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Short communication

Evaluation of solid state form of troglitazone by solid state NMR spectroscopy

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Abstract

The solid state forms of troglitazone drug substance and diastereomers were characterized using solid state nuclear magnetic resonance (SSNMR) spectroscopic method. The SSNMR spectroscopy could distinguish the hydrated and the non-hydrated RR/SS forms more clearly than powder X-ray diffractometry (PXRD). The SSNMR result supported that troglitazone drug substance consists of diastereomers as a simple physical mixture. SSNMR spectroscopy was also able to characterize the solid state forms of troglitazone in tablets while PXRD was unable to because of interference from the pharmaceutical additives. Troglitazone was proved to exist in amorphous form in tablets, and keep its solid state form amorphous against heat and humidity. SSNMR spectroscopy thus provides very important information for the development of the pharmaceutical formulation of troglitazone.

Keywords: Amorphous; Anti-diabetic drug; Hygroscopicity; Solid state NMR; Troglitazone

1. Introduction

The solid state form (i.e. crystalline, polymorphs, solvates and amorphous solids) of a drug substance can have a significant impact on the drug's solubility, dissolution rate, stability in a pharmaceutical formulation, and bioavailability [1,2]. Formulation techniques have been developed to increase the bioavailability and aqueous dissolution of poorly water-soluble drugs by simultaneously reducing drug particle size and altering the drug crystal form [2,3]. One such technique is called solid dispersion, which is dispersion of a drug (in the desired solid state form) in an inert carrier matrix prepared by a melting (fusion), solvent, or melting-solvent method [2,3]. The amorphous form of a drug is generally more soluble, which is a useful property particularly if the drug has low aqueous solubility [2,4], however, amorphous solids are often susceptible to changes during storage. In some cases, pharmaceutical formulations placed under controlled storage conditions exhibit a slowing of dissolution because of crystallization of the active pharmaceutical ingredient (API) [5]. Thus, it is important to evaluate the solid state forms not only of the drug substance but also the drug product and its stored samples.

Powder X-ray diffraction (PXRD) is well known as a technique for the physical characterization of pharmaceutical solids. Regarding pharmaceutical formulations, however, the PXRD method sometimes fails to represent the changes of the solid state form because of the interference of the diffraction peaks derived from pharmaceutical additives. Furthermore, a humidity-controlled system is needed for the measurement of the solids that change their crystal structure easily by hygroscopicity due to humidity. Solid state nuclear magnetic resonance (SSNMR) spectroscopy is such an useful techniques. Recently many application studies using this technique have been reported [6–9]. SSNMR spectroscopy cannot only differentiate between different solid state forms of a material, but also intimately probes the structural aspects of each solid state form. Technically, it is relatively easy to handle a powdered sample like pharma-

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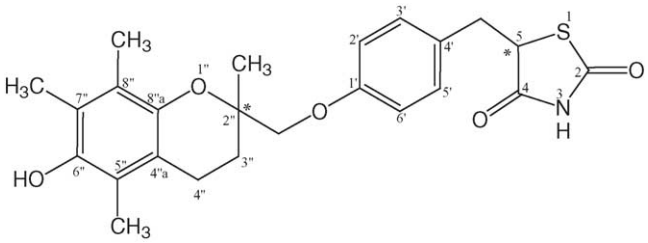

Fig. 1. Chemical structure of troglitazone.

ceutical solids and subject them to SSNMR measurement. Furthermore, this system would be rarely exposed to undue humidity during the measurement since the sample for SSNMR spectroscopy is filled in a rotor tightly closed with an end-cap.

Troglitazone is a novel oral antidiabetic drug that improves insulin sensitivity and responsiveness [10,11]. It has two asymmetric carbons, one at the 2-position of the chroman ring and one at the 5-position of the thiazolidine ring in its molecule as shown in Fig. 1, and is produced as a mixture of equal amounts of four optical isomers. The solid state form of troglitazone drug substance is characterized as a simple physical mixture of two diastereomers, and the water adsorption is due to the presence of the RR/SS diastereomer, which adsorbs water easily as a monohydrate [12]. It was reported that making troglitazone drug substance amorphous increases the solubility of the four stereoisomers [3]. So a spray-drying solid dispersion formulation technique was used for the manufacture of troglitazone tablets.

The objective of this study was to demonstrate the characterization of the solid state forms of the troglitazone drug substance, drug product and their hygroscopically treated samples by SSNMR.

2. Materials and methods

2.1. Sample and reagents

Troglitazone drug substance and diastereomers were synthesized by the Process Development Laboratories and the amorphous form of troglitazone drug substance was obtained from the Pharmaceutical Development Laboratories, Sankyo Co., Ltd. Troglitazone drug substance was placed into a desiccator of 75% RH at 25 °C, and picked up 10, 30, 60 min and 20 days after the placement for monitoring the change of SSNMR pattern. Other samples were placed into the desiccator for 20 days in order to make a hydrated form. The preparation methods are described in a previous paper [12]. The troglitazone drug product, 200 mg tablets (lot no. CH043), and its additives for the formulation were obtained from the Pharmaceutical Development Laboratories, Sankyo Co., Ltd.

The water content, expressed as % w/w, was measured by Karl–Fischer titration using a Moisture Meter (model AQ-5, 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.

All other reagents and solvents were commercially available and of analytical reagent grade.

2.2. Powder X-ray diffraction (PXRD)

The PXRD patterns of troglitazone were determined at ambient temperature and atmosphere using a diffractometer (RINT2200, Rigaku Corp., Japan) with Cu Kα radiation at 40 mA and 45 kV. Each sample was packed into an aluminum holder, and scanned with a diffraction angle of 2θ, increasing from 5° to 40°.

2.3. Solid state nuclear magnetic resonance (SSNMR) spectroscopy

Solid state ^{13}C Cross polarization/magic angle spinning (CP/MAS) NMR spectra were obtained using a Bruker Avance 300 MHz spectrometer operating at a carbon frequency of 75.476 MHz and equipped with a complete solids accessory and a Bruker 7 mm double-tuned CP probe. The total suppression of spinning sideband (TOSS) pulse sequence was used to suppress spinning sidebands. Samples were prepared in 7 mm zirconium rotors with PTFE endcaps. Measurement conditions were as follows: 90° proton rf pulse, 4.4 μs; contact time, 2 ms; pulse repetition time, 3 s; MAS frequency, 5.0 kHz; spectral width, 24 kHz; and acquisition time, 35 ms. The chemical shifts were referenced to the CH_3 of hexamethylbenzene ($\delta = 17.3$ ppm) by sample replacement. Spectral assignments were made by comparing chemical shifts observed in solution spectra [13] with those in the ^{13}C CP/MAS and interrupted decoupling spectra.

3. Results and discussion

3.1. SSNMR spectroscopy of troglitazone diastereomers

The RS/SR form of troglitazone has no hygroscopicity and the RR/SS form shows about 3.7% water uptake as a monohydrate. The crystal structures of the RS/SR form and the monohydrate of the RR/SS form have been already studied [14,15]. Troglitazone has hydrophilic function only at the both edges of its molecule (6″-OH and thiazolidinedione), and the other groups are hydrophobic. The molecules are connected by head-to-tail hydrogen bonds as a straight chain, and the molecular chains are piled up two dimensionally in the crystals. And the hydrated water breaks the hydrogen bonding into the lines of troglitazone molecules on hydration [16]. So, hydrated water would affect the chemical shifts of the carbon of thiazolidine ring and 6-position of the chroman ring on SSNMR spectra. Fig. 2 shows the PXRD patterns and Fig. 3

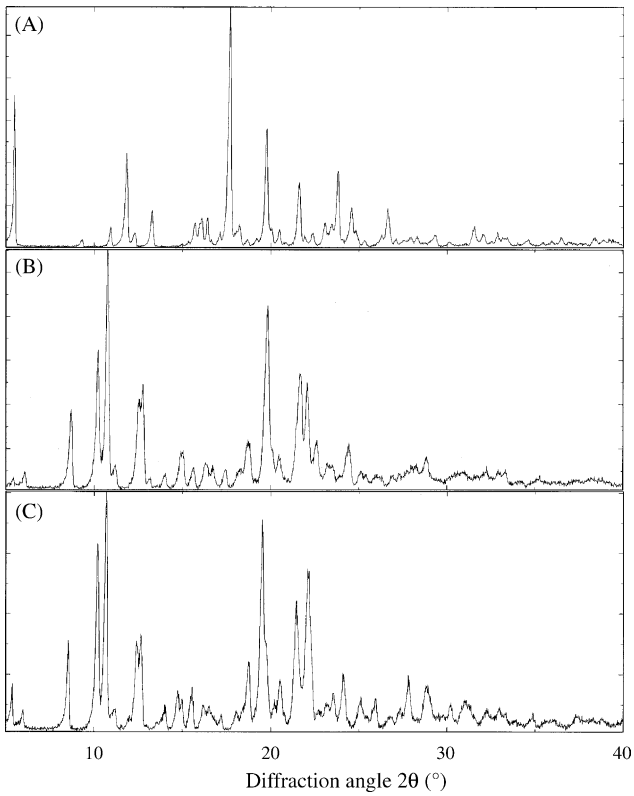

Fig. 2. PXRD patterns of troglitazone diastereomers: (A) RS/SR form, (B) RR/SS form and (C) hydrated RR/SS form.

shows the SSNMR spectra of troglitazone diastereomers. We can find the differences on not only PXRD but SSNMR patterns between the RS/SR and RR/SS forms. Although, the PXRD patterns of the hydrated and the non-hydrated RR/SS forms are slightly different, they are difficult to distinguish from each other. However, the SSNMR results represent the difference clearly during the hydration of the RR/SS form. The chemical shifts of 170 and 172 ppm, which were estimated to the 2-position of the thiazolidine ring, moved and gathered at the neighboring peak derived from the 4-position of the thiazolidine ring. At the same time, the chemical shift pattern around 145 ppm, which was assigned to the 6- and 8-position of the chroman ring, changed after hydration. These results indicate that monohydration caused the rebuilding of weaker hydrogen-bonding interactions, changed shielding, and shifted the carbonyl resonance to a lower magnetic field, and meet the hydrogen-bonding discussion from the reported crystal structures. Therefore, SSNMR spectroscopy is superior to PXRD for the identification of the hydration of the troglitazone RR/SS form.

3.2. SSNMR spectroscopy of troglitazone drug substance

Troglitazone drug substance has been characterized as a simple physical mixture of the RR/SS and the RS/SR forms, and the water adsorption is due to the hydration of the RR/SS diastereomer composing 50% of the drug substance [12]. Fig. 4 shows the SSNMR spectra of troglitazone drug substance through the hygroscopic treatment. The SSNMR peaks derived from the RS/SR form can be seen in both charts. All of the moved chemical shifts corresponded to those of the RR/SS form, which were described in the previous paragraph. This indicates that troglitazone drug substance consists of a crystalline RS/SR form and a crystalline RR/SS form with no interaction, like a “conglomerate” [17].

In this way, troglitazone drug substance is indicated as a physical mixture of diastereomers not only by DSC or PXRD but also SSNMR spectroscopy. Furthermore, SSNMR spectroscopy is thus proved to be a non-destructive way to eval-

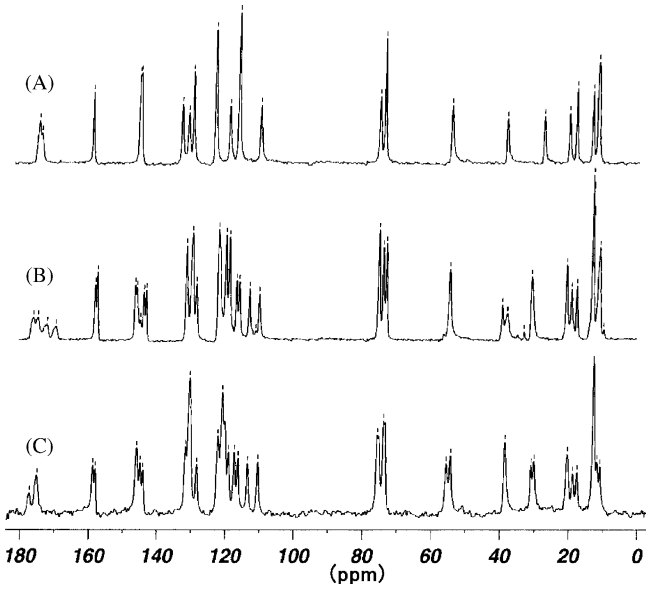

Fig. 3. SSNMR spectra of troglitazone diastereomers: (A) RS/SR form, (B) RR/SS form and (C) hydrated RR/SS form.

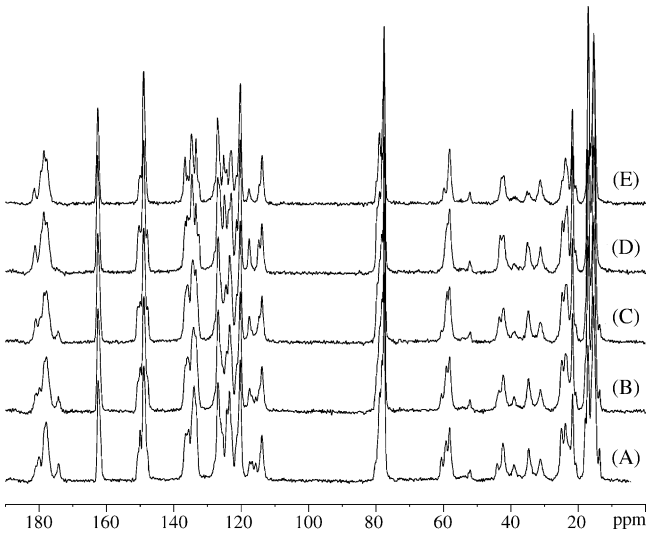

Fig. 4. Changing SSNMR spectra of troglitazone drug substance stored at 25 °C/75% RH: (A) initial, (B) 10 min, (C) 30 min, (D) 60 min and (E) hydrated troglitazone drug substance.

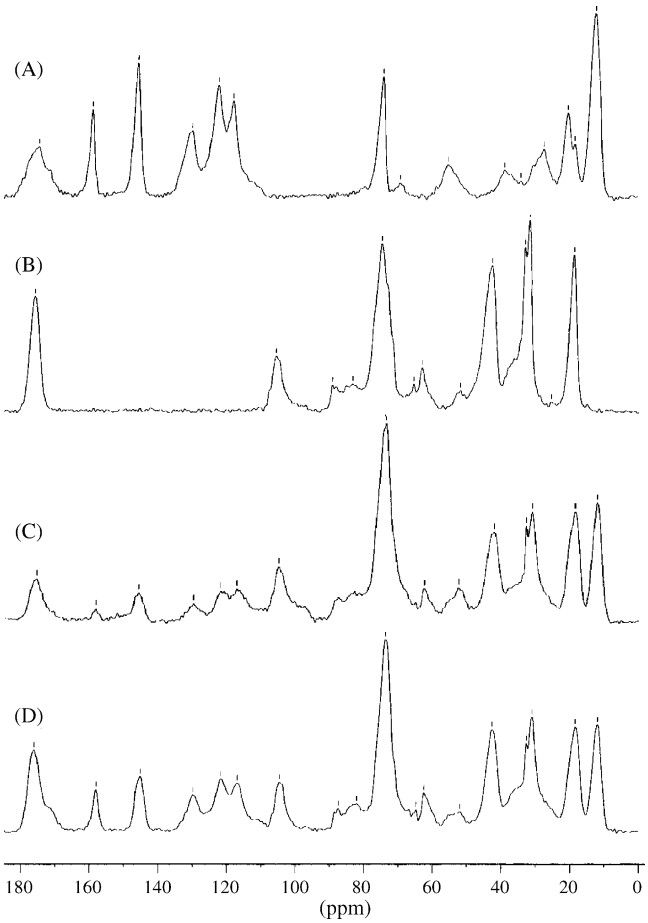

Fig. 5. SSNMR spectra of (A) amorphous form of troglitazone, (B) additives for the formulation, (C) troglitazone drug product and (D) troglitazone drug product stored at 40 °C/75% RH for 6 months.

uate the hydration of the RR/SS form in troglitazone drug substance.

3.3. SSNMR spectroscopy of troglitazone in tablets

We could not evaluate the solid state forms of troglitazone in tablets by PXRD because it was difficult to deduct the diffraction peaks derived from those of the pharmaceutical additives. Fig. 5(A)–(C) shows the SSNMR spectra of the amorphous form of troglitazone, additives for the formulation and troglitazone drug product. Most peaks in the spectrum of troglitazone drug product corresponded to the spectrum of the amorphous form of troglitazone or the additives. This just appeared to be like the superimposed pattern of the SSNMR charts of these two samples. And such sharp peaks as shown in Fig. 4(A), the spectrum of the crystalline troglitazone by SSNMR spectroscopy, were not observed in the spectrum of tablet as shown in Fig. 5(C). These results indicate that troglitazone exists not as crystals but in amorphous form in the drug product, and not a very strong interaction occurs between the troglitazone and its additives in the tablets.

3.4. Evaluation of the crystallographic stability of troglitazone in tablets

The SSNMR spectra of troglitazone drug product stored at 40 °C/75% RH for 6 months are shown in Fig. 5(C) and (D). No significant change on the spectrum was observed during the 6-month storage period. The peak width and the shape of the peaks derived from troglitazone drug substance in tablets were quite different from that of the crystalline troglitazone, as shown in Fig. 4. It is difficult to confirm the presence of the slight amount of the crystalline troglitazone because the peaks of the amorphous form are too broad, but troglitazone was generally proved to keep its amorphous form in tablets against heat and humidity. This provides very important information for the oral pharmaceutical formulation and assurance of the solubility of the API of troglitazone drug product during storage.

4. Conclusions

The SSNMR spectroscopy results for troglitazone drug substance and diastereomers were consistent with other characterizations previously reported [12,15]. Furthermore, SSNMR spectroscopy can distinguish the differences during the hydration of the RR/SS form. SSNMR spectroscopy indicated that the solid state form of troglitazone in tablets keeps its amorphous form. Such information is very important for the pharmaceutical development of the oral dosage form, especially for a low-soluble drug like troglitazone. In this study, SSNMR spectroscopy was proved to be a powerful technique for evaluating the solid state forms of the API which is a key factor for pharmaceutical development.

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