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Prediction of recrystallization behavior of troglitazone/polyvinylpyrrolidone solid dispersion by solid-state NMR

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ABSTRACT

The purpose of this study was to elaborate the relationship between the ^{13}C CP/MAS NMR spectra and the recrystallization behavior during the storage of troglitazone solid dispersions. The solid dispersions were prepared by either the solvent method or by co-grinding. The recrystallization behavior under storage conditions at 40 °C/94% RH was evaluated by the Kolmogorov–Johnson–Mehl–Avrami (KJMA) equation. Solid dispersions prepared by the solvent method or by prolonged grinding brought about inhibition of the nucleation and the nuclei growth at the same time. No differences in the PXRD profiles were found in the samples prepared by the co-grinding and solvent methods, however, ^{13}C CP/MAS NMR showed significant differences in the spectra. The correlation coefficients using partial least square regression analysis between the PXRD profiles and the apparent nuclei-growth constant or induction period to nucleation were 0.1305 or 0.6350, respectively. In contrast, those between the ^{13}C CP/MAS NMR spectra and the constant or the period were 0.9916 or 0.9838, respectively. The ^{13}C CP/MAS NMR spectra had good correlation with the recrystallization kinetic parameters evaluated by the KJMA equation. Consequently, solid-state NMR was judged to be a useful tool for the prediction of the recrystallization behavior of solid dispersions.

1. Introduction

Amorphization is one of the techniques to enhance the dissolution rate and/or bioavailability of sparingly soluble drug substances. Amorphized drug substances generally recrystallize easily, since they are physically unstable due to a higher energy state (Hancock and Zografi, 1997). Solid dispersions prepared with a polymer have been used to improve the physical stability of amorphous drug substances. It is well known that the sorts and amounts of polymer and preparation method affect the physical properties of the drug substance in a solid dispersion (Law et al., 2001; Crowley and Zografi, 2003; Yoshihashi et al., 2006). Especially, crystallinity of drug substance in solid dispersion is effective to the physical stability of solid dispersion (Yoshioka et al., 1994, Watanabe et al., 2001).

Since it is important to optimize the solid dispersion formulation and the preparation process, well-focused analytical tools are needed for predicting physical stability of solid dispersions (Yoshioka and Aso, 2007). Powder X-ray diffraction (PXRD) is widely used to evaluate the crystallinity of drug substances in solid dispersions. However, it is not always suitable for the evaluation of lower crystallinity because of the lower detection limit (Shah et al., 2006). Differential scanning calorimetry (DSC) is also used for the evaluation of amorphous materials (Yonemochi et al., 1999; Miyazaki et al., 2007). This technique is considered suitable to evaluate lower crystallinity materials by measuring thermal properties, such as glass transition temperature and/or melting point. But it often has difficulty in evaluating the thermal properties of drug substances in solid dispersions due to overlapped signals originating from the polymers, such as moisture desorption. In addition, thermal effects recorded at elevated temperatures must be interpreted cautiously and may not always be relevant under ambient conditions (Vippagunta et al., 2002).

Solid-state nuclear magnetic resonance (NMR) is well known as one of the characterization techniques for solid forms in pharmaceutical development. The ^{13}C cross polarization (dipolar decoupling) and magic angle spinning (CP/MAS) method is conventionally used to obtain high resolution ^{13}C NMR spectra (Tishmack et al., 2003; Berendt et al., 2006). It has been used to evaluate the physical properties of drug substances, e.g. crystallinity (Gustafsson et al., 1998), due to its high sensitivity to molecular conformation and the chemical environment in solid-state material.

In order to evaluate the physical properties by solid-state NMR, correct quantification of the spectra is necessary. Traditionally,

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an area or half bandwidth of specific peaks in solid-state NMR spectra has been used to quantify the spectra (Watanabe et al., 2002; Farrer et al., 2007). However, these traditional methods can only be used when the specific peaks are clearly separated from other peaks. Quantifying the NMR spectra of multicomponent system, such as solid dispersion, is often difficult by overlapping the specific peak of drug substance and that of other excipients.

Multivariate methods, such as partial least square regression (PLSR) and principle component regression (PCR), have been well utilized as spectra quantifying methods. These two methods are similar and should be selected according to the purpose of the study and/or used analytical tools. PLSR method can quantify the spectra using the region which is highly correlated with differences in the physical properties of the samples (Roggo et al., 2007). On the other hand, PCR method quantifies the major spectra changes which have a possibility of not reflecting all the physical property changes. Since changes in solid-state NMR spectra often include more than one different physical property (Tishmack et al., 2003; Berendt et al., 2006), PLSR was judged suitable for estimating the solid-state NMR spectra in this study.

Various studies have been performed using near infrared (NIR) and Raman spectroscopy in combination with PLSR to quantitate different solid-state forms of pharmaceutical compounds (Heinz et al., 2007; Kachrimanis et al., 2007). Using PLSR, it is possible to statistically extract qualitative and quantitative information from the spectra (Haaland and Thomas, 1988; Heinz et al., 2007). One of the advantages of employing PLSR is the ability to accurately define and quantify the specific peaks in complicated spectra, such as NIR and Raman spectra. For example, quantifying three different solid-state forms of indomethacin in ternary mixtures was achieved by using PLSR to evaluate NIR and Raman spectra (Heinz et al., 2007). The ability to improve the detectability of slight changes in samples has also been reported to be another advantage of PLSR analysis (Kachrimanis et al., 2007). PLSR can be applied not only to NIR and Raman spectroscopy, but also to solid-state NMR. Evaluation of the molecular order and disorder of lactose was reported as an example of applying PLSR to solid-state NMR (Gustafsson et al., 1998). Based on these reports, it has been considered that solid-state ^{13}C CP/MAS NMR combined with PLSR would be useful as an evaluation method for the physical properties of solid dispersions, such as quantifying the spectra leading to the prediction of recrystallization behavior.

Troglitazone (5-[4-(6-hydroxy-2,5,7,8-tetramethylchroman-2-ylmethoxy)-benzyl]-2,4-dioxothiazolidine), which was employed as a model compound in this study, is known to be a poor water soluble drug substance. The dissolution enhancement of troglitazone by preparing solid dispersions with polyvinylpyrrolidone (PVP) has been reported (Hasegawa et al., 2005). Considering that the dissolution property and apparent solubility of a poorly soluble drug substance in solid dispersions are affected by its crystallinity, the prediction of recrystallization behavior is important for establishing a quality control strategy.

The purpose of this study is to elaborate the relationship between the ^{13}C CP/MAS NMR spectra and recrystallization behavior during the storage of troglitazone/PVP solid dispersions, compared to the conventional PXRD method.

2. Materials and methods

2.1. Materials

Troglitazone was manufactured by Daiichi Sankyo. Co., Ltd. Polyvinylpyrrolidone (PVP) K-30 was purchased from BASF Japan Ltd. (Tokyo, Japan). All other reagents were of analytical grade.

2.2. Preparation

2.2.1. Physical mixture

A physical mixture (PM) was prepared by mixing troglitazone with PVP K-30 in a weight ratio of 2:1 using a mortar and pestle. The resultant mixture was sieved and mixed again.

2.2.2. Solid dispersions prepared by co-grinding

The PM was put into a zirconia cylindrical vessel with a zirconia rod. Co-grinding was carried out using a laboratory sized vibration mill (Sample mill TI-100: Heiko Seisakusho Co., Ltd.). The resultant masses were passed through a 150-mesh screen (opening 100 μm). To prevent thermal effects, 15 min cooling was conducted every 15 min during the runtime. In this article, '*n*' min ground mixture is abbreviated as '*n*' min GM. Each ground mixture was stored at 40 °C/94% RH in the humidity-controlled desiccator to evaluate the recrystallization behavior.

2.2.3. Solid dispersions prepared by the solvent method (solid dispersion (solvent))

The PM was dissolved in 2:1 (v/v) mixture of acetone and ethanol. This solution was evaporated at 50 °C. After drying, the resultant mass was passed through a 150-mesh screen. The sample was stored under the same conditions described above (Section 2.2.2).

2.3. Characterization

2.3.1. Powder X-ray diffraction (PXRD)

The PXRD patterns of the samples were measured using a Geiger Flex Rint-2200 diffractometer (Rigaku Co., Japan) with the CuKα radiation at 40 kV/40 mA. The samples were step-scanned at 0.02° intervals from 5.00° to 40.00° (2θ) at the rate of 4.00° min^{-1}.

The relative crystallinities of PM and solid dispersion (solvent) were defined as 100% and 0%, respectively. The relative crystallinity of each sample was calculated by a modified Hermans' method (Usui et al., 1998) as Eq. (1):

$$\text{relative crystallinity (\%)} = \frac{P_{\text{Samp}}/T_{\text{Samp}} - P_{\text{SD}}/T_{\text{SD}}}{P_{\text{PM}}/T_{\text{PM}} - P_{\text{SD}}/T_{\text{SD}}} \times 100 \quad (1)$$

where P_{Samp} is the area of diffraction peaks in PXRD pattern of samples; T_{Samp} is the area of whole PXRD pattern of sample; P_{PM} is the area of diffraction peaks in PXRD pattern of physical mixture; T_{PM} is the area of whole PXRD pattern of physical mixture; P_{SD} is the area of diffraction peaks in PXRD pattern of solid dispersion (solvent); and T_{SD} is the area of whole PXRD pattern of solid dispersion (solvent).

2.3.2. Differential scanning calorimetry (DSC)

Approximately 5 mg samples were placed in a sealed aluminum pan and scanned between 40 and 200 °C at 10 °C min^{-1} in differential scanning calorimeter (Thermo Plus DSC8230C, Rigaku Co., Japan) under a dry nitrogen gas purge.

2.3.3. Solid-state NMR

^{13}C CP/MAS NMR spectra were recorded using a Bruker Avance 400 instrument at ambient temperature. The spectrometer was operated at 100.62 MHz using a double air-bearing probe and zirconia rotors. The measurement conditions were as follows: spinning rate, 7 kHz; contact time, 1 msec; acquisition time, 25 ms; 90° proton pulse, 5 μs; delay between pulses, 4 s; and accumulation, 1024 times. The spectra were referenced to carbonyl in external glycine (176.03 ppm).

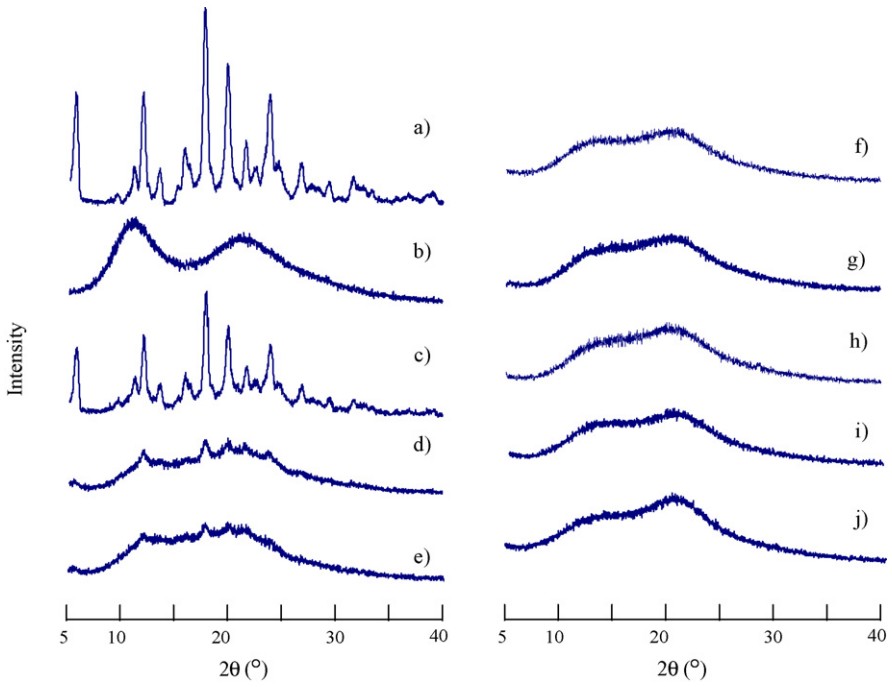

Fig. 1. PXRD patterns of troglitazone, PVP, PM, troglitazone/PVP solid dispersions. (a) Troglitazone, (b) PVP, (c) PM, (d) 15 min GM, (e) 30 min GM, (f) 60 min GM, (g) 120 min GM, (h) 180 min GM, (i) 240 min GM and (j) solid dispersion (solvent).

2.3.4. Multivariate regression analysis

Multivariate regression analyses of the PXRD patterns and solid-state ^{13}C CP/MAS NMR spectra were performed using the PLS1 program using the unscrambler software (CAMO). The full cross validation method was used with PLS regression to establish the calibration models.

3. Results and discussion

3.1. Recrystallization behavior of solid dispersions

Fig. 1 shows PXRD patterns of troglitazone, PVP, PM, ground mixtures and solid dispersion (solvent). Since PVP is a noncrystalline polymer, the peaks in the PXRD pattern of PM are derived from crystalline troglitazone. The solid dispersion (solvent) had no PXRD peaks and was defined as 0% of relative crystallinity. In the ground mixtures, the PXRD peaks for troglitazone disappeared over 60 min grinding. The PXRD patterns of the solid dispersions prepared by co-grinding over 60 min, were considered to be same as that of the solid dispersion (solvent). The solid dispersions, 60 min GM, 120 min GM, 180 min GM, 240 min GM and solid dispersion (solvent) were stored at 40 °C/94% RH in order to compare the recrystallization behavior.

Fig. 2 shows typical changes in the PXRD patterns during storage under 40 °C/94% RH. This figure indicated that recrystallization behavior was not always the same even though the initial PXRD patterns were similar. The changes in the relative crystallinities during storage for each solid dispersion are shown in Fig. 3. Preparation by the solvent method or by prolonged grinding brought about inhibition of the nucleation the nuclei growth at the same time.

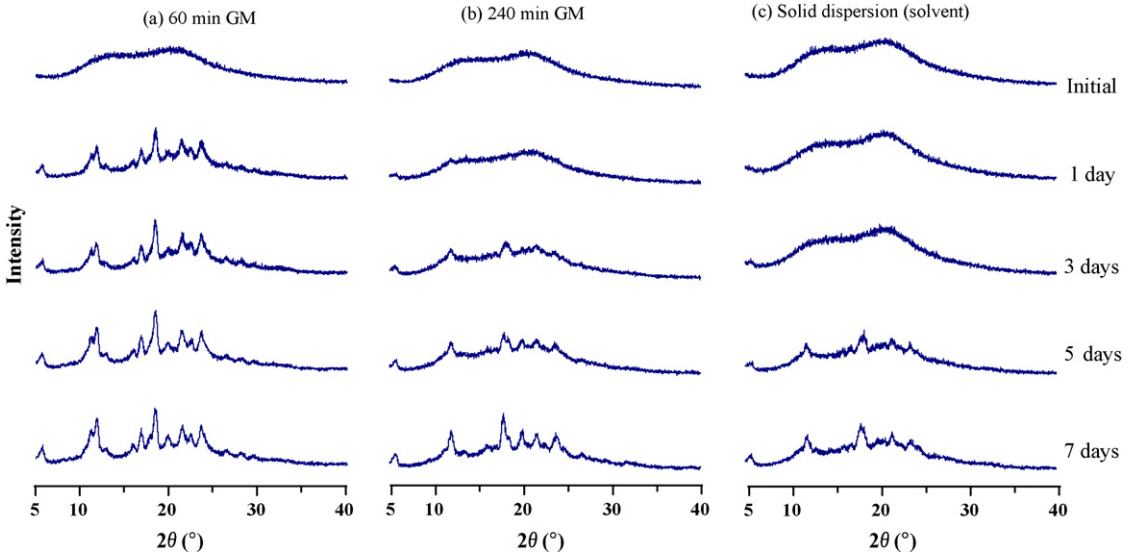

Fig. 2. Changes in PXRD patterns during storage at 40 °C/94% RH. (a) 60 min GM, (b) 240 min GM and (c) solid dispersion (solvent).

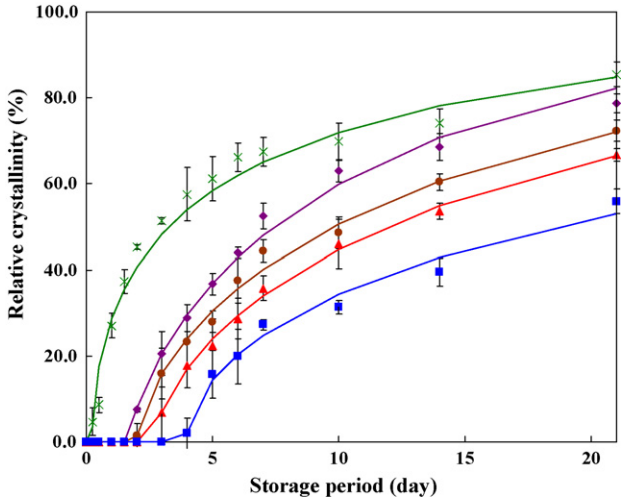

Fig. 3. Changes in relative recrystallinity (±standard deviation) during storage at 40 °C/94% RH. (×) 60 min GM, (♦) 120 min GM, (●) 180 min GM, (▲) 240 min GM, and (■) solid dispersion (solvent). The solid lines represent the fit to KJMA equation.

Kinetic analysis of the recrystallization behaviors of these samples was performed as follows. The solid lines in Fig. 3 were drawn using the Kolmogorov–Johnson–Mehl–Avrami (KJMA) equation, which is widely known in recrystallization studies (Price, 1990):

$$f = 1 - \exp\left[-\left(\beta(t-\tau)\right)^n\right] \quad (2)$$

where f is the fraction recrystallized, t is the storage period, n is the constant of the Avrami exponent for growth and nucleation, β is the apparent nuclei-growth constant, and τ is the induction period to the nuclei growth. Based on the following equation, which is the linearized form of Eq. (2), n, τ and β were determined as shown in Table 1.

$$\ln[-\ln(1-f)] = \ln\beta^n + n\ln(t-\tau) \quad (3)$$

The correlation coefficients (R^2) for each crystallization behavior calculated using Eq. (3) were not less than 0.94, based on linear regression analysis. These good coefficients indicate that the KJMA equation is suitable for estimating the crystallization behavior in this study. The very similar values of the Avrami exponents of each sample suggest that their recrystallization mechanisms are similar (Price, 1990). The lower β values and longer τ in the prolonged co-ground ground mixtures indicated that a prolonged grinding time physically stabilized solid dispersions. The solid dispersion (solvent) showed the lowest recrystallization constant and the longest induction period.

Based on these kinetic studies, the troglitazone/PVP solid dispersions prepared by different methods and/or conditions were revealed to have different physical stabilities. Since no differences were detected in the PXRD patterns before storage, PXRD was judged to be unsuitable for the prediction of recrystallization behaviors.

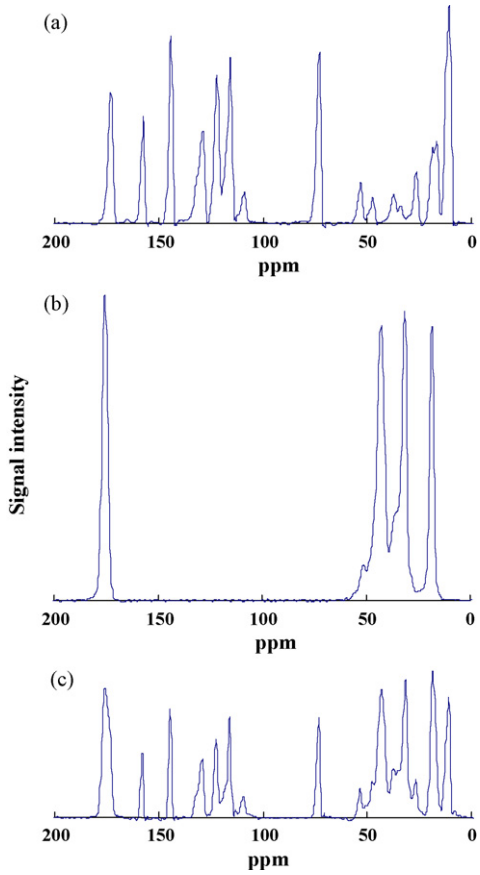

Fig. 4. ^{13}C CP/MAS NMR spectra of (a) troglitazone, (b) PVP, and (c) PM.

3.2. Solid-state NMR study for solid dispersions

Firstly, DSC was performed to detect the differences in each solid dispersion. However, the detection of the typical thermal properties of troglitazone in the solid dispersion was disturbed by moisture desorption profile of PVP (data not shown). Therefore it was also judged difficult to use DSC in order to detect the differences in each solid dispersion.

Solid-state NMR was performed to detect the different properties in each solid dispersion. Fig. 4 shows the ^{13}C CP/MAS NMR spectra of troglitazone, PVP K-30 and PM. In the ^{13}C CP/MAS NMR spectra of PVP K-30, carbon atoms in the main chain and the five-membered ring were detected at around 10–50 ppm and the carbonyl peaks were observed at around 176 ppm, respectively. Since the peaks around 70–150 ppm in the ^{13}C CP/MAS NMR spectra of PM were attributed to troglitazone, these peaks were used in the following analysis as the specific peaks of troglitazone in the solid dispersion.

As described in Section 3.1, no differences in the initial PXRD profiles were found in the samples prepared by the co-grinding and solvent methods. However, the ^{13}C CP/MAS NMR spectra showed remarkable differences in each solid dispersion before storage. As shown in Fig. 5, the troglitazone peaks in the initial ^{13}C CP/MAS NMR spectra of ground mixtures broadened and decreased their

Table 1
Change in the kinetic parameters of the KJMA equation.

	60 min GM	120 min GM	180 min GM	240 min GM	Solid dispersion (solvent)
n	0.52	0.75	0.69	0.67	0.56
$\beta \times 10^3$ (h^{-1})	6.8	4.4	3.1	2.6	1.5
τ (h)	5.8	39.8	47.3	64.8	95.3

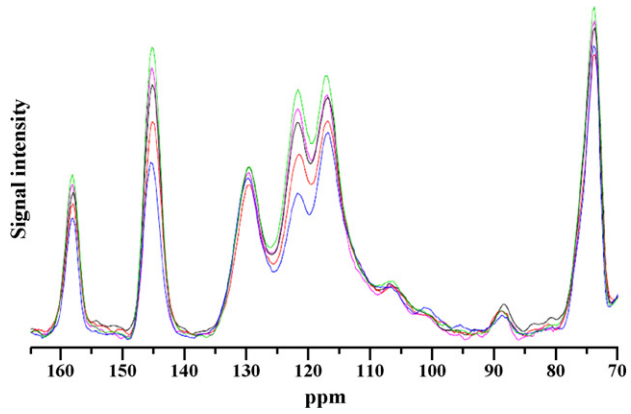

Fig. 5. ^{13}C CPMAS NMR spectra of troglitazone/PVP solid dispersion around 70–160 ppm. (Green line) 60 min GM, (pink line) 120 min GM, (black line) 180 min GM, (red line) 240 min GM and (blue line) solid dispersion (solvent).

intensity with prolonged grinding and solid dispersion (solvent) showed the most broadened and weakest troglitazone peaks. Since no chemical degradation was confirmed in any of the solid dispersions, the differences in the ^{13}C CP/MAS NMR spectra were considered to be those of molecular conformation, which cannot be detected by PXRD.

Since the isotropic chemical shifts are distributed by fluctuations in the bond length and bond angle, the peak in the ^{13}C CP/MAS NMR spectra of a molecular deformed sample becomes broadened (Shah et al., 2006). Decreasing peak intensity occurs by reduction of the cross polarization (CP) effect based on deprotonation, which results from remoting and/or removing the neighboring protons. When no chemical degradation has occurred, the decrease of the peak intensity in the ^{13}C CP/MAS NMR spectra indicates physical deprotonation (Smernik et al., 2002; Sheth et al., 2005). Therefore, the changes in the ^{13}C CP/MAS NMR spectra shown in Fig. 5 are judged to be those in the short range order of amorphous troglitazone in the solid dispersions, which indicates molecular deformation such as fluctuation of atomic bonds and/or deprotonation without chemical degradation.

Powder X-ray diffraction is known to be a suitable method to understand three-dimensional long range molecular order. However, this method only "sees" molecular order and disorder (Hancock and Zografi, 1997). That is to say the PXRD method is unsuitable for the evaluation of changes in short range order. Considering the difference in the detectability of short range order using PXRD and solid-state NMR, solid-state NMR is suitable for evaluation of differences which will affect the physical stability of drug substances in solid dispersions.

3.3. Correlation of the physical stability of the solid dispersions and the spectra

The relationship between the physical stability and the initial profiles of PXRD patterns or ^{13}C CP/MAS NMR spectra was evaluated by PLSR. First, the PXRD patterns and ^{13}C CP/MAS NMR spectra were divided into multi data points by 0.02° and 0.3 ppm, respectively. The evaluated initial PXRD patterns ranged 2θ = 5–40° (intensities of 1750 evenly distributed data points), or specific peaks of troglitazone in the ^{13}C CP/MAS NMR spectra (around 75, 100–130, 145, and 160 ppm, intensities of 250 evenly distributed data points) were used for X-matrix without any additional numeric pretreatments. The apparent nuclei-growth constant (β) and the induction period to nucleation (τ) were employed for Y-matrix as the characteristic value of physical stability. Figs. 6 and 7 show the relationship between actual and PLSR-predicted kinetic parameters. The correlation coefficients (R^2) between the PXRD pattern and the apparent nuclei-growth constant (β) or the induction period (τ) were 0.1305 and 0.6350, respectively, shown in Figs. 6(a) and 7(a). This indicates that there are no clear relationships between the actual and predicted apparent nuclei-growth constants or induction period to nucleation, and hence no correlation between the PXRD profiles and the recrystallization behavior. PXRD is a suitable method for the evaluation of long range order, in general (Hancock and Zografi, 1997). Therefore, this lower correlation coefficient indicates that long range order is not a critical physical property for the recrystallization behavior of solid dispersions. In contrast, good correlation was found for the actual and predicted kinetic parameters using ^{13}C CP/MAS NMR spectra. The correlation coefficients (R^2) between the ^{13}C CP/MAS NMR spectra and the apparent nuclei-growth constant (β) or the induction period (τ) were 0.9916 and 0.9838, respectively (shown in Figs. 6(b) and 7(b)). As discussed in Section 3.2, solid-state NMR can detect differences in the short range order of troglitazone in the solid dispersions. Therefore, the good correlation of the initial ^{13}C CP/MAS NMR spectra and the recrystallization kinetic parameters indicates that the short range order of drug substance is a critical physical property for the recrys-

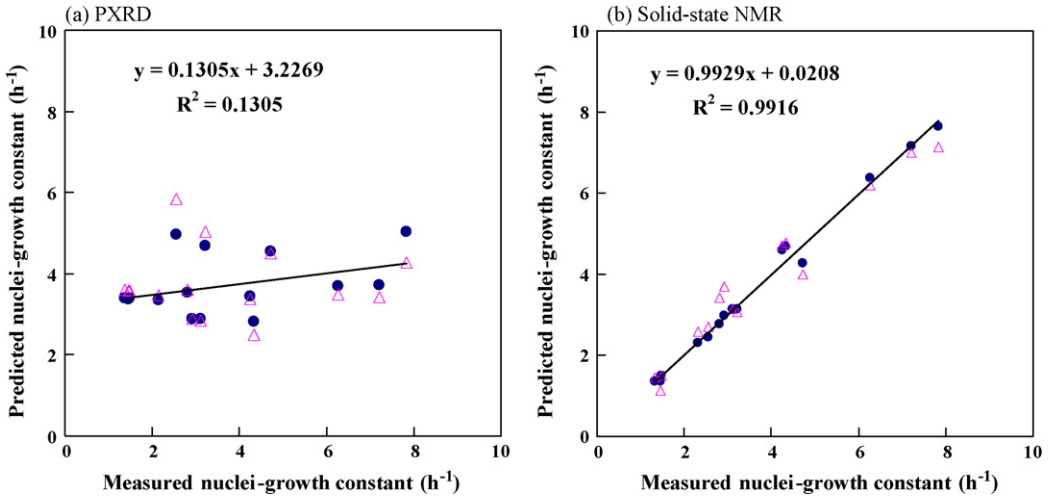

Fig. 6. Correlation between the actual and predicted nuclei-growth constants of solid dispersions (a) analyzed using PXRD patterns and (b) analyzed using ^{13}C CP/MAS NMR spectra. (●) calibration and (△) predicted.

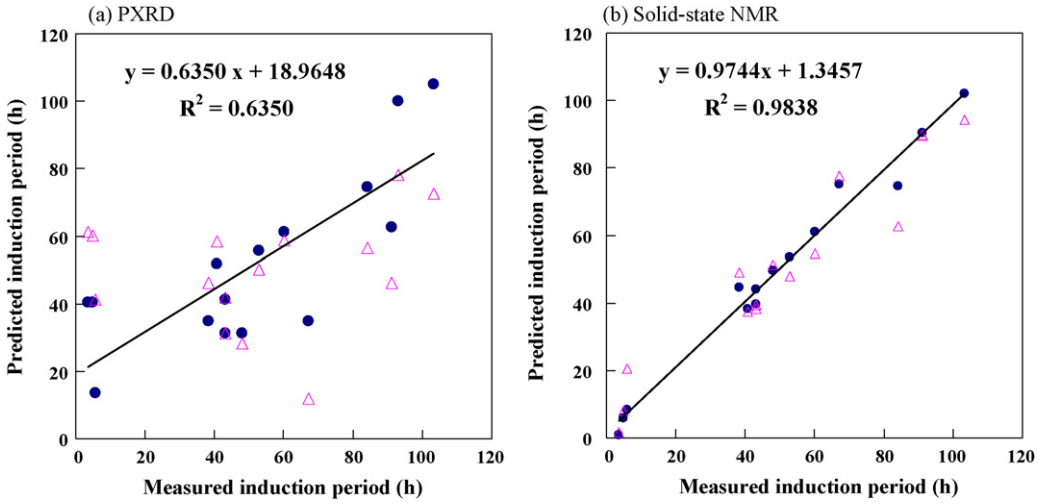

Fig. 7. Correlation between the actual and predicted induction periods of solid dispersions (a) analyzed using PXRD patterns and (b) analyzed using ^{13}C CP/MAS NMR spectra. (●) calibration and (△) predicted.

tallization behavior of solid dispersions. Therefore, it was found that solid-state NMR provides an appropriate method for predicting the recrystallization behavior of solid dispersions.

4. Conclusion

The troglitazone/PVP solid dispersions prepared by the co-grinding and solvent method showed different recrystallization behavior. Each solid dispersion before storage showed remarkable differences in the ^{13}C CP/MAS NMR spectra, even though no differences were found in the PXRD pattern. The good correlation between the ^{13}C CP/MAS NMR spectra quantified by PLSR and the recrystallization kinetic parameters evaluated by the KJMA equation indicated that the short range order is a critical physical property in the recrystallization of solid dispersions. Solid-state NMR combined with a multivariate method as the spectra quantifying method is concluded to be a useful tool for predicting the recrystallization behavior of solid dispersions.

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