

CRYSTAL FORMS OF AN ANGIOTENSIN II RECEPTOR ANTAGONIST BR-A657

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The compound BR-A657 is an angiotensin II receptor antagonist. The objective of this work was to investigate the existence of polymorphs and pseudopolymorphs of BR-A657 and the transformation of crystal forms. Three crystal forms of BR-A657 have been isolated by recrystallization and characterized by powder X-ray diffractometry, differential scanning calorimetry, and thermogravimetric analysis. After storage of three days at 0% RH (silica gel, 20°C), 52% RH (saturated solution of Na₂Cr₂O₇·2H₂O/20°C) and 95% RH (saturated solution of Na₂HPO₄/20°C), Forms 2 and 3 were transformed to Form 1.

Keywords: BR-A657, crystal form, polymorphism, pseudopolymorphism, transformation

Introduction

Pharmaceutical solids can exist in different crystal forms, such as crystalline, amorphous, or glass, and also in solvated or hydrated states [1, 2]. Polymorphism defines as the ability of a substance to exist as two or more crystalline phases that have different arrangements and/or conformations of the molecules in the crystal lattice. Polymorphs share the same chemical composition but have different crystal structures. Because of their structural differences, polymorphs may have different physico-chemical properties. For example, polymorphs can have different density, habit, melting properties, vapor pressure, solubility, dissolution rate, tableting and mechanical properties [1–6].

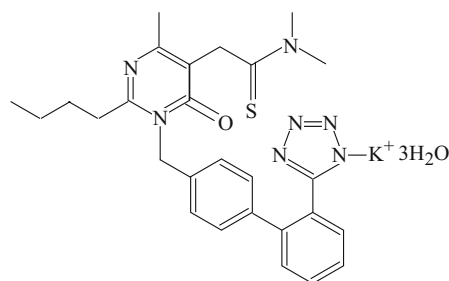
Solvates are molecular complexes that have incorporated the crystallizing solvent molecule in their lattice. When the solvent incorporated in the solvate is water, it is called a hydrate. To distinguish solvates from polymorphs, which are not molecular compounds, the term pseudopolymorph is used [2, 3]. Identification of possible hydrate compounds is also important since their aqueous solubilities can be significantly less than their anhydrous forms [7–11]. Conversion of an anhydrous compound to a hydrate within the dosage form may reduce the dissolution rate and extent of drug absorption.

Crystal form includes polymorphs, solvates, and amorphous forms as defined in the International Conference on Harmonization (ICH) Guideline Q6A [12].

Crystal form affects properties such as drug absorption, rate of dissolution, elimination rate and stability in galenic preparations [13–18]. The successful

utilization of a crystal form of significantly greater thermodynamic activity (i.e., solubility) than the stable modification may provide, in some instances, therapeutic blood levels from otherwise inactive drugs.

The compound BR-A657 (Scheme 1), 2-*n*-butyl-5-dimethylaminothiocarbonylmethyl-6-methyl-3-[2-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl-pyrimidin-4(3H)-one potassium salt trihydrate (C₂₇H₃₀N₇SK·3H₂O), is an angiotensin II receptor antagonist developed by Boryung Pharmaceutical Co. Ltd.



Scheme 1 Chemical structure of BR-A657

In the case of a new drug substance, it is important that crystal form data be generated prior to the initiation of pivotal clinical studies and primary stability batches. Companies have experienced market shortages because they have observed unpredicted changes in crystal form, which ultimately resulted in problematic quality release and stability testing of the finished dosage form [19]. The aim of this study was to investigate the existence of polymorphs and pseudopolymorphs of BR-A657 and the transformation of these crystal forms.

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Experimental

Materials

BR-A657 was provided from Boryung Pharmaceutical Co. Ltd., Korea. Other extra pure chemicals were purchased from a reagent commercial company.

Preparation of crystal forms

Form 1

A suspension of provided one in methanol was heated to 40°C for 30 min. The hot solution was filtered to remove most nuclei and then left undisturbed for one week at room temperature. The resulting solid was filtered and dried for one week in the desiccators to give Form 1.

Form 2

A suspension of Form 1 in acetonitrile was heated to 40°C for 30 min. The hot solution was filtered to remove most nuclei and then left undisturbed for one week at room temperature. The resulting solid was filtered and dried for one week in the desiccators to give Form 2.

Form 3

A suspension of Form 1 ethanol was heated to 40°C for 30 min. The hot solution was filtered to remove most nuclei and then left undisturbed for one week at room temperature. The resulting solid was filtered and dried for one week in the desiccators to give Form 3.

Methods

Powder X-ray diffraction

Powder X-ray diffraction patterns under ambient conditions were collected on Rigaku DMAX-III A (Japan) diffractometer using graphite monochromatized CuK_α radiation ($\lambda=1.54178 \text{ \AA}$). The isothermal measurement conditions were; target, Cu; voltage, 30 kV, current, 10 mA. The PXRD patterns of the samples were compared with regard to peak position and relative intensity, peak shifting, and the presence of lack of peaks in certain angular regions.

Thermal analysis

Thermal analysis methods used in this study included differential scanning calorimetry (DSC), thermogravimetric analysis (TG). DSC patterns were recorded with a Shimadzu DSC-50 instrument (Shimadzu, Kyoto, Japan). The temperature was usu-

ally scanned from 40 to 300°C at 10°C min⁻¹. 5 mg of sample was used for each study. TG analysis was performed on all samples indicated by DSC as being possible solvates or hydrates. TG patterns were recorded with a Shimadzu TGA-50 instrument (Shimadzu, Kyoto, Japan). The temperature was usually scanned from 40 to 300°C at 10°C min⁻¹. 5 mg of sample was used for each study.

Transformation

A certain amount (20 mg) of polymorphs was taken and placed in weighing dish. They were stored in desiccator of 0% RH (relative humidity) (silica gel, 20°C), 52% RH (saturated solution of $\text{Na}_2\text{Cr}_2\text{O}_7 \cdot 2\text{H}_2\text{O}/20^\circ\text{C}$) and 95% RH (saturated solution of $\text{Na}_2\text{HPO}_4/20^\circ\text{C}$).

The transformation behavior of polymorphs was monitored by powder X-ray diffraction (XRD) analysis, DSC and TG.

Results and discussion

DSC curves of Forms 1–3 are illustrated in Figs 1–3. The DSC curve of Form 1 shows two endothermic peaks, one endothermic peak at 60–110°C and the second melting peak at 273.2°C. On TG curve of Form 1 (Fig. 4), the mass loss corresponding to the DSC endotherm at 60–110°C was 9.58%, which was equal to the stoichiometric value calculated for the trihydrate of BR-A657 (9.09%). The DSC curve of Form 2 shows two endothermic peaks, one endothermic peak at 60–110°C and the second melting peak at 271.8°C. On TG curve of Form 2 (Fig. 5), the mass loss corresponding to the DSC endotherm at 60–110°C was 9.49%, which was equal to the stoichiometric value calculated for the trihydrate of BR-A657 (9.09%). Form 3 shows two endothermic peaks, one endothermic peak at 60–110°C and the second melting peak at 266.9°C. On TG curve of

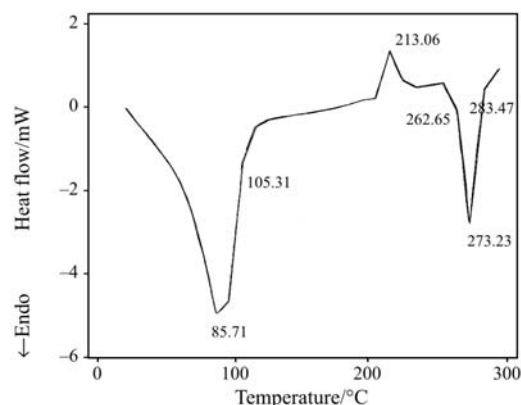


Fig. 1 DSC curve of Form 1

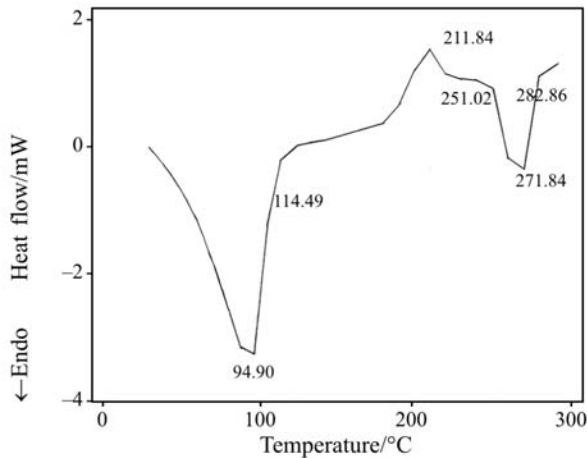


Fig. 2 DSC curve of Form 2

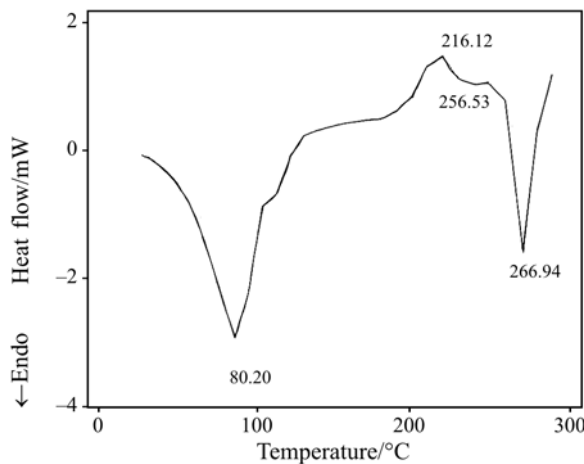


Fig. 3 DSC curve of Form 3

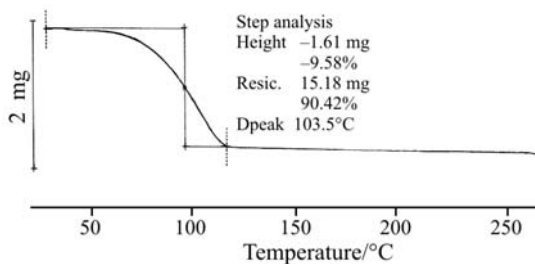


Fig. 4 TG curve of Form 1

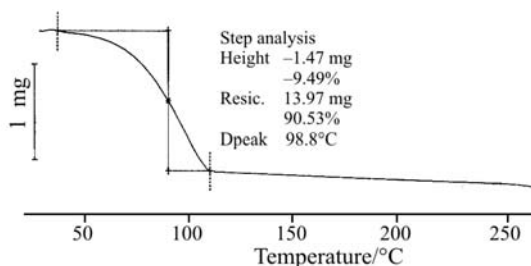


Fig. 5 TG curve of Form 2

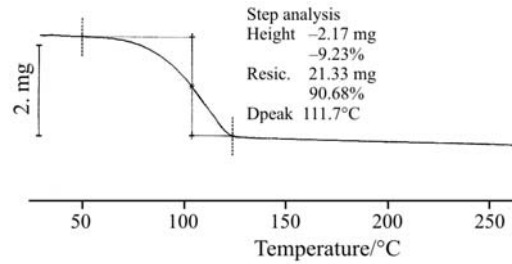


Fig. 6 TG curve of Form 3

Form 3 (Fig. 6), the mass loss corresponding to the DSC endotherm at 60–110°C was 9.17%, which was equal to the stoichiometric value calculated for the trihydrate of BR-A657 (9.09%).

The powder X-ray diffraction patterns of Forms 1–3 are illustrated in Figs 7–9 and they showed distinct differences. Tables 1–3 list 2θ angles,

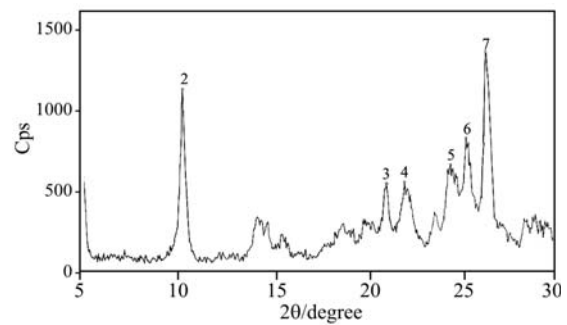


Fig. 7 Powder X-ray diffraction pattern of Form 1

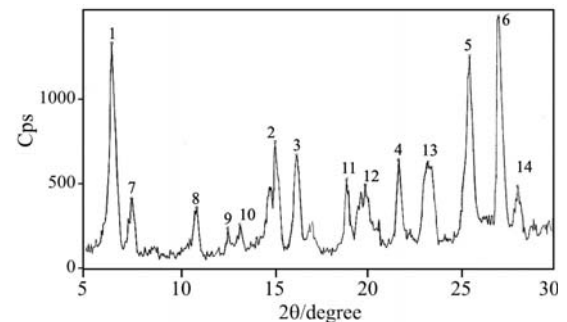


Fig. 8 Powder X-ray diffraction pattern of Form 2

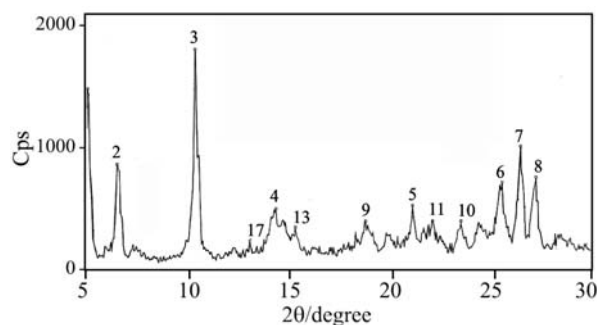


Fig. 9 Powder X-ray diffraction pattern of Form 3

Table 1 Characteristic diffraction peaks of Form 1 up to 30°

2θ/degree	<i>d</i> -space/Å	Relative intensity/%
5.1	17.3268	44
10.4	8.5057	84
21.1	4.2104	39
22.05	4.0311	40
24.5	3.6332	48
25.35	3.5133	60
26.45	3.3696	100

Table 2 Characteristic diffraction peaks of Form 2 up to 30°

2θ/degree	<i>d</i> -space/Å	Relative intensity/%
6.55	13.494	100
7.45	11.8657	23
10.9	8.1166	22
13.25	6.6819	12
14.75	6.0056	24
15.15	5.8479	23
16.25	5.4544	31
18.95	4.6829	20
19.95	4.4504	19
21.65	4.1046	24
23.3	3.8176	25
25.55	3.4862	41
27.15	3.2843	46
27.4	3.255	21
28.0	3.1865	15
28.85	3.0945	10

Table 3 Characteristic diffraction peaks of Form 3 up to 30°

2θ/degree	<i>d</i> -space/Å	Relative intensity/%
5.1	17.3268	82
6.55	13.494	48
10.4	8.5057	100
13.05	6.7838	14
14.35	6.172	28
15.3	5.7909	20
18.75	4.7324	23
21.05	4.2202	29
22.05	4.0311	23

d-spaces and relative intensities of characteristic diffraction peaks up to 30° of three crystal forms.

After storage of three days at 0% RH (silica gel, 20°C), 52% RH (saturated solution of

Na₂Cr₂O₇·2H₂O/20°C) and 95% RH (saturated solution of Na₂HPO₄/20°C), Forms 2 and 3 were transformed to Form 1.

Conclusions

Three crystal forms of BR-A657 were prepared by recrystallization from different solvents. The crystal forms were characterized by Powder X-ray diffractometry, differential scanning calorimetry, and thermogravimetric analysis. Three crystal forms of BR-A657 were trihydrates. After storage of three days at 0, 52 and 95% RH, Forms 2 and 3 were transformed to Form 1.

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