.6°, 10.3°, 10.7°, and 12.6° disappeared and the 2θ peaks at 5.5°, 19.6°, 21.5°, and 22.1° were decreased at 120 °C. This results from the fact that the L form crystals melted at around this temperature. The PXRD pattern at 130 °C was not changed from that at 120 °C. The whole peak intensity was decreased at 150 °C as some of the H form crystals melted even at this temperature, as determined from the result of the DSC experiment on troglitazone. There were no peaks at 175 °C as not only the L form but also most of the H form crystals had melted. Since, the crystallinity of troglitazone changed at each temperature level, apparent crystallinity was calculated from the ratio of the peak area to the total area and was plotted against temperature as shown in Fig. 4d. The peak area/total area ratio of all samples was 0.40–0.45 at 30 °C and was not affected by the milling process. This indicator for all samples was reduced by heating and especially dropped at about 120 and 175 °C owing to melting of the L and H form crystals, respectively. Moreover, this indicator for all samples was below 0.10 at 175 °C, the melting point of the H form crystals, which indicated that all samples did not have the crystallinity at this temperature. This tendency was the same for all samples.

The surface free energy and acidic–basic parameters of the unmilled and milled troglitazone were determined by inverse gas chromatography as shown in Table 2. The surface free energy of troglitazone was increased by milling. Moreover, the K_A of troglitazone was higher than the K_D, indicating strong acidic property of troglitazone. This acidic property, contributed to by the imino and phenolic hydroxyl groups whose pK_a's are 6.1 and 12.0, respectively, was enhanced by milling. The reason for this is speculated to be that the inside of crystals containing polar functions such as the imino group and phenolic hydroxyl group appeared on the surface by milling. The crystal structure of troglitazone has been revealed (Vyas et al., 1999; Kobayashi et al., 2000, 2001a,b). The imino group in the thiazolidine and

Table 2
Surface free energy parameters of troglitazone

	Surface free energy (mJ/m^2)	K_A	K_D
Unmilled	39.7	131.0	4.5
Impact-milled	46.2	145.6	0.0
Jet-milled	48.4	158.3	0.0

K_A: acidic parameter; K_D: basic parameter.

Table 3
Dissolution percent of troglitazone (unmilled, impact-milled and jet-milled) with or without PVP in the dissolution media

	Dissolution percent at 60 min	
	−PVP	+PVP
Unmilled	5.0 ± 2.1	3.3 ± 0.6
Impact-milled	9.4 ± 1.7	7.0 ± 1.0
Jet-milled	9.4 ± 2.3	10.3 ± 1.2

phenolic hydroxyl groups forms pairs in the crystals regardless of whether they are the L or H form. Milling renders free some of these pairs on the surface of the crystals.

Table 3 shows the dissolution percent at 60 min of unmilled and milled troglitazone. It is generally noted that milling is an effective method to improve the dissolution property of a drug substance. The dissolution percent at 60 min of milled troglitazone became slightly higher than that of unmilled troglitazone irrespective of PVP. However, this degree of improvement by milling was not satisfactory. We have already reported that making solid dispersion was effective to improve the dissolution property of troglitazone (Hasegawa et al., 2005).

The dissolution percent of troglitazone from solid dispersions (SDs) prepared with PVP by a closed melting method increased with an increase in water content in the physical mixtures (PMs) and heating temperature. In this study, it was investigated how the physical property of troglitazone affects the dissolution property of the SD. The dissolution percent at 60 min ($D_{60\,min}$) of SDs prepared from milled troglitazone against water content in PMs during heating is shown in Fig. 5. $D_{60\,min}$ was higher than that from the SDs of unmilled troglitazone in the case of low water content in PMs. In addition, SDs prepared from milled troglitazone showed almost 100% dissolution when not less than 7.5% of water was added in PMs while for unmilled troglitazone this was when not less than 12.8% of water was added. There was

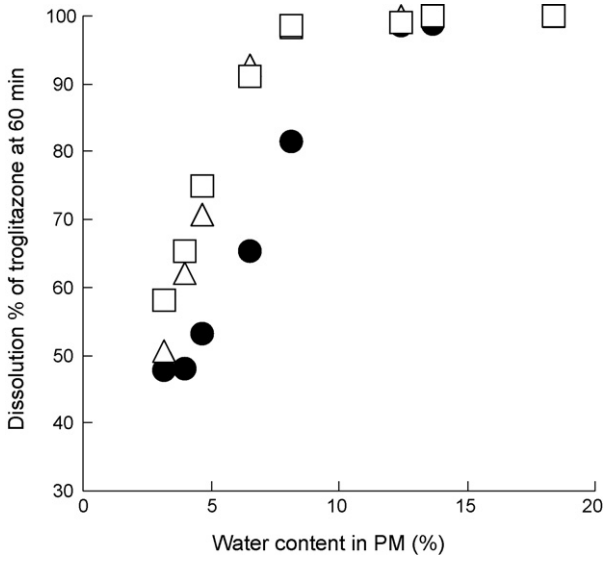

Fig. 5. Effects of water content in PM on dissolution percent of troglitazone at 60 min. Circles: unmilled troglitazone; triangles: impact-milled troglitazone; squares: jet-milled troglitazone.

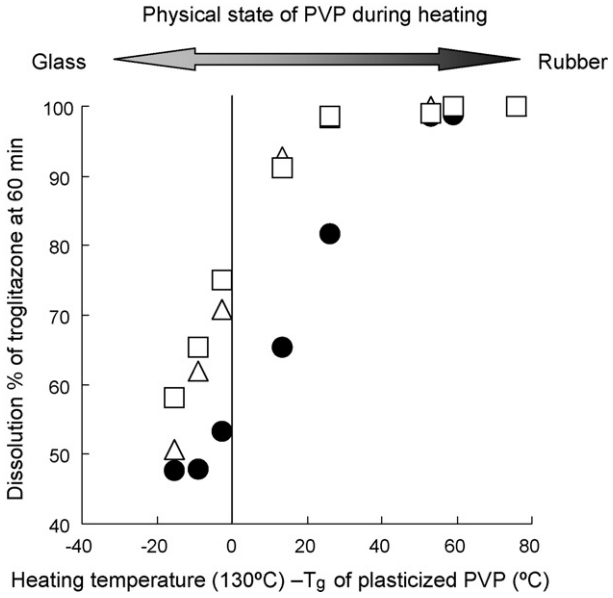

Fig. 6. Relationship between the physical state of PVP during heating (heating temperature (130 °C)–T_g of plasticized PVP) and dissolution percent of troglitazone at 60 min. Circles: unmilled troglitazone; triangles: impact-milled troglitazone; squares: jet-milled troglitazone.

no significant difference between the milling methods, jet and impact milling, except for 2.9% of water content in the PMs. Dissolution of SDs was improved to around 50% since half of the crystals (L form) melted at 130 °C and changed to the amorphous state in the SDs when they solidified.

Next, in order to correlate the physical state of PVP with the $D_{60\,min}$ of SDs, the plots in Fig. 5 were converted to a relationship between the physical state of PVP and $D_{60\,min}$ using the relationship between water content in PVP and T_g, as shown in Fig. 6. The difference between the heating temperature and T_g of plasticized PVP is used as an indicator of the physical state of PVP, namely, glass or rubbery (Lai et al., 1999). When this value is plus, the physical state of PVP is thought to be rubbery, indicating high mobility. In contrast, when this value is minus, the physical state of PVP is thought to be glassy, indicating low mobility. In the case of unmilled troglitazone, the $D_{60\,min}$ was almost 50% when the indicator was around zero. Additionally, the PM containing unmilled troglitazone must be heated above at least 50 °C higher than the T_g in order for the SD to show 100% dissolution. On the other hand, in the case of milled troglitazone, the $D_{60\,min}$ was above 70% when the indicator was around zero. Moreover, the PM could be heated sufficiently above only 20 °C higher than T_g in order for the SD to show 100% dissolution. As shown in Fig. 4d, milling did not affect the change in crystallinity with increase in temperature. It was unlikely that the troglitazone crystals became amorphous spontaneously by themselves. In this study, the T_g value of each sample was defined as the midpoint between the set and end temperatures of the DSC measurement. As glass transition of polymers occurs within a broad temperature range, polymers change from a glassy to a rubbery state in part even when the indicator is below zero. It was speculated that milled troglitazone could easily dissolve into rubbery state PVP. However, there was

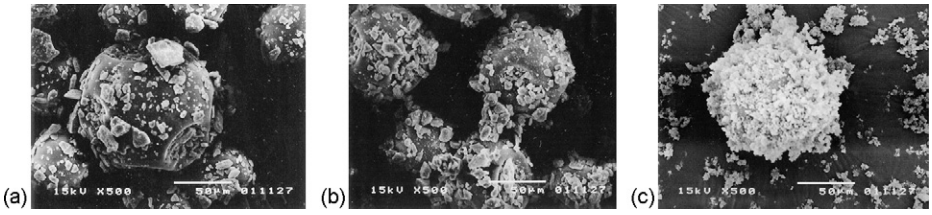

Fig. 7. SEMs of PMs. Each PM contains following troglitazone: (a) intact troglitazone, (b) impact-milled troglitazone and (c) jet-milled troglitazone.

no observed difference between the two milling methods. The reason for the easier dissolution of milled troglitazone into PVP is considered below.

The SEMs of the PMs are shown in Fig. 7. It was observed that troglitazone drug substances were adhered onto the surface of PVP. Amount of jet-milled troglitazone adhered onto PVP is more than that of unmilled and impact-milled troglitazone. Adhesion force of finer particles like jet-milled troglitazone was stronger and the number of fine particles existed in the PM when it was mixed at the mass ratio. It was speculated that jet milling facilitates the interaction between troglitazone and PVP. The amount of troglitazone dissolving into rubbery state PVP increased with an increase in the specific surface area of the drug substance. However, because of the similarity between the impact- and jet-milled samples in Figs. 5 and 6, this could not fully support the speculation that milled troglitazone easily dissolves into rubbery state PVP.

DSC studies of PMs were conducted to confirm the existence of interaction between troglitazone and PVP as shown in Fig. 8. In this study, in order to eliminate the evaporation heat of the water in the PMs, heating was held at 100 °C for 3 min. Since, the SDs were prepared by heating at 130 °C, the melting of the H form should be discussed here. There was a difference in the DSC curves between the PM and drug substance alone since PVP inhibited the crystallization and re-melting behavior of the melted L form with increased temperature. In the case of drug substance alone, the crystallized L form re-melted and affected the melting of the H form. Actually, the melting point at which the H form separates from the L form has been reported to be about 194 °C (peak top) (Suzuki et al., 2002). The melting points of the H form in the PM containing unmilled troglitazone were 159 °C (onset temperature) and 184 °C (peak temperature). On the other hand, the melting points of the H form in the PM containing impact-milled troglitazone were 154 °C (onset temperature) and 173 °C (peak temperature). Besides, the melting points of the H form in the PM containing jet-milled troglitazone were 154 °C (onset temperature) and 171 °C (peak temperature). It is commonly believed that the melting point shifts to a lower temperature if the specific interaction between drug and carrier occurs more strongly. Therefore, these results indicated that the specific interaction between troglitazone and PVP during heating could occur more easily by milling. As described in Table 2, the polar functions such as the imino and phenolic hydroxyl groups appeared on the surface by milling. Since, these functional groups exposed on the surface of the crystals play a role in interaction with molten PVP during heating, milled troglitazone can dissolve into PVP more easily than unmilled troglitazone. This is the reason why there is a similarity between the impact- and jet-milled samples in Figs. 5 and 6. It has been reported that the interaction between indomethacin and CrosPVP can easily occur during heating when the PM is subjected to a high-speed elliptical-rotor type blender (Theta-Composer) (Fujii et al., 2005). In this case, also, inside of indomethacin crystals appeared on the surface by milling with the Theta-Composer and this facilitated the interaction during heating.

FT-IR spectroscopy was employed to study the interaction in solid dispersions between drug and carrier (Taylor and Zografi, 1997). FT-IR spectra of troglitazone, PVP, PMs and SDs are shown in Fig. 9. Troglitazone has an N–H stretching vibration at 3294 cm^{-1}. Also, PMs have the peak at the same wave number

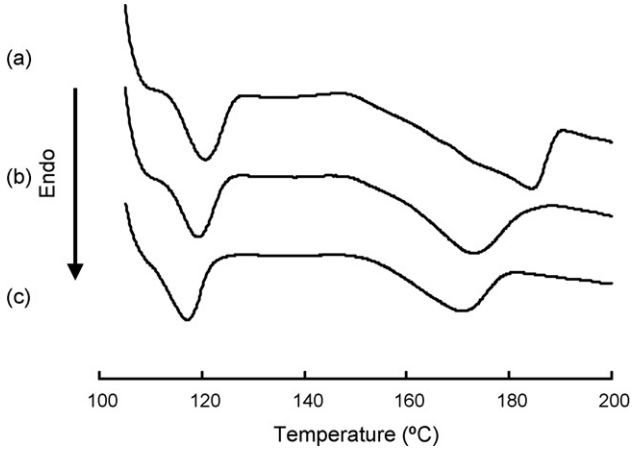

Fig. 8. DSC curves of PMs. Each PM contains the following troglitazone: (a) unmilled troglitazone, (b) impact-milled troglitazone and (c) jet-milled troglitazone.

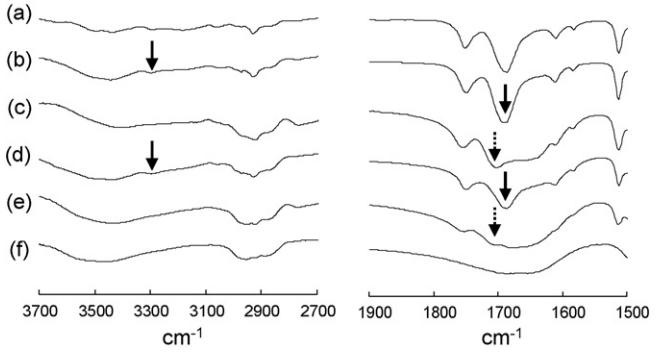

Fig. 9. IR spectra in the range of 1500–1900 and 2700–3700 cm^{-1} of (a) troglitazone, (b) PM (troglitazone: PVP = 1:2), (c) SD (troglitazone: PVP = 1:2), (d) PM (troglitazone: PVP = 2:1), (e) SD (troglitazone: PVP = 2:1) and (f) PVP. Slid and dotted arrows indicate the specific peak of PMs and SDs, respectively.

(arrows indicate), irrespective of the troglitazone–PVP ratio. On the other hand, these peaks were not observed in SDs. They might shift somewhere, although they could not be specified since their peaks were weak. Regarding C=O stretching vibrations, troglitazone has peaks at 1686 and 1752 cm^{-1}. These peaks are observed at the same wave number in the spectra of PMs. PVP also has a C=O stretching vibration at 1684 cm^{-1}. In the case of SDs, the characteristic peak at 1704 cm^{-1} was observed, irrespective of troglitazone–PVP ratio (dotted arrows indicate). It may be considered that C=O stretching vibrations of PVP change in SDs. Therefore, it is speculated that hydrogen bonding between the N–H of troglitazone and the C=O of PVP can be formed.

4. Conclusion

SDs prepared from milled troglitazone, irrespective of milling method, showed almost 100% dissolution when not less than 7.5% of water was added in PMs while for unmilled troglitazone this was when not less than 12.8% of water was added. The PM containing unmilled troglitazone must be heated above at least 50 °C higher than the T_g to obtain an SD showing 100% dissolution, while the PMs containing milled troglitazone could be heated sufficiently above only 20 °C higher than the T_g to obtain an SD showing 100% dissolution. The melting points of troglitazone in PMs containing milled troglitazone, irrespective of milling method, were lower than those in PMs containing unmilled troglitazone. These results indicated that specific interaction could occur more easily during heating between milled troglitazone and PVP during preparation by a closed melting method. In addition, Fourier transform infrared study indicated that hydrogen bonding could occur between the N–H of troglitazone and the C=O of PVP.

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