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International Journal of Pharmaceutics 302 (2005) 103–112
international journal of pharmaceutics
www.elsevier.com/locate/ijpharm

Effects of water content in physical mixture and heating temperature on crystallinity of troglitazone-PVP K30 solid dispersions prepared by closed melting method

Susumu Hasegawa [a,*], Takeshi Hamaura [a], Naho Furuyama [a], Akira Kusai [a], Etsuo Yonemochi [b], Katsuhide Terada [b]

[a] *Pharmaceutical Development Laboratories, Sankyo Co., Ltd., 1-12-1, Shinomiya, Hiratsuka, Kanagawa 254-0014, Japan*
[b] *School of Pharmaceutical Sciences, Toho University, 2-2-1, Miyama, Funabashi, Chiba 274-8510, Japan*

Received 12 April 2005; received in revised form 27 May 2005; accepted 18 June 2005
Available online 15 August 2005

Abstract

Troglitazone, which possesses two asymmetric carbons, is obtained as a mixture of four isomers present in equal amounts. Troglitazone (Lot T003) has two melting points, about 120 and 175 °C. To increase the bioavailability of insoluble troglitazone, troglitazone-polyvinylpyrrolidone K30 (PVP) solid dispersions (SDs) were prepared with water by a unique closed melting method. In this study, the effects of the water content in the physical mixture (PM) and the heating temperature on the apparent crystallinity of troglitazone in SDs prepared by this method were investigated. When the water content in the PM was controlled at 3%, although the apparent crystallinity of troglitazone in the SD prepared by heating at 105 °C did not decrease (99%), that of the SDs prepared by heating at 130 and 150 °C were reduced to 54 and 11%, respectively. This result indicated that the meltage of troglitazone varies depending on the heating temperature. The apparent crystallinity of troglitazone in the SDs decreased with increase in water content in the PM. In particular, SDs prepared by heating at 130 and 150 °C showed 0% apparent crystallinity when the water content in the PM were more than 13 and 8%, respectively. When the heating temperature used was higher than the glass transition temperature of PVP plasticized with water, troglitazone crystals were dissolved in the rubbery PVP. Therefore, even if the heating temperature is lower than the melting point of troglitazone during preparation, controlling the water content in the PM at a high level can produce a troglitazone SD with 0% apparent crystallinity.

Keywords: Troglitazone; PVP; Solid dispersion; Water content; Heating temperature; Crystallinity

1. Introduction

Troglitazone is an oral antidiabetic drug (Yoshioka et al., 1989, 1991) that improves insulin sensitivity and responsiveness. Troglitazone also lowers hepatic

* Corresponding author. Tel.: +81 463 31 6425; fax: +81 463 31 6475.
E-mail address: suhase@sankyo.co.jp (S. Hasegawa).

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doi:10.1016/j.ijpharm.2005.06.021

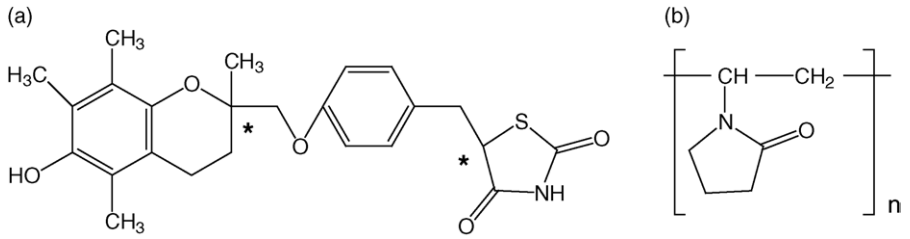

Fig. 1. Chemical structures of troglitazone and polyvinylpyrrolidone. Asterisks represent asymmetric carbons.

glucose production. This compound is not only effective in insulin-dependent diabetes mellitus patients, but also in non-insulin-dependent diabetes mellitus patients (Fujiwara et al., 1988; Suter et al., 1992).

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. 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). On the other hand, the solubility of each isomer of troglitazone is about 10 μg/mL in water, which low solubility results in low bioavailability (Suzuki et al., 2002).

Solid dispersions (SDs) have traditionally been used as an effective method to improve the dissolution properties and bioavailability of poorly water-soluble drugs (Chiou and Riegalman, 1971; Serajuddin, 1999; Leuner and Dressman, 2000). The melting technique is one of the most widely used methods to prepare amorphous solid dispersions although drug degradation must be taken into account as high temperature conditions are used (Hancock and Zografi, 1997; Serajuddin, 1999). In order to lower the heating temperature, a twin-screw extruder has been developed as one solution. The twin-screw extruder can apply shear force to the physical mixture (PM) of drug and carrier and produce an SD at a lower temperature than the melting point of the drug (Nakamichi et al., 2002). However, in this study, SDs obtained using a unique closed melting method were prepared in order to confirm the effects of water content and temperature in the PM without shear stress.

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 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 this study, water was selected as a volatile plasticizer, and SDs of troglitazone with polyvinylpyrrolidone K30 were prepared by a unique closed melting method. The effects of the water content in the physical mixture (PM) and the heating temperature on the apparent crystallinity of troglitazone in SDs prepared by this method were investigated.

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. Physical mixtures (PMs)

PMs were prepared by mixing troglitazone with PVP in a weight ratio of 1:2 using a high shear mixer.

2.2.1.1. Solid dispersions (SDs) prepared by closed melting method. One gram of the PM was weighed into glass ampoules (20 mL) and the water content was controlled by storing at various equilibrium relative humidity levels (adsorption method) or by adding some water directly (charging method). The glass ampoules were sealed. And the glass ampoules were heated for 90 min at 105, 130 or 150 °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 each temperature in order to eliminate the water from the SD systems. The resultant SDs were sieved through a 300 μm sieve.

2.2.1.2. Solid dispersions prepared by unsealed melting method. These samples were prepared according to the adsorption method in Section 2.2.1.1 without sealing of the glass ampoules.

2.2.2. Solid dispersions prepared by the solvent method

About 5 g of PM was dissolved in 20 mL of a 1:2 mixture of ethanol and acetone. This solution was dried in a Rotavapor RE-111 rotary evaporator (Shibata, Tokyo, Japan). The resultant solid dispersion was used as it was.

2.3. Characterization

2.3.1. Solubility

About 10 mg of troglitazone sample was put into a glass tube. Ten millilitres of phosphate buffer was added and the suspension was incubated at 37 °C. After 20 min, 1 mL of suspension was filtered with a PVDF filter Mini-Uniprep™ (5 mm in inside diameter, and pore size of 0.45 μm, Whatman Inc., USA). The filtrate was immediately measured by HPLC. The ODS column used was 4.6 mm i.d. × 150 mm, particle size: 5 μm (Beckman Coulter Inc., USA). The mobile phase was water:acetonitrile:glacial acetic acid (400:600:1) with a flow rate of 1 mL/min. The wavelength of the UV detector (Shimadzu, Kyoto, Japan) was set at 225 nm, and the injection volume was 10 μL.

2.3.2. Dissolution

The dissolution of troglitazone from solid dispersions and physical mixtures was determined using 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. As troglitazone is an acidic compound, its solubility increases at high pH range as shown in Table 1. The pH of the test solution, pH 9, was determined based on the solubility of troglitazone. Each sample (PM or SD) containing 100 mg of troglitazone was 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).

Table 1
Solubility of troglitazone drug substance at various pHs (1.2–9.7)

pH	Dissolved amount (μg/mL)
1.2	<1
6.8	<1
8.0	6
8.5	13
9.0	41
9.7	151

2.3.3. Differential scanning calorimetry (DSC)

DSC measurement of troglitazone was carried out in hermetically sealed aluminum pans using a Thermo plus 8230L (Rigaku, Tokyo, Japan) calibrated with indium. Troglitazone was heated under a dry nitrogen gas purge between 40 and 200 °C at a rate of 10 °C/min. The glass transition temperature (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 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.

2.3.4. Powder X-ray diffraction (PXRD)

The 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) 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}.

2.3.5. 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.

2.3.6. Moisture sorption isotherm

One gram of troglotazone, PVP and PM were weighed into glass bottles and stored at 25 °C with various equilibrium relative humidity levels until a constant weight was obtained. Then, the water content was estimated by the Karl Fischer method. Theoretical value of PM was calculated from the water content of troglitazone and PVP.

2.3.7. Apparent crystallinity of troglitazone drug substance estimated from PXRD

The apparent crystallinity of troglitazone drug substance at various temperatures (30, 100, 120, 130, 150 and 175 °C) was estimated from the peak area/total area of PXRD. The apparent crystallinity at 30 and 175 °C were specified to be 100 and 0%, respectively.

2.3.8. Apparent crystallinity of troglitazone in SD estimated from dissolution

As the SD prepared by the solvent method was confirmed to be completely amorphous by DSC and PXRD, this SD was used for the calculation of apparent crystallinity. The apparent crystallinity of the PM and SD prepared by the solvent method were specified to be 100 and 0%, respectively. The SD and PM were mixed in a certain ratio, such that the SDs had apparent crystallinity of 0, 10, 20, 30, 40, 50, 60, 70, 80, 90 and 100%, respectively. A dissolution test of the resultant mixtures was conducted. A regression curve was obtained by plotting the mixture ratio and percent dissolution at 60 min. There was a negative relationship between the mixture ratio and the percent dissolution. The apparent crystallinity of the SDs prepared by the melting method was calculated using the equation of this regression curve.

3. Results and discussion

A typical DSC thermogram of troglitazone drug substance (Lot T003) is shown in Fig. 2. There were two endothermic peaks at about 120 and 175 °C. It has been reported from a hot stage microscopic study that these endothermic peaks were 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 troglitazone drug substance at about 120 °C is due to the melting of the RR/SS form and the other peak at about 175 °C is due to the melting of the RS/SR form (Suzuki et al., 2002). In this paper, the RR/SS form with melting point at about 120 °C and the RS/SR form with melting point at about 175 °C are abbreviated as the L form and the H form, respectively.

The PXRD patterns of troglitazone drug substance (Lot T003) at various temperatures (30, 100, 120, 130, 150 and 175 °C) are shown in Fig. 3a. Although there were few changes in the PXRD at 30 and 100 °C, 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 remarkably decreased at 120 °C. This results from the fact that the L form crystals melted at 120 °C. The PXRD pattern at 130 °C was not changed from that

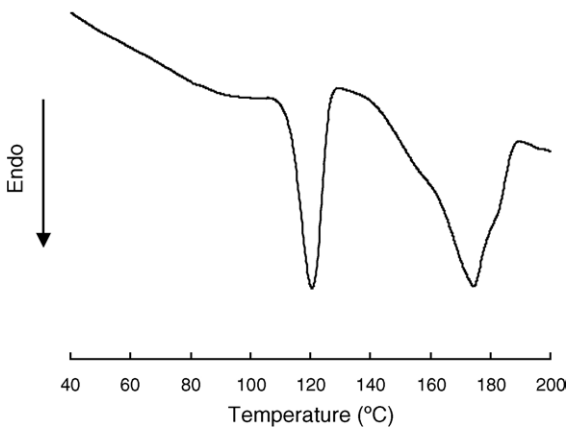

Fig. 2. DSC thermogram of troglitazone.

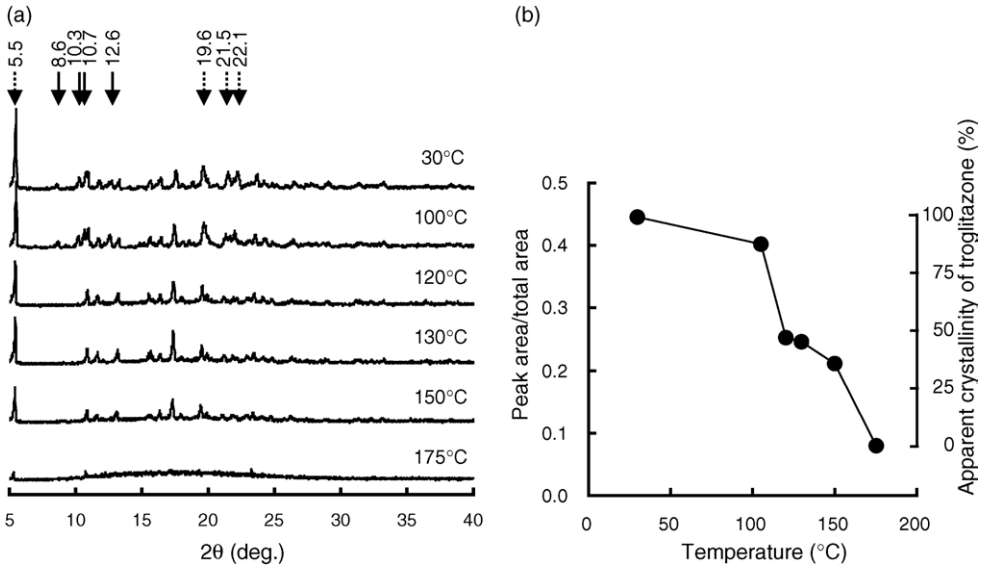

Fig. 3. (a) PXRD data of troglitazone at various temperatures and (b) relationship between temperature and area ratio (peak area/total area).

of 120 °C. The whole peak intensity was decreased at 150 °C as a part of the H form crystals melted at even 150 °C, 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 melted. Since the crystallinity of troglitazone changed at each temperature level, apparent crystallinity was calculated from the peak area/total area and was plotted against temperature as shown in Fig. 3b. The peak area/total area was 0.44 at 30 °C and was reduced to 0.25 at 120 °C owing to melting of the L form crystals. Moreover, it was reduced to 0.08 at 175 °C owing to the melting point of the H form crystals. The apparent crystallinity of troglitazone was reduced to almost half (48%) at 120 °C, to 36% at 150 °C and to 0% at 175 °C depending on the change in the physical state of troglitazone.

In this study, SDs were prepared by the unique closed melting method. Attention was paid to the changes in the physical state (crystallinity) of troglitazone at each temperature used for the preparation of the SDs (105, 130 and 150 °C). To be more precise, neither the L form nor the H form melts at 105 °C, only the L form melts at 130 °C, and the L form and a part of the H form melt at 150 °C.

Fig. 4 shows a typical dissolution profile of the PM and its SDs. The dissolution percent of the PM remained at an extremely low level (about 3%). On the other hand, the dissolution percent of troglitazone from the SDs prepared by heating at 130 °C with an amount of water increased remarkably compared to that from the PM. Moreover, there is a great difference in the dissolution percent, depending on the water content in PMs. The dissolution rate of the SD prepared by heating at 130 °C with 2.9 and 18.4% of water were about 40

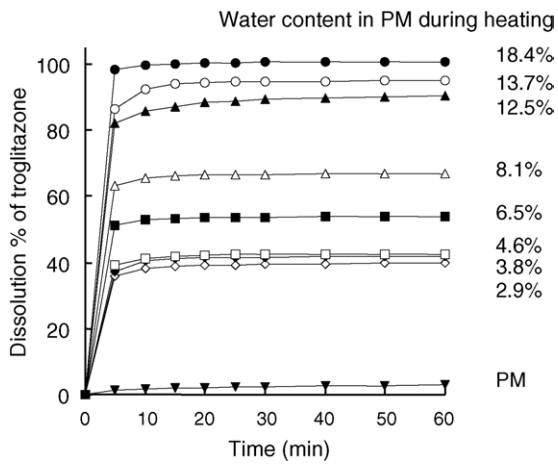

Fig. 4. Typical dissolution profiles of troglitazone from PMs and SDs. SDs were prepared from PMs containing a certain amount of water (2.9–18.4%) by heating at 130 °C.

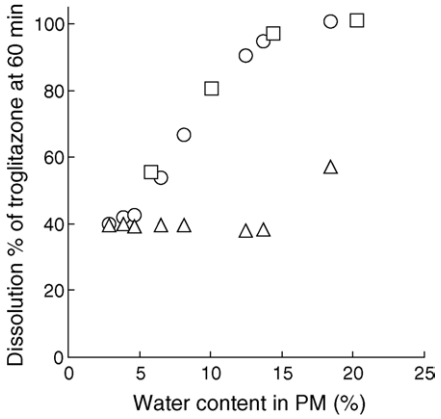

Fig. 5. Effect of water content in PM on dissolution percent of troglitazone at 60 min. Samples were prepared by heating at 130 °C under the various conditions. Triangle: open, circle: closed (charging method), square: closed (adsorption method).

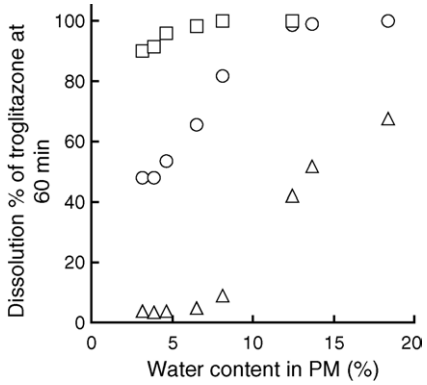

Fig. 6. Effects of water content in PM and heating temperature on dissolution percent of troglitazone at 60 min. Triangle: 105 °C, circle: 130 °C, square: 150 °C.

and 100%, respectively. The dissolution rates increased with an increase in water in the PMs. The solubility of troglitazone at pH 9 was 41 μg/mL as shown in Table 1. The theoretical concentration was 200 μg/mL in each vessel in this study, at which concentration troglitazone was dissolved completely in the dissolution media. Therefore, the dissolution of troglitazone from the SDs was supersaturated. This supersaturation was maintained for 60 min. Without HPMC, the dissolution percent of troglitazone decreased gradually with time (data not shown). It has been reported that HPMC could strongly inhibit the precipitation (recrystallization) of drugs (Usui et al., 1997). From the dissolution pattern, the dissolution property could be evaluated using the dissolution percent at 60 min ($D_{60\,\mathrm{min}}$) in subsequent evaluation.

Fig. 5 shows the relationship between water content in the PM and the $D_{60\,\mathrm{min}}$ of SDs prepared by heating at 130 °C. The $D_{60\,\mathrm{min}}$ of SDs prepared in sealed glass ampoules was increased with an increase in water content in the PM. There were no differences in dissolution by controlling for water content in PMs stored at various equilibrium relative humidity levels (adsorption method) or by adding water directly (charging method). It was speculated that both adsorbed and charged water in the PMs was redistributed in sealed glass ampoules during heating at 130 °C. Thus, subsequent experiments were conducted by the charging method. In contrast, the $D_{60\,\mathrm{min}}$ of SDs prepared in unsealed glass ampoules was scarcely dependent on the water content in the PM because of water volatilization during heating. Since half of the crystals (L form) melted at 130 °C and changed to amorphous state in the SDs, dissolution of SDs prepared in unsealed glass ampoules was improved to around 40% in the case of 2.9–13.7% water content in the PM. It was speculated that the water had evaporated before playing a role as a plasticizer. In the case of 18.7% of water content in the PM, dissolution of the SDs prepared in unsealed glass ampoules was improved to 57% as it took time for water to evaporate.

As shown in Fig. 6, the effects of water content and the heating temperature on the $D_{60\,\mathrm{min}}$ of SDs were examined. The dissolution property of SDs prepared by heating at 150 °C was satisfactory (not less than 90%) even when the water content in the PM was low. The $D_{60\,\mathrm{min}}$ of the SDs prepared by heating at 130 °C was slightly below 50% when the water content in the PM was about 4%. However, it increased with an increase in water content in the PM and was almost 100% when the water content in the PM was 12.5% and above. The $D_{60\,\mathrm{min}}$ of SDs prepared by heating at 105 °C was extremely low and was the same as that of PM with water content of below 6.5%. The $D_{60\,\mathrm{min}}$ increased with an increase in water content in the PM but only up to 68% within the range of the water content in PM in this study. Commonly, in the melting method, amorphous solid dispersion is prepared by heating above the melting point of the drug and cooling off. However, in this study, it was shown that it was possible to prepare

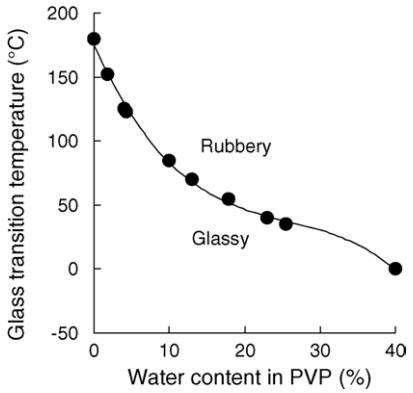

Fig. 7. Relationship between the water content in PVP and glass transition temperature. The line represents the fit to polynomial regression.

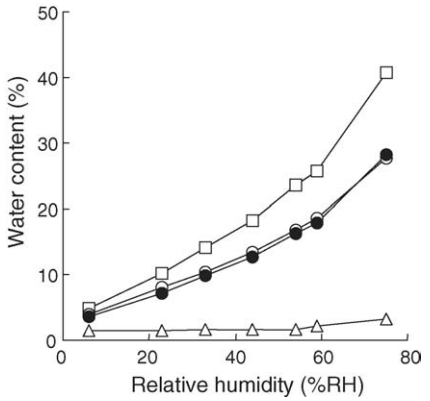

Fig. 8. Moisture sorption isotherm (25 °C) of troglitazone, PVP and PM. Triangle: troglitazone, square: PVP, open circle: PM (actual), closed circle: PM (calculated).

a solid dispersion whose dissolution percent was 100% even when the heating temperature during the preparation was 130 °C, below the melting point of the H form. It is preferred that the heating temperature during the preparation is as low as possible from the viewpoint of avoiding degradation of the drug. Why was it possible to prepare a solid dispersion whose dissolution percent was 100% even when the heating temperature during the preparation was below the melting point of the H form? It is speculated that glass transition temperature (T_g) of PVP is a factor.

Fig. 7 shows a negative relationship between water content and the T_g of PVP. Glass transition of polymers occurs within a broad temperature range. Therefore, T_g was defined as the middle point between the onset and the end of the T_g in this study. The T_g of PVP decreased with an increase in water content. This result indicated that water acted as a plasticizer for PVP, and the T_g of PVP can be controlled by the water content. It has been reported that the Gordon–Taylor equation is not suitable to predict the T_g values of a PVP–water system above a water fraction of around 0.1 (Hamaura and Newton, 1999). Therefore, the curve fitting was performed using polynomial regression in this study.

The moisture adsorption isotherm (25 °C) of troglitazone, PVP and PM is shown in Fig. 8. Troglitazone had the non-hygroscopicity at any relative humidity while PVP had the hygroscopicity. There is a similarity in adsorption pattern of PM between the actual and calculated value. Additionally, as the DSC thermogram of troglitazone in the presence of water under closed conditions did not change (data not shown), it was considered that there was little interaction between troglitazone and water. Therefore, it was thought that water mainly interacted with PVP and acted as a plasticizer for PVP.

Therefore, as the water content in PVP could be calculated from that in the PM, the T_g value of PVP could be estimated. In order to correlate the physical state of PVP with the $D_{60\,min}$ of SDs, the plots in Fig. 6 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. 9. The difference between the heating temperature and T_g of plasticized PVP is used as an indicator of the physical (glass or rubber) state of PVP (Lai et al., 1999). When this value is plus, the physical state of PVP is thought to be a rubbery state that shows high mobility. In contrast, when this value is minus, the physical state of PVP is thought to be a glassy state that shows low mobility. $D_{60\,min}$ remarkably increased with increase in this indicator at around zero irrespective of heating temperature. This indicates that the physical change (glass to rubber) of PVP affects the dissolution property of SDs. The $D_{60\,min}$ of SDs prepared by heating at 105 °C (below the melting point of the L form) was extremely low when the indicator was minus, which showed PVP was the glassy state. Once the indicator changed to plus, the $D_{60\,min}$ increased with an increase in the indicator. When the indicator was 51 °C, the $D_{60\,min}$ was 68%. It is speculated that the plasticized PVP having high mobility dissolved troglitazone crystals during heating and

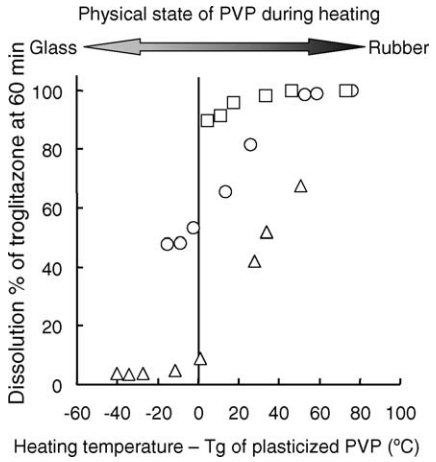

Fig. 9. Relationship between the physical state of PVP during heating (heating temperature, T_g of plasticized PVP) and dissolution percent of troglitazone at 60 min. Triangle: 105 °C, circle: 130 °C, square: 150 °C.

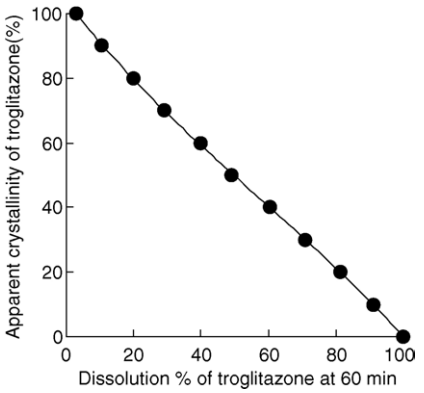

Fig. 10. Dissolution percent of troglitazone at 60 min from the samples of PM (crystallinity: 100%) and SD (crystallinity: 0%) mixed in certain ratios.

amorphous SDs were obtained although some crystals existed without change. By the same token, the $D_{60\,min}$ of SDs prepared by heating at 130 °C (above the melting point of the L form and below the melting point of the H form) increased with an increase in the indicator and was 100% when the indicator was 53 °C and above. When the sample showing a $D_{60\,min}$ of 100% (high water content) was heated at 130 °C, it was a limpid liquid. It has been reported that the dissolution property of a drug is improved by preparing its solid dispersions by dissolving the drug in a melted carrier such as PEG (Owusu-Ababio et al., 1998; Joshi et al., 2004). The $D_{60\,min}$ of the SDs was about 50% when the water content was as low as 5% since the L form melted even though almost all of the H form had not dissolved into the PVP that was in the glassy state at this temperature. As a result, it was speculated that half of the troglitazone crystals (L form) were transformed to an amorphous state. Heating the PM at 150 °C caused the SDs to have a $D_{60\,min}$ of not less than 90%, as some part of the H form of troglitazone started to melt at 150 °C.

Next, the relationship between the dissolution property of the SDs and the apparent crystallinity of troglitazone is discussed. It has already been confirmed that troglitazone in an SD having a crystallinity of 36% exists in two physical states, crystal and amorphous, using microthermal analysis (μTA) (Hasegawa et al., 2004). As the SD prepared by the solvent method was confirmed to be completely amorphous by DSC and PXRD, this solid dispersion was used for the calculation of apparent crystallinity. Fig. 10 shows the relationship between the apparent crystallinity of troglitazone in SD and the dissolution percent of troglitazone from the SD at 60 min. There was a negative relationship between apparent crystallinity and dispersion percent. In turn, the $D_{60\,min}$ of SD increased with an increase in amorphous troglitazone in SD. Considering the dissolution pattern in Fig. 4, it was speculated that only the amorphous part in SD dissolved in a few minute and the crystal part hardly dissolved since the dissolution of the PM having an apparent crystallinity of 100% remained at an extremely low level. Thus, the amorphous content in SD could be estimated from the regression curve. In order to determine a relationship between the physical state of PVP and the apparent crystallinity of troglitazone in SDs, the plots in Fig. 9 were converted, as shown in Fig. 11. When the PVP was in the glassy state, although the apparent crystallinity of troglitazone in the SD prepared by heating at 105 °C did not decrease (99%), that of the SDs prepared by heating at 130 and 150 °C were reduced to 54 and 11%, respectively. The difference in pattern at each temperature was speculated to be dependent on the physical state of troglitazone during heating. The apparent crystallinity of troglitazone in the SDs decreased with an increase in water content in the PM. In particular, SDs prepared by heating at 130 and 150 °C showed 0% apparent crystallinity when the water content in the PM were more than 12.5 and 8.1%, respectively.

Table 2
Comparison of apparent crystallinity estimated from PXRD and dissolution

Temperature during sample preparation (°C)	Apparent crystallinity of troglitazone[a] (%)	Apparent crystallinity of troglitazone in SDs[b] (Physical state of PVP)			
		2.9[c]	6.5[c]	13.7[c]	18.4[c]
105	89	99 (G)	97 (G)	45 (R)	29 (R)
130	46	54 (G)	36 (R)	1 (R)	0 (R)
150	36	11 (R)	2 (R)	0 (R)	0 (R)

[a] The apparent crystallinity of troglitazone estimated from the PXRD of the drug substance is based on the data presented in Fig. 3b.
[b] The apparent crystallinity of troglitazone in SDs estimated from their dissolution is based on the data presented in Fig. 10. The physical state of PVP is described in parentheses. Glassy state and rubbery state are abbreviated as G and R, respectively.
[c] Water content in PM (%).

The apparent crystallinity of troglitazone determined by PXRD and dissolution from SDs is summarized in Table 2. The physical states of PVP during heating are also shown in this table. The apparent crystallinity of troglitazone in SDs prepared by heating at 105 and 130 °C with 2.9% of water showed good agreement with that calculated from PXRD. In this case, the water content was so low that it could not plasticize PVP. At 130 °C, only the L form of troglitazone melted and it became amorphous in the solid dispersion irrespective of the physical state of PVP since PVP was in the glassy state that showed low mobility during heating. On the other hand, there is a difference (36 and 11%) in the case of heating at 150 °C. Since the apparent crystallinity of troglitazone drug substance estimated from PXRD changed from 46 to 36%, 10% of troglitazone drug substance (H form) was thought to be in liquid form when the heating temperature was changed from 130 to 150 °C. Regarding the apparent crystallinity of troglitazone in SDs, PVP was in a rubbery state that showed high mobility during heating at 150 °C and a number of the H form crystals dissolved in it during heating. As a result, more troglitazone became amorphous in the SDs when solidified. A decrease in the apparent crystallinity of troglitazone in SDs prepared by heating at 105 °C was caused by only dissolution of troglitazone crystals into rubbery state PVP during heating irrespective of the physical change of troglitazone. An entire amorphous SD could not be prepared by heating at 105 °C in this study, but may be prepared by increasing the water content in the PM which would increase the liquidity of PVP.

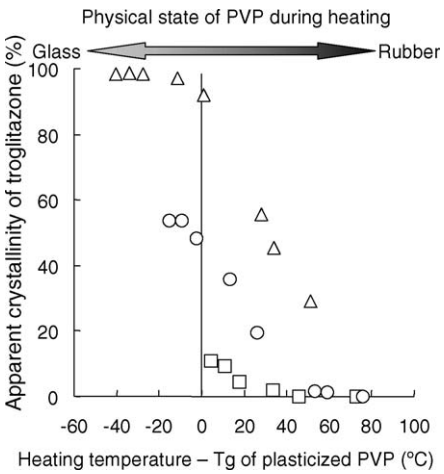

Fig. 11. Relationship between the physical state of PVP during heating (heating temperature, T_g of plasticized PVP) and apparent crystallinity of troglitazone in SDs. Triangle: 105 °C, circle: 130 °C, square: 150 °C.

4. Conclusions

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 preparation. 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 during heating, a troglitazone SD with an apparent crystallinity of 0% can be obtained.

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