Journal of Crystallization Process and Technology, 2016, 6, 1-10
Published Online January 2016 in SciRes. http://www.scirp.org/journal/jcpt
http://dx.doi.org/10.4236/jcpt.2016.61001

Crystal Type Iof Azilsartan Polymorphs: Preparation and Analysis

Yuhua Ge*, Tingting Li, Jingjing Cheng

School of Chemistry and Chemical Engineering, Southeast University, Nanjing, China
Email: 101004698@seu.edu.cn

Received 8 July 2015; accepted 25 January 2016; published 28 January 2016

Abstract

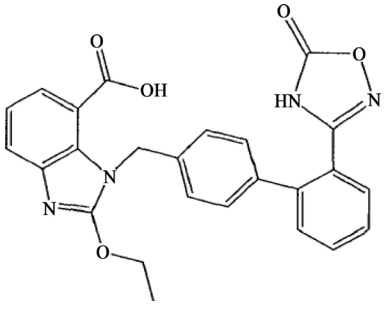
Azilsartan (2-ethoxy-1-([2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl)-1H-benzimidazole-7-carboxylic acid) is a new angiotensin II receptor antagonist used in the treatment of hypertension. This paper describes the preparation of type I crystal and its single crystal diffraction data, the comparison of the powder diffraction data for both type I and II crystals as well as their stability and solubility in methanol.

Keywords

Azilsartan, Single Crystal Diffraction, Powder Diffraction, Solubility, Stability

1. Introduction

The structure of Azilsartan (2-ethoxy-1-([2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl)-1H-benzimidazole-7-carboxylicacid) is shown below. It is reported firstly by Takeda in its prodrug formazilsartanme-doxomil ((5-methyl-2-oxo-1,3-dioxol-4-yl)methyl ester). This drug is an angiotensin II receptor ant-agonist.



How to cite this paper: Ge, Y.H., Li, T.T. and Cheng, J.J. (2016) Crystal Type Iof Azilsartan Polymorphs: Preparation and Analysis. *Journal of Crystallization Process and Technology*, **6**, 1-10. http://dx.doi.org/10.4236/jcpt.2016.61001

Its mechanism is the selective block of the binding of angiotensin II with receptor AT_1 and thus the resulting. It can be prescribed as a treatment for hypertension by itself or in com-bination with other anti-hypertension drugs, blood vessel constriction [1]. It does not function through the biosynthetic pathway of an-giotensin II, thus avoids affecting the concentration of bradykinin as ACE inhibitors. Azilsartan has no common side effects such as dry cough [2].

Different types of crystals from the same drug can have different solubility and absorbility in our body and thus impact on its clinical efficacy and safety. Therefore, crystal types may directly affect the quality and efficacy of drugs. The study of the polymorphiccrystal types of Azilsartan will facilitate the improvement of its stability during preparation and storage. The research will also help to improve the bioavailability and efficacy and to reduce toticity [3].

Azilsartan is a white powder. Four types of crystalline powder have been reported with respective melting points (mp) of 122 - 123 (type III), 163 - 164 (type II), 180 - 181 (type IV), and 198˚C - 206˚C (type I) [4]-[6]. The preparation of type II and III crystals has been reported [4] [6]. Type II crystal is obtained from DMF and acetone; whereas type III crystal is from DMF and isopropanol. The preparation of type IV crystal from THF has also been reported [5]. However, only powder diffraction data for these crystal types have been reported and no single crystal diffraction data are available. Furthermore, the stability and solubility of these crystal types have not been carefully investigated.

We have obtained type I crystal of Azilsartan from methanol. The crystals melt at 198˚C - 201˚C and are not hydroscopic. The advantage of this method is the low toxicity of methanol solvent and thus the suitability for pharmaceutical application. We analyze the single crystal diffraction, measure the solubility of type I and II crystals in methanol with HPLC, determine their G_T values under different temperatures, and compare their stability.

2. Experimental

2.1. Reagents and Instruments

All reagents were analytical pure grade and were used without further purification. Melting points were determined using microscopic melting point apparatus. Single crystal diffraction data were obtained with Enraf-Nonius CAD4 X-ray diffractometer. Powder diffraction data were obtained with Bruker D8-Discover X-ray diffractometer. DSC data were obtained with Mettler-Toledo differential scanning calorimeter (the rate of heating is 10˚C/min).

2.2. Preparation of Azilsartan Type I and II Crystals

Type I crystal: Methanol (100 mL) was added to an Erlenmeyer flask containing Azilsartan (2 g) and the mixture was stirred for 30 minutes. Another 100 mL of methanol was added to obtain a clear solution. To another flask was added 30 mL of the above clear solution, added 0.1 g valine, 6 mL water, and 5 mL methanol. The mixture was stirred for 30 minutes to obtain a clear solution. After two weeks,colorless crystals (0.13 g, mp 198˚C - 201˚C) were obtained.

Type II crystal: Type II crystals were prepared as white powder (mp 164 - 166) according to reported.

2.3. Structural Determination of Azilsartan Type I Crystals

All data were obtained at 20˚C under MoKa ray (λ = 0.71073 Å) and ω-scanning method. Structure was solved and refined with SHELXL-97. Single crystal diffraction data were summarized in **Table 1**.

2.4. Determination of the Solubilities of Azilsartan Type I and II Crystals in Methanol

Sample Preparation: The powdered crystals (0.5 g) were each added to a flask with 15 mL methanol. The mixture was heated to 55˚C and the temperature was maintained for 1 hour. An aliquot (10 μL) of the solution was taken and mixed with 10 mL of the HPLC eluent (discussed below). This solution was further diluted with the same eluent (1 mL solution with 3 mL eluent) and filtered. The original sample solution in methanol was cooled to 50˚C, 45˚C, 40˚C, 35˚C and 30˚C. Samples at each temperature were prepared in the same manner.

Measurement: Measurement was done at 253 nm using WUFENGLC100 HPLC with reverse phase C18 column, eluent acetonitrile: water: acetic acid (57:43:1 by volume), temperature 30˚C, flow rate 1.0 mL/min [7].

Table 1. Single crystal diffraction data for Azilsartan type I crystal.

Parameter	Crystal I
Chemical formula	$C_{25}H_{20}N_4O_5$
Formula weight	456.45
Crystal system	Monoclinic
Space group	$P2_1/C$
a (A˚)	9.6590 (19)
b (A˚)	11.329 (2)
c (A˚)	20.046 (4)
α (˚)	90
β (˚)	90.30 (3)
γ (˚)	90
V ($A^{\circ 3}$)	2193.54
Formula units (Z)	4
μ (Mo Ka) (mm^{-1})	0.099
T (K)	293 (2)
Reflections	4284
Parameters	308
Completeness (%)	99.8
R-Factor(%)	6.48
R indexes (on $F^2 > 2\sigma(F^2)$)	R1 = 0.0648; wR^2 = 0.1460
R(all data)	R1 = 0.1423; wR^2 = 0.1817
Goodness-of fit(S)	1.005
θ min.; max	2.03;25.38
$\Delta\rho$ min.; max. (e $A^{\circ -3}$)	−0.204;0.179

3. Results and Discussion

3.1. DSC Curve of Azilsartan Type I and II Crystals

The differential scanning calorimetry (DSC) curve of Azilsartan type I crystal (**Figure 1**) shows an endothermic process around 195˚C. An exothermic process follows immediately accompanied by loss of mass due to decomposition (mp 198˚C - 201˚C). **Figure 2** shows similar observation with type II crystal around 163˚C (mp 164˚C - 166˚C). The endothermic peaks of both crystal types are quite small. The decomposition temperature of type I crystal is higher than that of type II, which means that crystal type I is more stable than type II, consistent with the solubility data as discussed later.

3.2. Crystal Structure of Azilsartan Type I Crystal

Figure 3 is ORTEP Drawing of Azilsartan Type I Crystal (prob = 50) and **Figure 4** is Ball-and-Stick Illustration of the Structure of Azilsartan Type I Crystal. The values of selected bond length, bond angle, dihedral angle, and torsional angle in Azilsartan type I crystal are summarized in **Table 2** and **Table 3**. In the oxadiazole moiety, the torsional angles for C1-N1-C2-N2 and N1-C1-O2-N2 are −0.8(4) and −1.5(4)˚, respectively, indicating that the ring is almost planar. The torsional angle for N1-C2-C3-C4 is 68.9(5)˚, suggesting that the oxadiazole ring and the benzene ring are not exactly perpendicular to each other. The two benzene rings are also not perpendicular to each other, with the torsional angle for C3-C8-C9-C10 being 118.3(4)˚. The dihedral angles between ring I [O(2)N(2)C(2)N(1)C(1)] and ring III [C(3)C(4)C(5)C(6)C(7)C(8)] and between ring III and ring IV [C(9)C(10)C(11)C(12)C(13)C(14)] are 71.9(2) and 60.04(19)˚, respectively, indicating a lack of coplanarity for these rings. On the other hand, ring II [N(3)C(16)N(4)C(17)C(22)] and ring V [C(17)C(18)C(19)C(20)C(21)C(22)] are almost coplanar, with a dihedral angle of 2.33(19)˚. The carboxylic acid group on C21 has a torsional angle of 37.4(6)˚ (C22-C21-C23-O3).

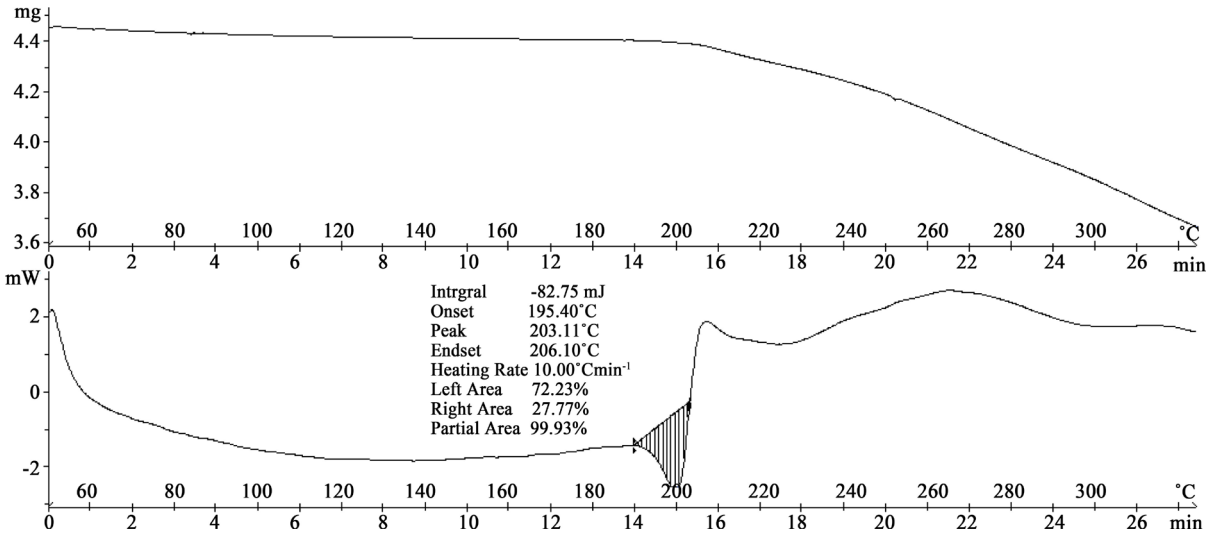


Figure 1. DSC Curve of Azilsartan type I crystal. (The rate of heating is 10˚C/min).

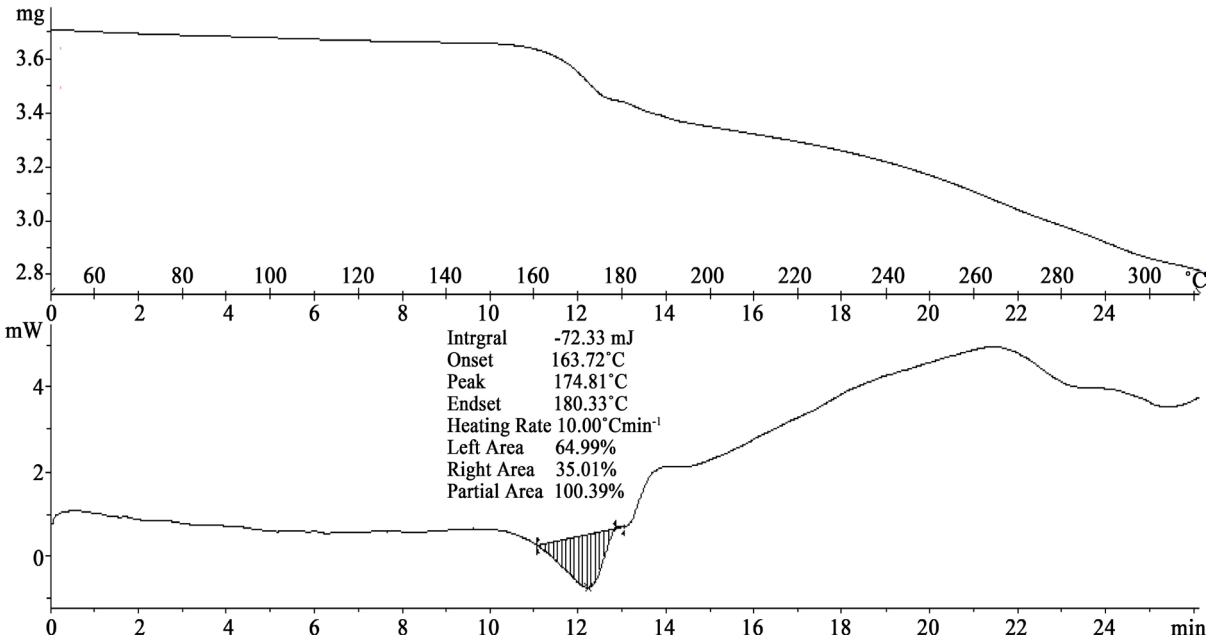


Figure 2. DSC Curve of Azilsartan type II crystal. (The rate of heating is 10˚C/min).

Table 2. Selected bond length, bond angle, and dihedral angle values in Azilsartan type I crystal.

Bond Length (Å)			
N1-C1	1.359 (5)	N1-C2	1.369 (4)
O1-C1	1.203 (4)	C1-O2	1.355 (4)
O2-N2	1.446 (4)	N2-C2	1.288 (4)
O3-C23	1.222 (4)	O4-C23	1.308 (4)
N3-C16	1.370 (4)	N3-C22	1.387 (4)
N3-C15	1.463 (4)	N4-C16	1.299 (4)
N4-C17	1.400 (4)	O5-C16	1.332 (4)
O5-C24	1.437 (4)		

Continued

Bond Angle (˚)			
C1-N1-C2	108.5 (3)	O1-C1-O2	123.8 (4)
O1-C1-N1	130.7 (4)	O2-C1-N1	105.4 (3)
C1-O2-N2	109.8 (3)	C2-N2-O2	103.8 (3)
N2-C2-N1	112.4 (3)	N2-C2-C3	124.2 (3)
N1-C2-C3	123.4 (3)	C16-N3-C22	105.5 (3)
C16-N3-C15	123.5 (3)	C22-N3-C15	131.1 (3)
C16-N4-C17	103.0 (3)	N3-C15-C12	114.0 (3)
C16-O5-C24	118.2 (3)	N4-C16-N3	115.9 (3)
N4-C16-O5	128.3 (3)	C18-C17-N4	128.1 (3)
O5-C16-N3	115.9 (3)	N3-C22-C21	134.0 (3)
N4-C17-C22	110.9 (3)	O3-C23-O4	122.7 (4)
N3-C22-C17	104.8 (3)	O4-C23-C21	114.3 (3)
O3-C23-C21	123.0 (3)	O5-C24-C25	106.9 (3)

Dihedral Angles (˚)					
Crystal: Ring	I	II	III	IV	V
I O(2)N(2)C(2)N(1)C(1)					
II N(3)C(16)N(4)C(17)C(22)	35.9 (2)				
III C(3)C(4)C(5)C(6)C(7)C(8)	71.9 (2)	47.1 (2)			
IV C(9)C(10)C(11)C(12)C(13)C(14)	76.7 (2)	68.2 (2)	60.04 (19)		
V C(17)C(18)C(19)C(20)C(21)C(22)	38.05 (19)	2.33 (19)	46.78 (18)	65.93 (18)	
VI N(3)C(16)N(4)C(17)C(18)C(19)C(20)C(21)C(22)	37.11 (17)	1.28 (17)	46.87 (16)	66.94 (16)	1.05 (15)

Table 3. Torsional angle values in Azilsartan type I crystal.

Torsional Angle (˚)			
N1-C2-C3-C4	68.9(5)	N2-C2-C3-C8	74.7(5)
C1-N1-C2-N2	−0.8(4)	O1-C1-O2-N2	179.9(4)
C3-C8-C9-C10	118.3(4)	C16-N3-C15-C12	−115.7(4)
C13-C12-C15-N3	14.1(5)	C22-N3-C15-C12	62.5(5)
C23-C21-C22-N3	7.5(7)	N4-C17-C22-C21	−178.5(3)
N4-C17-C22-N3	−1.3(4)	N4-C17-C18-C19	177.8(4)
C22-C21-C23-O3	37.4(6)	C24-O5-C16-N4	3.2(6)
C22-N3-C16-N4	0.2(4)	C16-O5-C24-C25	170.4(4)
N1-C1-O2-N2	−1.5(4)		

In the crystal, the main molecular interaction is hydrogen bonding interaction. As seen in **Table 4**, the distance between H1… N4 is longer than that of H4…O3, indicating a stronger hydrogen bond in O4–H4…O3. The bond O4–H4… O3 is almost linear, ideal for hydrogen bond formation [8] the strength of this hydrogen bond is also reflected in the short O3… O4 distance (the reported range is 3.2 - 4.0 Å) [9]. The C18–H18… O1 intermolecular hydrogen bond is weaker, with the hydrogen much closer to the donor atom (C18).

The crystal lattice-packing graph along axis b and c are shown in **Figure 5** and **Figure 6**, respectively, whereas the space-filling model is depicted in **Figure 7**. There are π-π stacking interactions between the imidazole rings of neighboring cells. The distance between the centers of the rings is 5.557 Å and the vertical distance between the two rings is 3.507 Å.

3.3. XRD Data for Azilsartan Type I and II Crystals

The simulated and observed powder diffraction graphs of Azilsartan type I crystal were shown in **Figure 8** and **Figure 9**, respectively. Peaks were observed at 2θ values of 9.01˚, 12.91˚, 15.52˚, 18.38˚, 19.43˚, 21.50˚, 23.58˚, and 26.72˚, in good agreement with the simulated values. These values are also consistent with the reported val-

Table 4. Hydrogen-bonding parameters in Azilsartan type I crystal.

D–H…A	D–H…(Å)	H…A (Å)	D…A (Å)	D–H…A (˚)
N1–H1…N4	0.86	2.068	2.915(4)	168.04
O4–H4…O3	0.819	1.862	2.681(4)	179.73
C18–H18…O1	0.93	2.57	3.458(5)	160

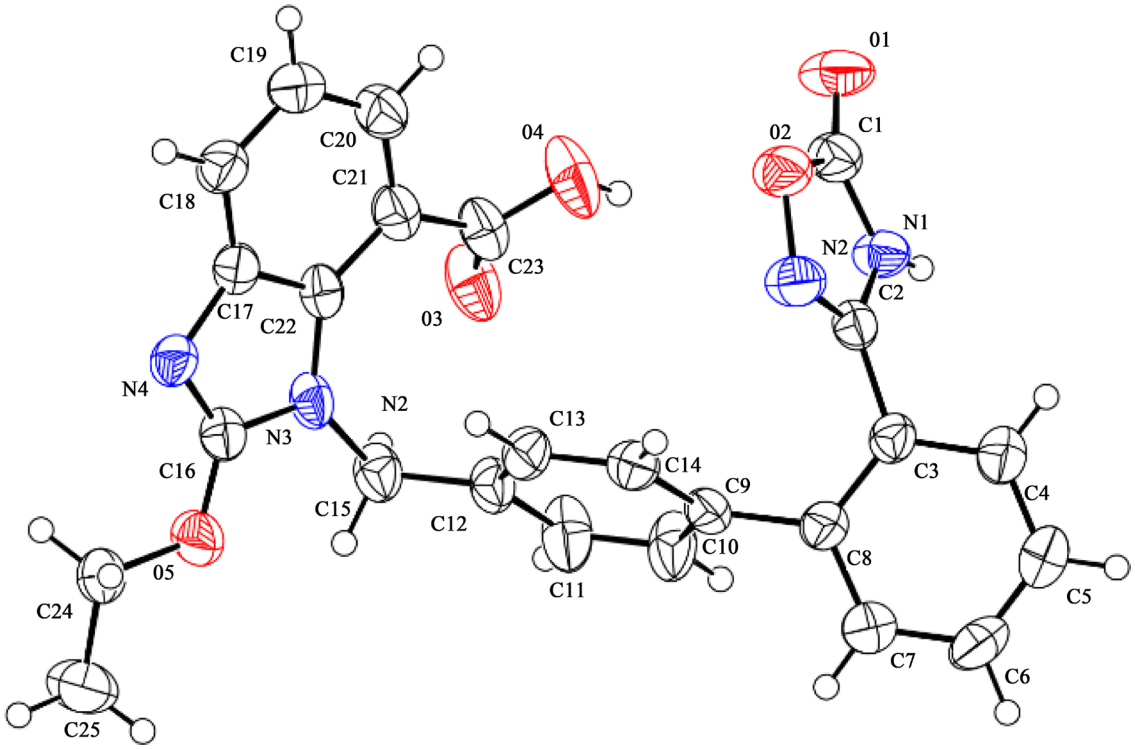


Figure 3. ORTEP drawing of Azilsartan type I crystal (prob = 50).

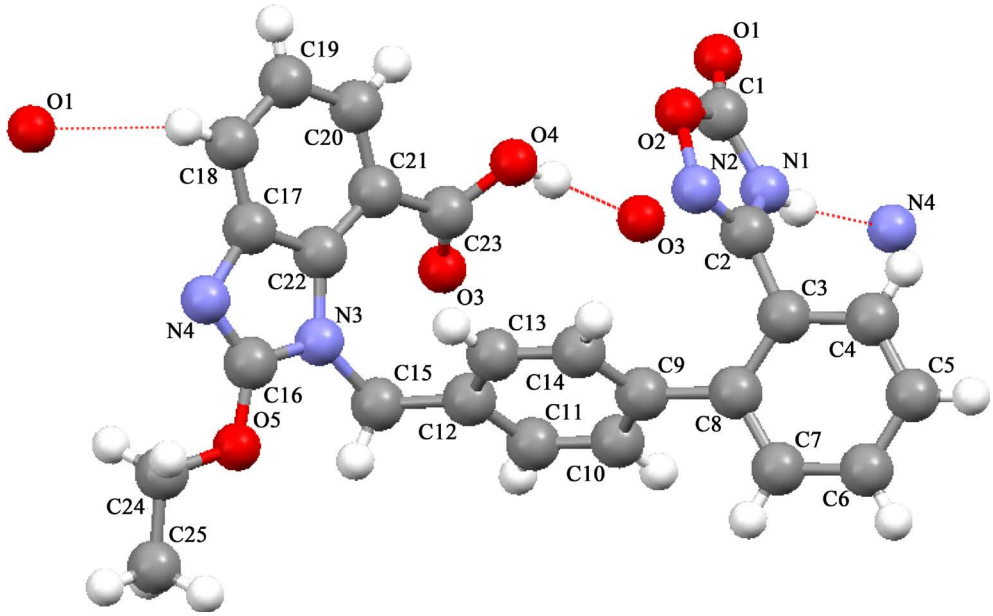


Figure 4. Ball-and-stick illustration of the structure of Azilsartan type I crystal (dashed line indicating hydrogen bonds).

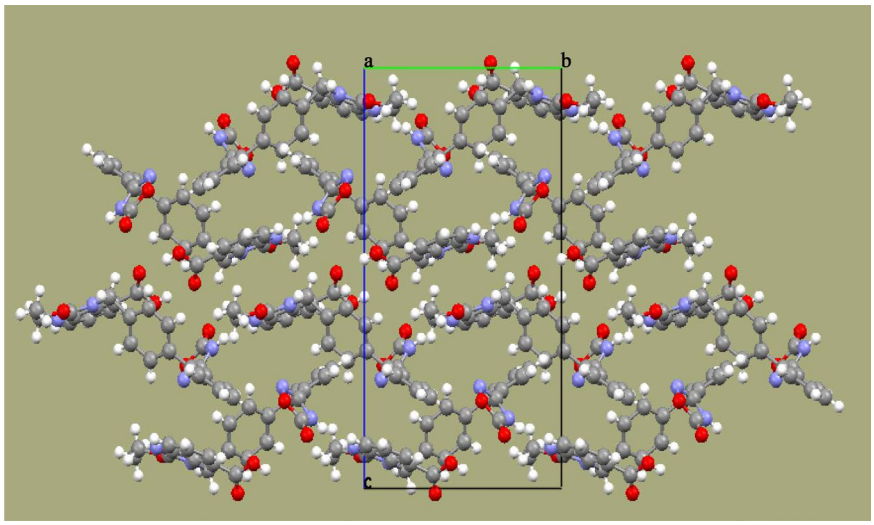


Figure 5. Crystal lattice-packing graph along axis a.

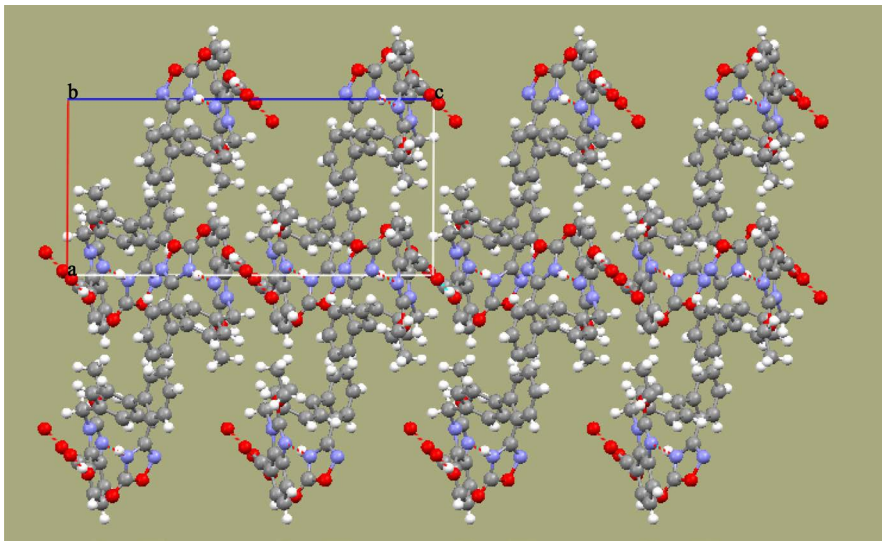


Figure 6. Crystal lattice-packing graph along axis b.

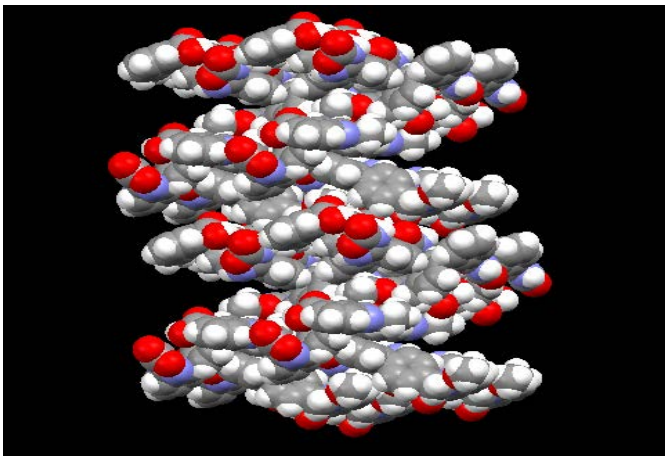


Figure 7. Space-filling model of crystal I for Azilsartan.

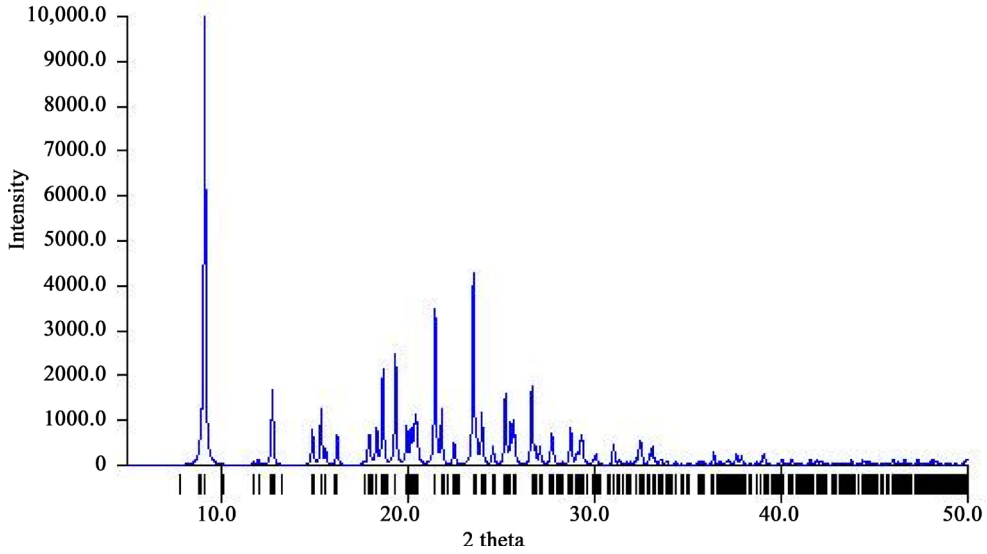


Figure 8. Simulated powder diffraction graph of Azilsartan type I crystal.

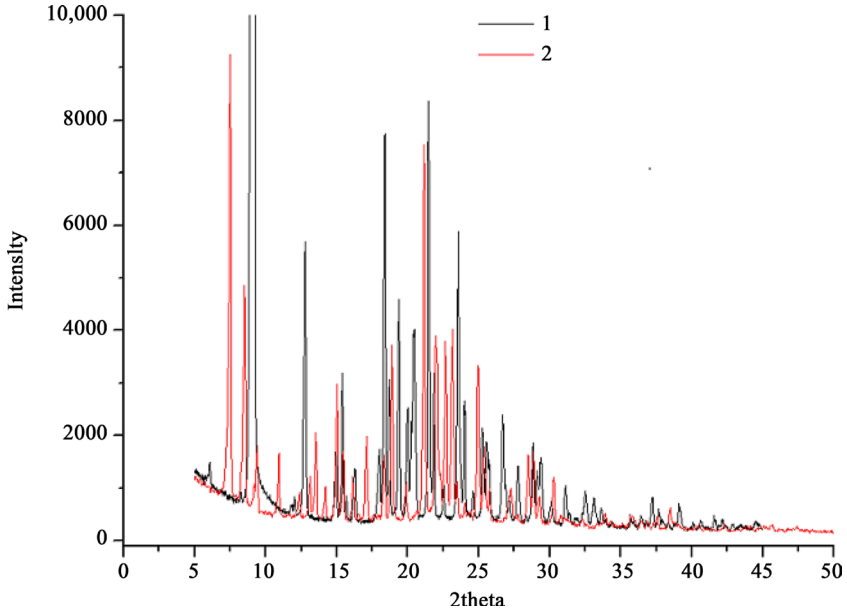


Figure 9. Overlaid powder diffraction graph of Azilsartan crystals (1 is type I, 2 is type II).

ues for a powder obtained from methanol and water [6]. The powder diffraction graphs of the two crystals were overlaid in **Figure 9** for comparison. The different DSC curves and powder diffraction data have demonstrated that type I and II crystals are different.

3.4. Solubility in Methanol and Stability of Azilsartan Type I and II Crystals

The thermostability of different crystals can be inferred from their solubility in the same solvent. The solubility data in methanol are shown in **Figure 10(a)**. In the temperature range of 30˚C - 55˚C, the solubility of type I crystal is always lower than that of type II crystal and phase transformation is not observed. The solubility data and the melting point data both suggest that type I crystal is more stable than type II.

The enthalpy of solution (ΔH_s) can be calculated from the equation $\ln C_S = -\Delta H_S/R*(1000/T) + \beta$ by plotting the logithium of molar concentration against 1000/T as shown in **Figure 10(b)** [10]. The ΔH_s values for type I and II crystals are calculated to be 25.87 and 23.63 J/mol, respectively.

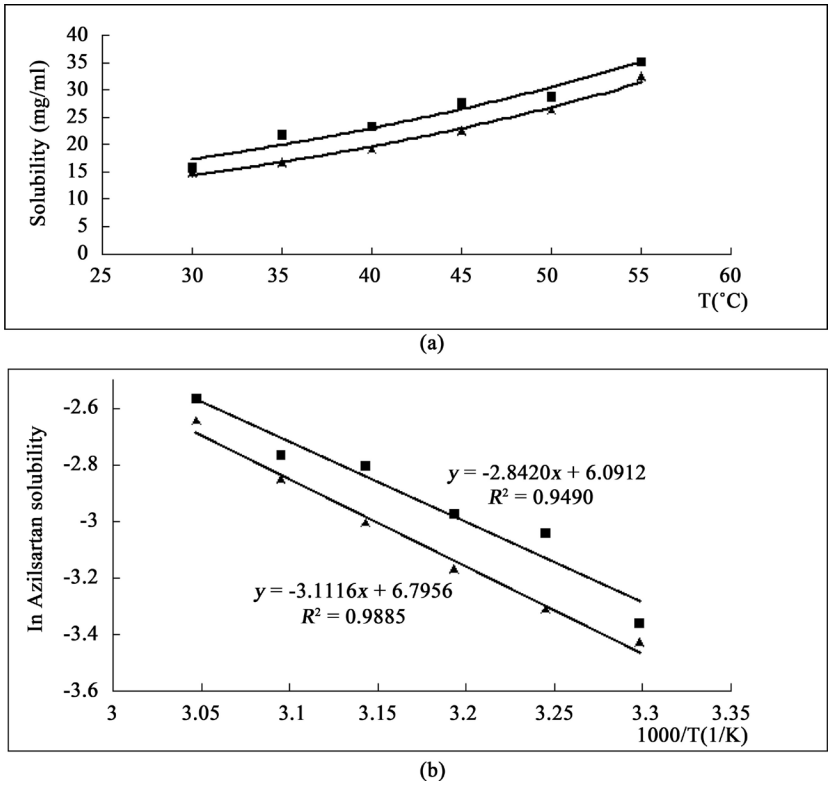


Figure 10. Solubility of the Azilsartan crystals in methanol (Triangle represents type I and square represents type II).

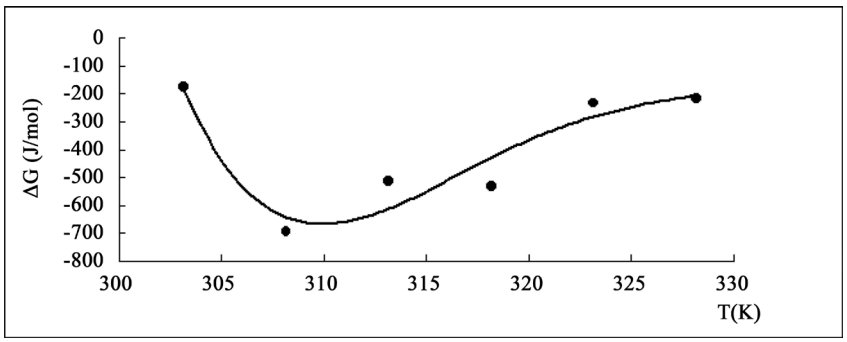


Figure 11. ΔG_T values of Azilsartan crystals at different temperatures.

The difference in Gibbs free energy of the two crystal types, ΔG_T, has been calculated using the reported method [10]. The value ΔG_T initially decreases and then increases with rising temperature but stays negative (**Figure 11**).

4. Conclusion

Our results suggest that Azilsartan type I crystal is a single crystal. Single crystal structure indicates that cell lattice in type I crystal is formed from hydrogen bonding and π-π interactions. Type I crystal has higher melting point than type II crystal. It is not hydroscopic and less soluble in methanol. Phase transformation is not observed in the experimental temperature range. Overall, type I crystal is more stable.

Supporting Information

CIF files of crystals 1 were deposited with the CCDC, CCDC No. 1029310

References

[1] Singh, P., Fung, W.F. and Song, J.C. (2010) Focus on… Azilsartan: A Next-Generation Angiotensin II Receptor Blocker for the Treatment of Hypertension. *Formulary*, **45**, 342-349.

[2] Lam, S. (2011) Azilsartan: A Newly Approved Angiotensin II Receptor Blocker. *Cardiology in Review*, **19**, 300-304. http://dx.doi.org/10.1097/crd.0b013e31822e9ba3

[3] Qiang, G., Lu, Y. and Du, G. (2009) The Present Situation and Development Direction of the Research for Polymorphic Drugs in China. *Chinese Journal of New Drugs*, **18**, 1196-1200.

[4] Xu, Y., Zhou, H., Liu, W. and He, G. (2013) Azilsartan Polymorph and Preparation Method Thereof. Chinese Patent CN103319473A.

[5] Wang, X., Shui, Q., Tang, C., Liu, S., Ouyang, Q. and Shi, H. Azilsartan Crystal Form and Its Preparation and Application of the Same. Chinese Patent CN103880829A.

[6] Chen, Q., Zhu, Y., Zhang, L. and Ding, L. (2012) Polycrystalline Substance of Azilsartan and Preparation Method Thereof. Chinese Patent CN102766139B.

[7] Wu, B., Cui, H., Wang, J.and Wang, D. (2013) Hplc Analysis Method of Azilsartan. Chinese Patent CN103743826A.

[8] Chen, X. and Cai, J. (2007) Single Crystal Structural Analysis: Principles and Practice. Science Press, Beijing, 127-128.

[9] Steed, J.W. and Atwood, J.L. (2009) Supramolecular Chemistry. 2nd Edition, Wliley, Chichester. http://dx.doi.org/10.1002/9780470740880

[10] Pranzo, M.B., Cruickshank, D., Coruzzi, M., Caira, M. R. and Bettini, R. (2010) Enantiotropically Related Albendazole Polymorphs. *Journal of Pharmaceutical Sciences*, **99**, 3731-3742 http://dx.doi.org/10.1002/jps.22072