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Note

Solid-state characterization of an NR2B selective *N*-methyl D-aspartate (NMDA) antagonist polymorphs

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Abstract

(−)-6-{2-[4-(3-Fluorophenyl)-4-hydroxy-piperidin-1-yl]-1-hydroxyethyl}-3,4-dihydro-quinolin-2(1H)-one (compound A) is an NR2B selective *N*-methyl D-aspartate (NMDA) antagonist that has shown at least two polymorphs, forms I and II. In this report, we prepared two polymorphs, forms I and II and their crystal forms were identified and characterized by single crystal X-ray diffractometry, differential scanning calorimetry (DSC) and variable temperature powder X-ray diffractometry (VT-PXRD). The results of DSC and VT-PXRD suggested that compound A has at least three polymorphic forms: I, II and a new form III, and that forms II and III showed an enantiotropic relationship. We also performed single crystal X-ray analyses of specific conditions based on the results of VT-PXRD. The unit cell dimensions in crystallographic parameter and molecular arrangements of form I were quite different from forms II and III. Whereas, the crystal structures of forms II and III were similar with the exception of the C58–C59–C61–C62 torsion angle.

Keywords: Solid form selection; Polymorph; Crystal structure; Variable temperature powder X-ray diffractometry; Enantiopropic polymorphs

1. Introduction

The solid-state characterization of drug candidates is poised to become essential in drug development, since the solid form selection strategies, which can directly affect the cost and time for development (Chemburkar et al., 2000; Huang and Tong (2004)), are developed based on the results of the characterization (Bastin et al., 2000; Engel et al., 2000; Kojima et al., in press; Morris et al., 1994; Ware and Lu (2004)). Most importantly, the study of the relationship between polymorphs and pseudopolymorphs can aid in the appropriate solid form selection for development, because polymorphs and pseudopolymorphs show different physicochemical properties (Gandhi et al., 2000; Kojima et al., 2007; Maurin et al., 2002; Otsuka et al., 1993; Yoshihashi et al., 2002).

(−)-6-{2-[4-(3-Fluorophenyl)-4-hydroxy-piperidin-1-yl]-1-hydroxyethyl}-3,4-dihydro-quinolin-2(1H)-one (compound A, Fig. 1) is an *N*-methyl D-aspartate (NMDA) NR2B receptor antagonist and was selected as a crystalline drug candidate for the treatment of neurodegenerative disorders such as Parkinson's and Alzheimer's diseases, in migraine and in depression (Fig. 1) (Kawai et al., 2007). During the investigation of synthesis, two polymorphs, forms I and II were discovered and a potential polymorph, form III was detected. In this report, we have prepared two polymorphs, forms I and II and characterized their crystal forms using single crystal X-ray diffractometry, differential scanning calorimetry (DSC) and variable temperature powder X-ray diffractometry (VT-PXRD) with heating and cooling. In addition, the relationship among polymorphs including the new form III is discussed.

2. Experimental

2.1. Materials

(−)-6-{2-[4-(3-Fluorophenyl)-4-hydroxy-piperidin-1-yl]-1-hydroxyethyl}-3,4-dihydro-quinolin-2(1H)-one (compound A,

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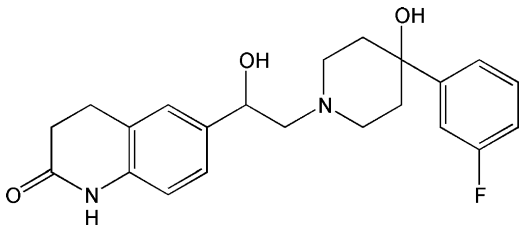

Fig. 1. Chemical structures of compound A.

Fig. 1), was synthesized at Global Research and Development, Nagoya Laboratories, Pfizer, Japan. The absolute configuration was not assigned. All solvents were purchased from Wako Pure Chemical Industries (Osaka, Japan).

2.2. Preparation of polymorphs

Form I was obtained by recrystallization from 2-propanol solution saturated with compound A and then stirring overnight at room temperature. Seed crystals of form II were obtained by heating form I up to 180 °C, keeping it at that temperature, and subsequently cooling it back down to room temperature at a cooling rate of 5 °C/min. A larger amount of form II was obtained by recrystallization from 2-propanol solution saturated with the drug and seeding a small amount of form II obtained as described above.

2.3. Powder X-ray diffractometry

Powder X-ray diffraction patterns were collected using a RINT-TTR (Rigaku, Tokyo, Japan) with Cu Kα radiation generated at 300 mA and 50 kV. Samples were placed on aluminum rotation-plates and rotated at 60 rpm at room temperature. Data were collected from 3° to 35° (2θ) at a step size of 0.02° and a scanning speed of 4°/min.

2.4. Thermal analysis

Differential scanning calorimetry was performed using a DSC 6200 system (Seiko Instruments, Chiba, Japan). A DSC thermogram was obtained in an aluminum pan system with a pinhole using a sample weight of ca. 3 mg and a heating rate of 5 °C/min under a nitrogen flow. Thermal gravimetric analysis (TGA) was performed using a TG/DTA 6200 system (Seiko Instruments, Chiba, Japan). A TGA thermogram was obtained under the same conditions as those for DSC.

2.5. Variable temperature powder X-ray diffractometry

VT-PXRD of form I was also performed using a RINT-TTR with low and medium temperature attachments (Rigaku, Tokyo, Japan) at a heating rate of 5 °C/min with the temperature being targeted for 1 min before recording. Data were collected under the same conditions as in the PXRD patterns recording.

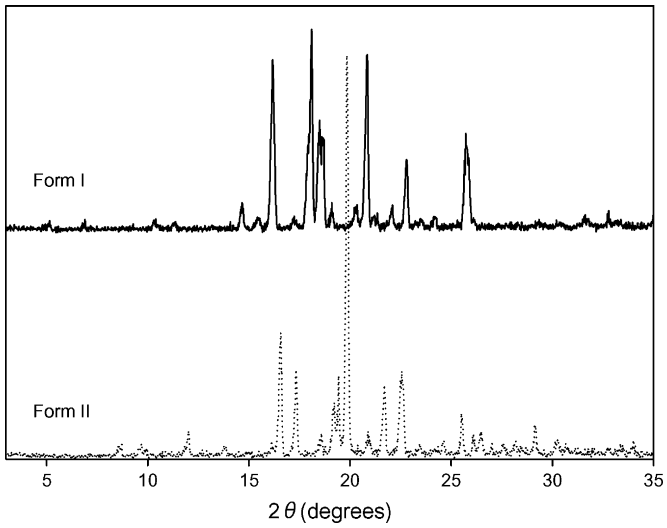

Fig. 2. PXRD patterns of forms I and II.

2.6. Single crystal X-ray diffractometry

Single crystal X-ray diffraction data were recorded on a SMART APEX II CCD X-ray diffractometer (Bruker AXS, Madison, WI, USA) with a Mo anode source at 20, 25 and 50 °C for the analyses of forms I, II and III, respectively. The crystal structures were solved and refined using SHELXTL software (Version 5.1, Bruker AXS).

3. Results and discussion

The PXRD patterns suggested that two polymorphs of compound A, forms I and II, were obtained by recrystallization (Fig. 2). The thermal behaviors of forms I and II were also evaluated by DSC and TGA. The DSC curve of form I showed that endothermic peaks at 157.9 °C corresponded with transformation, and those at 196.0 °C corresponded with a melting event (Fig. 3). Whereas, the DSC curve of form II showed that endothermic peaks at 33.3 °C corresponded with transformation and those at 196.2 °C corresponded with a melting event. In addition, the TGA curves of forms I and II showed that both

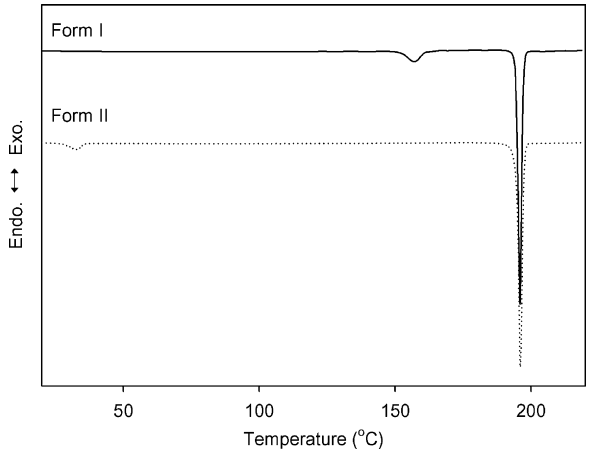

Fig. 3. DSC thermograms of forms I and II.

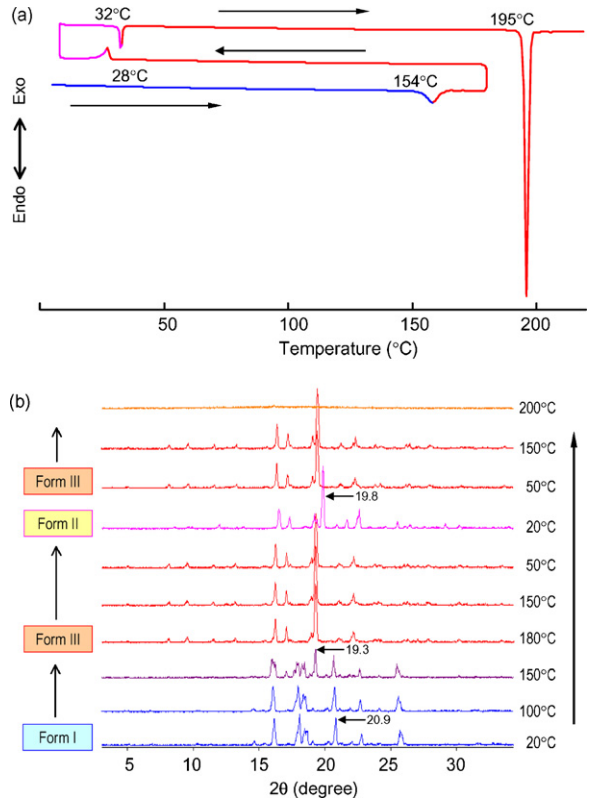

Fig. 4. DSC thermogram (a) and PXRD patterns (b) on a step thermal program.

crystalline forms were anhydrous (data not shown). These results suggested that at least three polymorphs including forms I and II have been shown to exist during thermal analyses.

In order to investigate the potential polymorph, form III, VT-PXRD and DSC with heating and cooling were performed. The characteristic X-ray diffraction peak at 20.9° (2θ) of form I on the PXRD pattern at 20 °C disappeared and a new peak at 19.3° (2θ) of new form appeared over 150 °C with an endothermic peak detected by DSC (Fig. 4). The characteristic X-ray diffraction peak at 19.3° (2θ) also disappeared with cooling and then the peak at 19.8° (2θ) of form II appeared at 20 °C with an exothermic peak. Then, the characteristic X-ray diffraction peak at 19.8° (2θ) of form II disappeared with heating, and the peak at 19.3° (2θ) appeared again at 50 °C with an endothermic peak. These results suggested that compound A should have at least three polymorphs forms I, II and a new form III, and that forms II and III showed an enantiotropic relationship.

The crystal structure of forms I, II and III were analyzed by single crystal X-ray diffractometry. The single crystal X-ray diffraction data for forms I and II were recorded at room temperature, and that of form II was recorded at 50 °C for characterization of form III based on the results of VT-PXRD and DSC. The results of crystallographic data and their structures are shown in Table 1 and Fig. 5, respectively. Every crystal was monoclinic and the space group was $P2$ (1). Unit cell dimensions in crystallographic parameter and molecular arrangements of form I were quite different from those of either forms II or III. Forms II and III, however, showed similar structural conformations with head to head arrangement (Fig. 5). Hydrogen bonding

Table 1
Crystallographic data of polymorphs

	Form I	Form II	Form III
Temperature (°C)	20	25	50
Crystal system	Monoclinic	Monoclinic	Monoclinic
Space group	$P21$	$P21$	$P21$
Unit cell dimensions			
a (Å)	6.0245(4)	10.2007(9)	10.6798(13)
b (Å)	19.2427(12)	10.6341(9)	10.7484(13)
c (Å)	17.0151(11)	17.7985(15)	17.280(2)
α (°)	90	90	90
β (°)	90.6720(10)	95.590(2)	91.764(2)
γ (°)	90	90	90
Volume (Å^3)	1972.4(2)	1921.5(3)	1982.6(4)
Z	4	4	4
Calculated density (g/cm^3)	1.295	1.329	1.288
$R1$	0.0486	0.0380	0.0589

of N(1)–H(1)–O(78) and N(51)–H(51)–O(28) were observed in both of forms II and III, whereas hydrogen bonding of O(77)–H(77)–N(13) and O(27)–H(27)–N(63) were observed in form I, in addition to the hydrogen bonding of N(1)–H(1)–O(78) and N(51)–H(51)–O(28) as numbering in Fig. 6. Two conformation molecules were also observed in the crystal packing of forms II and III. To compare the difference between forms II and III, two structural conformations were superimposed (Fig. 6). The molecular conformation (a) of forms II and III overlapped. The main difference was found in the molecular conformation (b) and provided by the C58–C59–C61–C62 torsion angle with −120.64° and −159.60° for forms II and III, respectively.

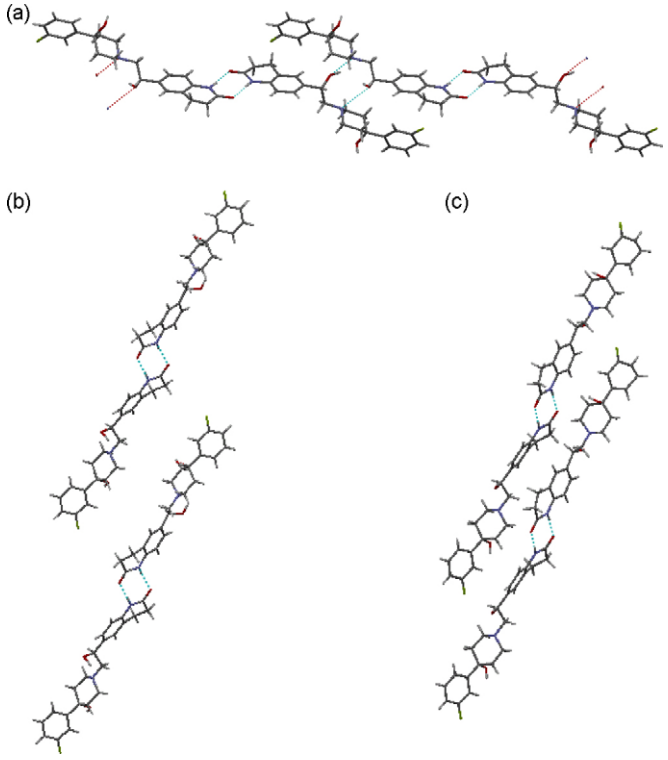

Fig. 5. Packing patterns of form I (a), form II (b), and form III (c).

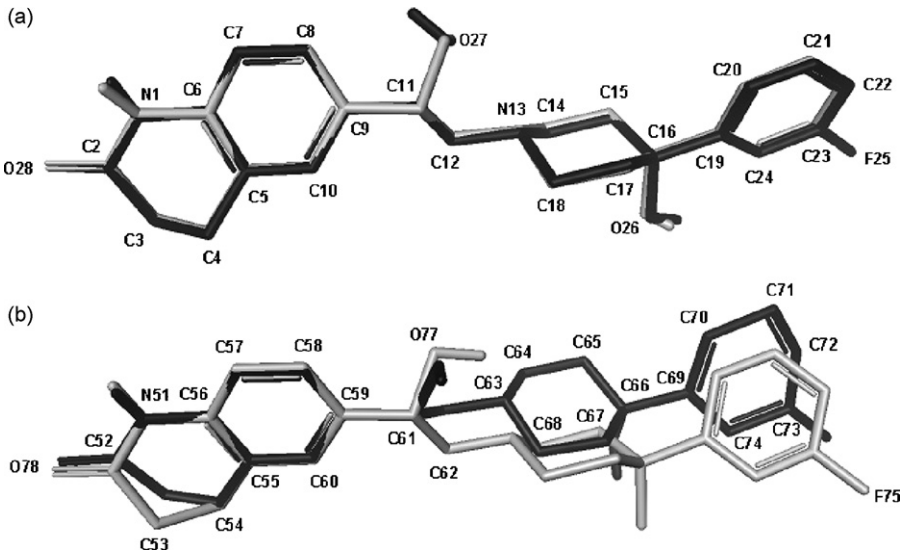

Fig. 6. Atomic numbering and superimposed two structural conformation molecules (a) and (b) of forms II (gray line) and III (black line). Each form has two conformation molecules in the crystal.

4. Conclusion

We have prepared and characterized polymorphs of pharmaceutical compound A, and demonstrated the relationship between the crystals. Compound A has at least three polymorphic forms: I, II, and a new form III possibly showing different physicochemical properties, while forms II and III showed an enantiotropic relationship. These results suggested that the determination of storage temperature should be determined carefully because the transition temperature was detected around the ambient condition. We also performed single crystal X-ray analyses under specific conditions based on the results of VT-PXRD. The unit cell dimensions in crystallographic parameter and molecular arrangements of form I were quite different from those of forms II and III. Whereas, the crystal structures of forms II and III were similar except for the torsion angle of the molecule in two structural conformations.

In pharmaceutical development, the solid-state characterization of drug candidates, for example, an analysis of the relationship between polymorphs, is essential for providing a correct view of the solid form selection strategy. In this study, we characterized forms I, II and III of compound A, and provided information for the selection of storage condition of the compound.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.ijpharm.2007.11.060.

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