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Evaluation of solid dispersions on a molecular level by the Raman mapping technique

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ABSTRACT

Troglitazone containing two asymmetric carbons has four isomers. Crystalline troglitazone consists of two crystalline diastereomer-pairs, RR/SS and RS/SR, which have different melting points. Using a closed melting method, troglitazone–polyvinylpyrrolidone solid dispersions with various crystallinities were prepared. Raman spectroscopy and its mapping technique were applied to discriminate between the crystalline RR/SS, crystalline RS/SR and amorphous form of troglitazone in solid dispersions. The results of the Raman mapping of solid dispersions showed the co-existence of crystal and amorphous forms, and which diastereomer-pairs remained as crystals, in addition to the distribution of the drug. Moreover, the distribution of PVP could be illustrated from the Raman mapping data. Thus, Raman spectroscopy and its mapping technique are useful tools to evaluate crystal and amorphous states, including discrimination of crystalline diastereomer-pairs in solid dispersions. In addition, by describing the distribution of the drug and the carrier, it could be guessed how drug crystals become amorphous during preparation from the point of view of the distribution of the amorphous form of the drug substance and the carrier.

1. Introduction

Many active pharmaceutical ingredients can exist in different polymorphic forms. Polymorphism is especially important for active pharmaceutical ingredients because it may affect the chemical stability and such physico-chemical behavior as the dissolution rate and bioavailability, which affect the safety and efficacy. The existence of drugs in an amorphous form is also an important factor for similar reasons. Several methods have been suggested to improve the dissolution characteristics of poorly water-soluble drugs because the amorphous form is thought to be more desirable than the crystal form from the view point of the solubility and dissolution rate. The solid dispersion technique is one of the most effective and widely used methods (Chiou and Riegelman, 1971; Leuner and Dressman, 2000; Gohel and Patel, 2003). Hydrophilic synthetic polymers have been widely investigated as carrier substances for solid dispersions (Broman et al., 2001; Savolainen et al., 2003). It is reported that polyvinylpyrrolidone inhibits the crystallization of the drug in solid dispersions by generating interaction with numerous organic molecules and by its antiplasticising effect (Taylor and Zografi, 1997; Thybo et al., 2007).

Troglitazone, used as the model drug in this study, has two asymmetric carbons as shown in Fig. 1 and is produced as a mixture of equal amounts of four isomers. These isomers compose two diastereomer-pairs, RR/SS and RS/SR, which have different melting points. In this report, the RR/SS and RS/SR are abbreviated as the L-pair and H-pair, respectively. Drug substance of troglitazone manufactured by method B (Suzuki et al., 2003) exists as a simple physical mixture of equal parts in these diastereomer-pairs, which have melting points of ca. 120 °C (L-pair) and ca. 175 °C (H-pair) (Suzuki et al., 2002). The solubility of each isomer of troglitazone is about 10 μg/mL in water, which could result in low bioavailability (Suzuki et al., 2002). Therefore, the improvement of the solubility is important. It has already been reported that the dissolution profile of troglitazone could be improved when solid dispersions of troglitazone with polyvinylpyrrolidone, the carrier, were manufactured by the closed melting method. The drug substance in solid dispersions is thought to transform into an amorphous form by melting and dissolving in the rubbery carrier. Accordingly, the amount of water, as the volatile plasticizer, as well as the heating temperature, is thought to affect the crystallinity of the drug substance and therefore the dissolution rate (Hasegawa et al., 2005).

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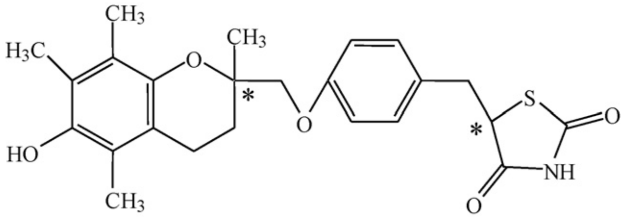

Fig. 1. Chemical structure of troglitazone. Asterisks represent asymmetric carbons.

As troglitazone contains two diastereomer-pairs with different melting points, the impact of the preparing condition of solid dispersions on each diastereomer-pair could be different. Since diastereomer-pairs have different physicochemical properties, diastereomer-pairs remained as crystals and differences in the crystallinity are important factors in the quality of drug products. Therefore, the physical state of the drug, whether it is in a crystal state or an amorphous state, should be thoroughly evaluated, including which diastereomer-pairs remain as crystals in a solid dispersion. In the literature concerning solid dispersions, there are few reports describing the distribution of drugs, although there are many reports on the stability, crystallinity and interaction between the drug and the carrier. The distribution of troglitazone was evaluated using electron probe micro-analysis (EPMA) (Hasegawa et al., 2004). However, EPMA can visualize only the distribution of elements of the drug substance and cannot evaluate the diastereomer-pairs or the physical state of the drug substance. The simultaneous evaluation of the distribution, physical state of drugs including discrimination of diastereomer-pairs remaining as crystals in solid dispersions might offer information about the effect of the preparing conditions on diastereomer-pairs. Many techniques, such as XRPD, NMR, FT-IR and Raman spectroscopy, are reported to be useful tools to determine crystal and amorphous states and to discriminate between polymorphs (Spiegeleer et al., 2005; Sheikhzadeh et al., 2006). However, it is thought to be difficult to analyze the active ingredients contained in tablets using XRPD, NMR and IR because additives like diluents intercept the analysis (Auer et al., 2003). On the other hand, it has been pointed out that nonaromatic, noncrystalline, hydrophilic excipients often have poor Raman scatters in comparison with drug substances that are normally aromatic heterocycles, making it easier to identify the drug peaks even if the drug is present in a much lower concentration than the excipients (Taylor and Langkilde, 2000; Ward et al., 2005). Raman spectroscopy has been utilized for the characterization of various solid-state forms of tablets, including polymorphs, solvates, amorphous materials, salts (Taylor and Langkilde, 2000; Wilkström et al., 2005; Gift and Taylor, 2007). Furthermore, Raman spectroscopy is a nondestructive and rapid measurement method and requires no sample preparation.

The aim of this study was to discriminate between the crystalline L-pair, the crystalline H-pair and the amorphous form by the Raman spectroscopy. In addition, it was conducted to evaluate which remained as crystals in solid dispersions using the Raman mapping technique in order to recognize the effect of the preparing condition on each diastereomer-pair.

2. Materials and methods

2.1. Materials

The drug substance of crystalline troglitazone, Lot T003, was manufactured at Daiichi Sankyo Co., Ltd. The drug substance of crystalline troglitazone, Lot T003, was manufactured at Daiichi Sankyo Co., Ltd. Different synthesis processes of this drug substance result in the creation of different solid states with different physical properties. The drug substance used in this study, Lot T003, was manufactured by method B (Suzuki et al., 2003). The crystallization process of method B is as follows.

Water heated above 55 °C was added to acetone solution in which troglitazone dissolved. The volume of water to the amount of troglitazone was 1.3 times (v/w). Then, this solution was gradually cooled from 55 to 25 °C over a period of 130 min. After cooling, 2.3 times (v/w) of water was dropped at a constant rate into the mixture for 120 min. Subsequently, the crystalline H-pair began to crystallize first and then the crystalline L-pair began to crystallize.

The isolated crystalline L-pair and crystalline H-pair were also manufacturCd at Daiichi Sankyo Co., Ltd. Polyvinylpirrolidone K30 (PVP, X50 = ca. 52 μm) was purchased from BASF Japan, Ltd.

2.2. Sample preparation

2.2.1. Amorphous troglitazone

The crystalline L-pair and H-pair were heated at the temperature of each form's melting point under a nitrogen atmosphere in a differential scanning calorimeter, respectively. After cooling in liquid nitrogen, the resultant solid was used as the amorphous troglitazone.

2.2.2. Physical mixtures

Physical mixtures (PMs) were prepared by mixing troglitazone with PVP in a weight ratio of 2:1 using an agate mortar and pestle.

2.2.3. Solid dispersions

Solid dispersions (SDs) were prepared by the closed melting method as follows. From the PMs, 1 g was placed into each vial and stored in a humidity controller. After the humidity conditioning, PMs which contained 3.6 or 12.8% water were obtained.

After the humidity conditioning, the vials were sealed and heated for 90 min at 105 °C, 130 °C or 150 °C. Then the vials were opened and dried for 10 min at each heating temperature in order to remove the water. The samples were collected from the vials and sieved through a 300-μm sieve to control the particle size and to attain homogeneity. The names of the SDs prepared under the conditions above are stated in Table 1.

Table 1
Names of SDs prepared under various conditions

	Name					
	SD-a	SD-b	SD-c	SD-d	SD-e	SD-f
Water contents of PMs after humidity conditioning		3.6% ($T_g = 132$ °C)			12.8% ($T_g = 70$ °C)	
Heating temperature, Ht (°C)	105	130	150	105	130	150
Relationship between Ht, Mp and T_g	Ht < Mp < T_g	Mp < Ht < T_g	Mp < T_g < Ht	T_g < Ht < Mp	T_g < Mp < Ht	T_g < Mp < Ht

Ht: heating temperature; Mp: melting point of the L-pair; T_g: glass transition temperature of PVP after humidity conditioning.

2.3. Raman spectroscopy

The Raman spectra of the crystalline troglitazone and SDs were recorded with a LabRam HR 800 (Horiba Jovan Yvon) equipped with a 633-nm He–Ne laser. The laser excitation was focused using a 50 objective (OLYMPAS Corporation) and the scattered light was totally transmitted through the notch filter towards the confocal hole and entrance slit of the spectrograph. The stokes-shifted Raman scatter was dispersed using a 600 groove/min grating onto a peltier-cooled changed-coupled device (CCD, Andor Technology PLC) to capture a spectrum. The spectra of crystalline troglitazone were recorded more than once and reproducible results were obtained.

In addition, the Raman spectra of the PM and SDs were obtained in a 200-μm-square area after being compressed at low pressure. Each spot size was about 2-μm and 400 spectra were collected from each 200-μm-square in SDs.

2.4. 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 the anolyte and the catholyte, respectively. About 0.1 g of the sample was weighed accurately, quickly transferred to the titration vessel, and dissolved in the anolyte.

3. Results and discussion

First, the Raman spectra of the crystalline troglitazone were collected. Fig. 2 shows the Raman spectra of the isolated L-pair and H-pair, the crystalline troglitazone manufactured by method B (Suzuki et al., 2003), and PVP, the carrier, over the spectral range 1500–1800 cm^{-1}. Both the L-pair and H-pair had peaks at 1585, 1611 and 1747 cm^{-1}. Each diastereomer-pair had a characteristic peak as shown by the arrows in Fig. 2. The L-pair had a characteristic peak at 1730 cm^{-1} and the H-pair had a characteristic peak at 1685 cm^{-1}. As Taylor and Zografi (1997) reported that 1600–1750 cm^{-1} is the region where the carbonyl stretching is typically observed, these peaks are thought to be related to the carbonyl stretching. Since the molecular species is identical, the spectral differences between L-pair and H-pair represent differences in interaction within the different forms (Grunenberg et al., 1995; Taylor and Zografi, 1997; Cambell Roberts et al., 2002). From the Raman spectra of each diastereomer-pair, it was possible to discriminate between two diastereomer-pairs based on their Raman spectra using the characteristic peaks.

Fig. 3 shows the Raman spectra of amorphous troglitazone made by the melt-quench method from the crystalline L-pair and H-pair, respectively. Relative to the crystalline pairs, the spectra of the amorphous form had broader, less resolved peaks that reflected the random nature of the amorphous form. In addition, the specific peaks of the L-pair and H-pair disappeared and the Raman spectra of the amorphous form were quite similar, although the amorphous forms were made from the L-pair or the H-pair. In other words, the amorphous form had different Raman spectra from those of the crystal form because differences in the interactions between molecules result in differences in the Raman spectra. In particular, the peak at 1747 cm^{-1} which both the L-pair and H-pair possess and which is also related to carbonyl stretching region (Taylor and Zografi, 1997) showed an increase in full-width at half maximum when compared with the crystal. Since Murphy et al. (2005) used the full-width at half maximum to distinguish crystalline and amorphous regions, the full-width at half maximum and the shape of the peak around 1747 cm^{-1} was used to discriminate between the crystal and amorphous forms in this report. In addition, used as a carrier, PVP did not have a sharp peak but had a small broad peak whose top was around 1661 cm^{-1}. Therefore, it could be thought that the peak of PVP did not affect that of troglitazone in the spectral region 1500–1800 cm^{-1}. These results indicated that the crystalline L-pair, crystalline H-pair and amorphous form of troglitazone in SDs could be determined using Raman spectra.

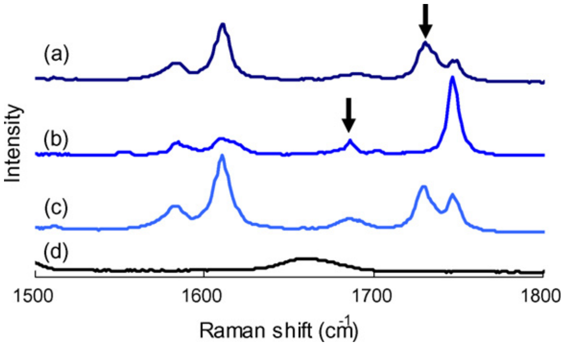

Fig. 2. Raman spectra of crystalline troglitazone and PVP over the spectral range 1500–1800 cm^{-1}: (a) L-pair; (b) H-pair; (c) Lot T003; (d) PVP. Arrows indicate the characteristic peak of the each diastereomer-pair.

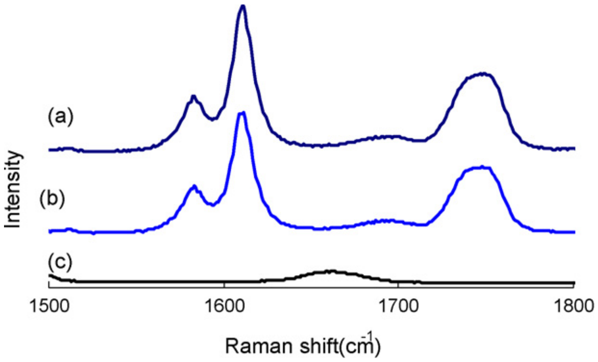

Fig. 3. Raman spectra of amorphous troglitazone (a and b) and PVP (c) over the spectral range 1500–1800 cm^{-1}. Amorphous troglitazone was prepared from (a) the L-pair and (b) the H-pair, respectively.

A previous study (Hasegawa et al., 2005) demonstrated that the crystallinity of troglitazone in SDs was affected by the preparing conditions, such as the water content of the PM and the heating temperature. In the PM in this study, two levels of water content and three heating temperatures were selected to make SDs of varying crystallinity. The selected heating temperatures were 105 °C, 130 °C and 150 °C. The temperature 105 °C is lower than the melting points of both the L-pair and H-pair, whereas 130 °C and 150 °C are temperatures that are higher than the melting point of the L-pair but lower than that of the H-pair. The water content was controlled by humidity conditioning of the PM before preparing SDs.

SDs were prepared at different heating temperatures using PMs which contained 3.6 or 12.8% water. Since it was reported that troglitazone had nonhygroscopicity at any relative humidity while PVP had hygroscopicity, it could be said that water mainly adsorbed to PVP (Hasegawa et al., 2005). As absorbed water acts as a plasticizer (Hamaura and Newton, 1999), the glass transition temperature (T_g) of PVP after humidity conditioning is lowered (Fitzpatrick et al., 2002). The calculated T_gs of PVP after the humidity conditioning were ca. 132 °C for PMs containing 3.6% water and ca. 70 °C for PMs containing 12.8% water. T_gs in this paper is defined as those after the humidity conditioning. The physical state of PVP was a rubbery state when the heating temperature was higher than T_g and a glassy state when the heating temperature was lower than T_g.

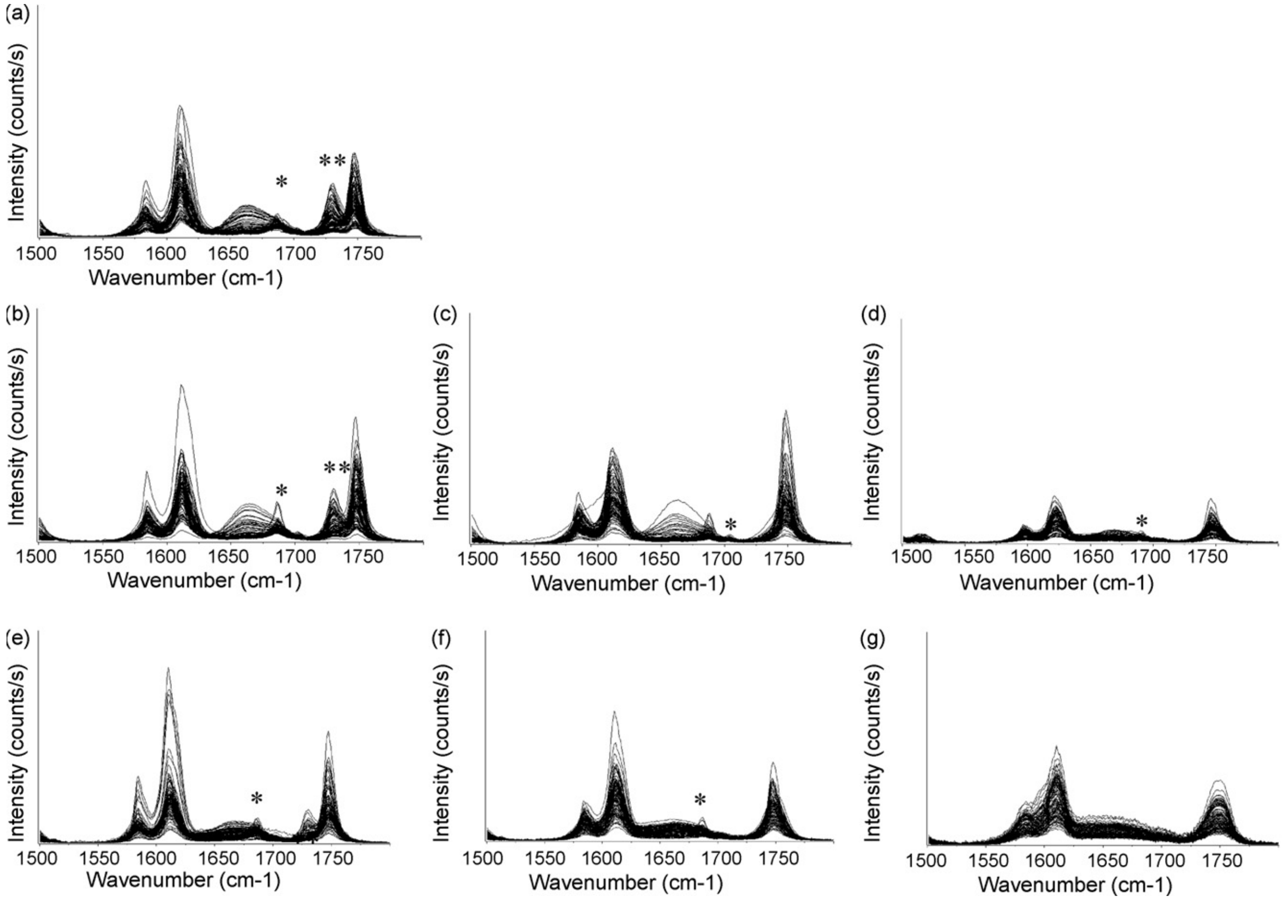

Fig. 4. All the Raman spectra of PM and SDs within 200 μm square (mapping areas). Asterisks indicate the characteristic peak of each diastereomer-pair (**, L-pair; *, H-pair): (a) PM; (b) SD-a; (c) SD-b; (d) SD-c; (e) SD-d; (f) SD-e; (g) SD-f.

The prepared SDs were milled gently, meshed to make them uniform and compressed at a low pressure to make a flat surface in order to make it easy to focus when the Raman spectra were collected. There might be several factors which induce crystallization and it has been reported that crystallization might be induced by compression (Elamin et al., 1994). However, in this instance, the pressure was quite low and no crystallization was detected from the XRPD analysis and the thermal analysis after compression (data not shown). After compression, the Raman spectra were collected within a 200-μm square in the SDs at 10-μm steps.

Fig. 4 shows all the Raman spectra of the PM and SDs collected from 200-μm square. There was no difference between the spectra of PM and those of SD-a, whose heating temperature was lower than the T_g and the melting point of the L-pair. However, other SDs showed that the intensity of the Raman spectra descended and that the spectra were broadened. This tendency became more predominant as the heating temperature and water content were increased. As the Raman spectra of amorphous troglitazone was broader and the intensity descended when compared to that of the crystal, it could be said that these changes of the Raman spectra in SDs indicated a lowering of the crystallinity of troglitazone. The dissolution test and XRPD results also indicated a lowering of the crystallinity.

Besides the lowering of crystallinity, Fig. 4 also indicates the coexistence of crystalline L-pair, crystalline H-pair and amorphous troglitazone in SDs, since there were the characteristic peaks of each diastereomer-pair, and both broad peaks and sharp peaks. Therefore, the visualization of crystalline diastereomer-pairs and amorphous troglitazone was conducted.

At first, the full-width at half maximum of troglitazone 1747 cm^{-1} peak was used to visualize the distribution of crystal and amorphous troglitazone in SDs because the full-width at half maximum around 1747 cm^{-1} of the amorphous troglitazone was different from that of the crystalline troglitazone. The color in Fig. 5 represents the full-width at half maximum around 1747 cm^{-1}. In Fig. 5, the large value of the full-width at half maximum (green regions) was thought to describe the amorphous regions. Fig. 5 shows SDs containing crystal regions and amorphous regions. The amorphous regions grew larger as the heating temperature and water content were increased.

In addition, the distribution of the crystalline L-pair, the crystalline H-pair and amorphous troglitazone were illustrated in order to visualize the distribution of diastereomer-pairs of the troglitazone and amorphous trolglitazone in SDs (Fig. 6). Diastereomer-pairs could be determined on the characteristic peak, at 1730 cm^{-1} for the L-pair and at 1685 cm^{-1} for the H-pair, respectively. When comparing the Raman spectra of SD-f, whose crystallinity was 0% based on the dissolution result and the X-ray diffraction pattern, to that of the amorphous troglitazone prepared from the drug substance (shown in Fig. 3), the peak of the crystal at 1747 cm^{-1} shifted to 1750 cm^{-1} for the solid dispersion and to 1745 cm^{-1} for amorphous troglitazone. Consequently, it was thought to be a favorable method to discriminate between the crystal and amorphous forms and the diastereomer-pairs and to illustrate them by identifying each spectrum.

In addition to the illustration of troglitazone, Fig. 7 shows the distribution of the PVP using the maximum peak intensities of PVP at the range of 1650–1670 cm^{-1}, which were not affected by the

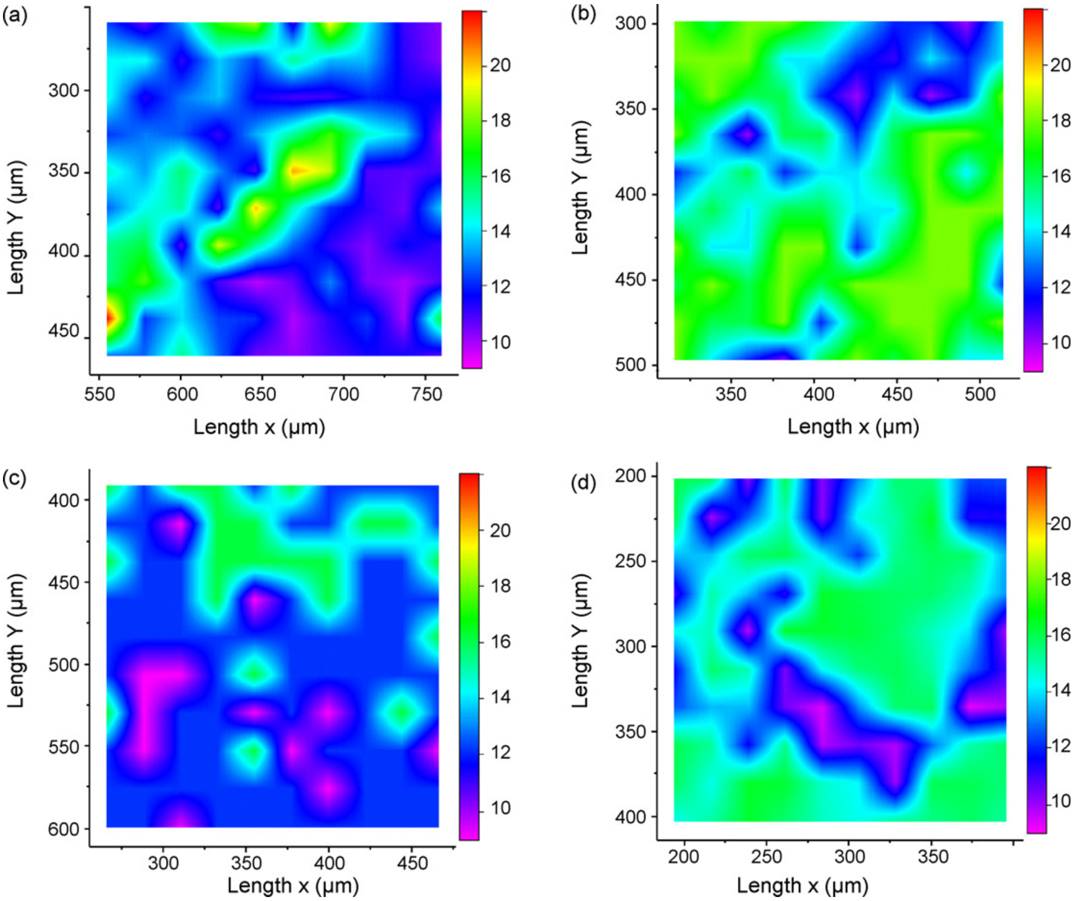

Fig. 5. Images of the crystal and amorphous regions in SDs described by the width at half maximum around 1747 cm^{-1} (green area was thought to be amorphous troglitazone): (a) SD-b; (b) SD-c; (c) SD-d; (d) SD-e.

peaks of troglitazone. Fig. 7 shows not only the distribution of the PVP, but also the physical state of the PVP, such as in a glassy state or a rubbery state during the sealed heating. As the PVP used in this study was manufactured by the spray dry method, its shape was spherical. The PVP of SD-b is illustrated as a round shape in Fig. 7a. As the heating temperature of this SD was lower than the T_g, PVP was thought to be in a glassy state during the sealed heating and maintained the spherical shape. On the other hand, the PVPs of SD-c, SD-d and SD-e are illustrated as indeterminate shapes in Fig. 7b–d, respectively. As the heating temperatures of these SDs were higher than T_gs, the PVP was thought to be in a rubbery state during the sealed heating and was deformed because the viscosity changed when the PVP was in rubbery state (Hancock and Zografi, 1997). Therefore, besides calculated T_gs, the illustration of the PVP also visually showed the physical state during sealed heating.

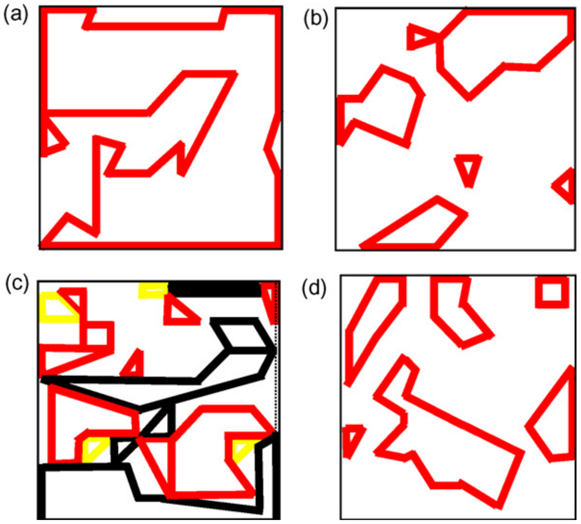

Fig. 6. Distribution of the crystalline L- and H-pairs in SDs: (a) SD-b; (b) SD-c; (c) SD-d; (d) SD-e. The area surrounded by bold lines shows the existence of crystalline troglitazone: Yellow, L-pair; Red, H-pair; Black, both L- and H-pairs.

The diastereomer-pairs and amorphous troglitazone in SDs are summarized in Table 2. In SD-a, for which the heating temperature was lower than the T_g and lower than the melting points of the L-pair and H-pair, only the crystalline L-pair and H-pair existed, the same as in the PM. On the other hand, in SD-d, amorphous troglitazone existed as shown in Fig. 6c in spite of its heating temperature of 105 °C being lower than the melting points of both the L-pair and H-pair. As PVP was illustrated as an indeterminate form in Fig. 7c and T_g was lower than the heating temperature, PVP was thought to be in a rubbery state during the sealed heating. In addi-

Table 2
Diastereomer-pairs and amorphous forms in SDs determined from Raman spectra

Name					
SD-a	SD-b	SD-c	SD-d	SD-e	SD-f
L[*]/H[*]	H/Amo.[*]	H[*]/Amo.[*]	L[*]/H[*]/Amo.[*]	H[*]/Amo.[*]	Amo.[*]

[*] L, H and Amo. mean the existence of crystalline L-pair, crystalline H-pair and amorphous troglitazone in SDs, respectively.

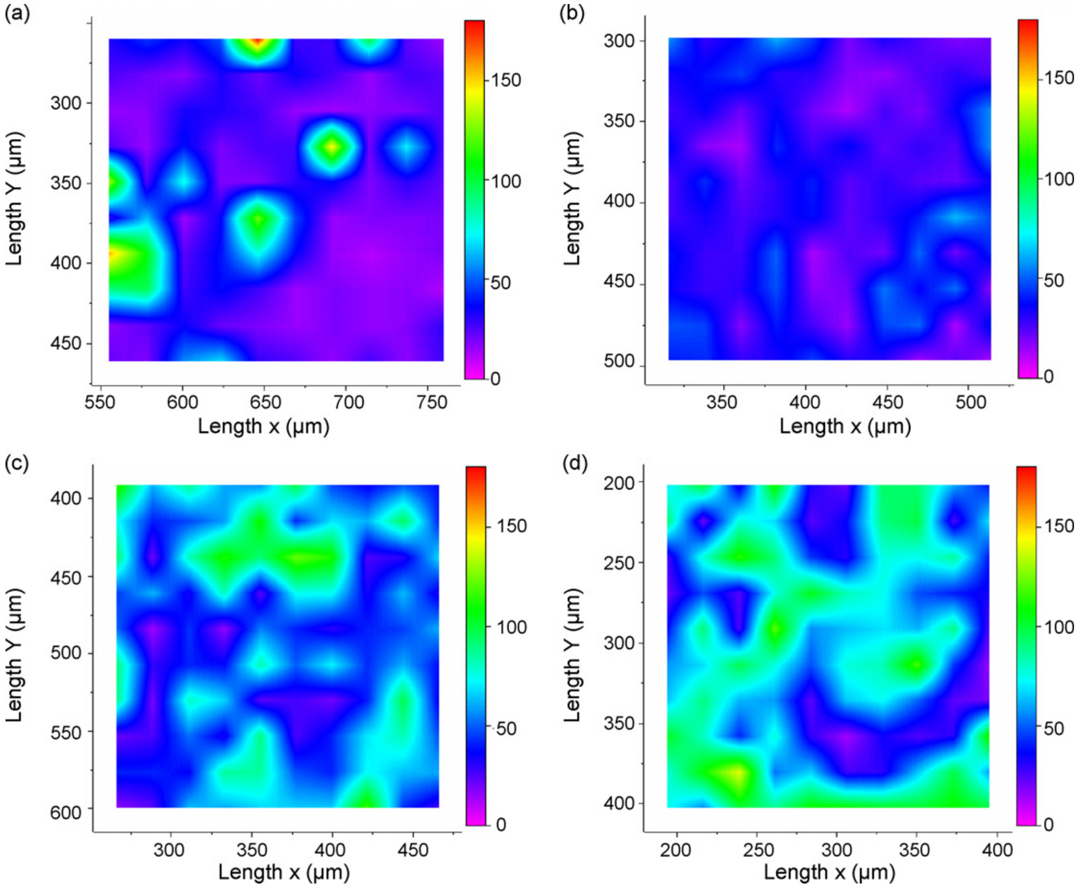

Fig. 7. Distribution of PVP represented using the maximum intensity over the spectral range of 1650–1670 cm^{-1}: (a) SD-b; (b) SD-c; (c) SD-d; (d) SD-e.

tion, when comparing the distribution of PVP to that of amorphous troglitazone (Fig. 8), most of the area was overlapped. Accordingly, from the distribution of PVP and amorphous troglitazone of SD-d, it could be guessed that troglitazone transformed into an amorphous state by dissolving in the rubbery PVP because it was said that one of a reason why the dissolution rates increased was dissolution of the drug in hydrophilic carrier (Liu and Desai, 2005). In Fig. 6c, the area of the crystalline L-pair (the area surrounded by the yellow line) was narrower than that of the crystalline H-pair (the area surrounded by the red line), it could be assumed that the amount of the L-pair dissolved in the rubbery PVP was larger than that of the H-pair.

It was demonstrated that the crystalline L-pair was not contained in the SDs prepared at a heating temperature higher than the melting point of the L-pair (Fig. 6a, b and d). For SD-b (Fig. 6a), for which the heating temperature was higher than melting point of L-pair and lower than the T_g, troglitazone was transformed into an amorphous state by melting because the PVP was thought to be in a glassy state during sealed heating. On the other hand, in SD-c (Fig. 6b), the water content was the same as SD-b and the

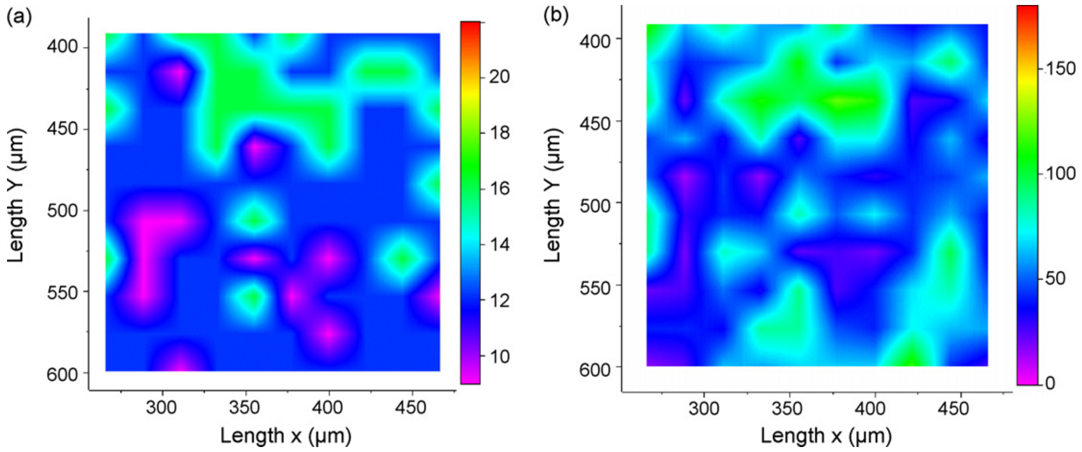

Fig. 8. Comparison of the distribution of amorphous troglitazone with that of the PVP in SD-d. (a) Images of amorphous troglitazone region (green area was thought to be the amorphous troglitazone region). (b) Distribution of PVP represented using the maximum intensity over the spectral range of 1650–1670 cm^{-1}.

heating temperature was higher than that, the distribution area of the crystalline H-pair was narrower than that of SD-b. As T_g indicates that PVP existed as a rubbery state during sealed heating, the crystalline H-pair was thought to be changed into an amorphous state by dissolving in the rubbery PVP. In addition, SD-f contained only amorphous troglitazone, although its heating temperature was lower than the melting point of the H-pair. XRPD pattern and dissolution results also showed that crystallinity of SD-f was 0% (data not shown). Since the heating temperature of the SD-f was higher than T_g and PVP was thought to exist as a rubbery state during sealed heating, all the crystalline H-pair was thought to transform into an amorphous state by dissolving into the rubbery PVP.

Thus, using the Raman mapping technique, crystalline L-pair, crystalline H-pair and amorphous troglitazone in the SDs could be discriminated. In addition, distribution of PVP could be visualized. From a comparison of the amorphous troglitazone to that of the PVP, the process of the crystal transforming into an amorphous form could be suggested.

4. Conclusion

SDs of troglitazone, which contains two diastereomer-pairs with different melting points, were prepared by the closed melting method under different preparing conditions, such as the heating temperature and the amount of water, used as the plasticizer. The SDs were evaluated using the Raman mapping technique. As a result, crystalline L-pair, crystalline H-pair and amorphous troglitazone in SDs could be evaluated by characteristic peaks of each diastereomer-pair and the shape variations of the peaks. The distribution map of the PVP showed the physical state of PVP during sealed heating. By describing the distribution of amorphous troglitazone and that of PVP, it could be guessed that the drug transformed into an amorphous state by dissolving in the rubbery PVP, since most of the distribution of the PVP and the amorphous form was overlapped when PVP existed as a rubbery state. Moreover, it could be assumed that the amount of the L-pair dissolved in the rubbery PVP was larger than that of the H-pair.

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