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Crystallographic evaluation of the conformation of quetiapine included in β-cyclodextrin

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Abstract

Single-crystal X-ray diffraction and theoretical calculations were conducted for insights into the β-cyclodextrin (β-CD)-quetiapine inclusion complex structure. β-CD and quetiapine form a host-guest inclusion complex at a ratio of 2:1 in which the β-CD molecules form head-to-head dimers with their secondary hydroxyl groups linked by multiple hydrogen bonds. Quetiapine is totally contained within the β-CD cavity and exhibits two kinds of disorder (parts 1 and 2) in opposite directions in the β-CD complex. To clarify the mobility of the guest molecule in the β-CD cavity, theoretical molecular conformational calculations, crystal optimization and crystal energy calculations were conducted using CONFLEX software. The results of theoretical molecular conformation calculations showed that the mobility of quetiapine is restricted because its tricyclic structure is covered by β-CD. The results of crystal energy calculations indicated that the conformation of disorder part 1, which has high occupancy, was more stable.

Keywords: cyclodextrin; inclusion compounds; crystal structure; crystallography; theoretical calculation

1. Introduction

Quetiapine (Fig. 1) is used in the treatment of schizophrenia and mania associated with bipolar disorders. The drug is a dibenzothiazepine derivative with piperadine and ethoxyethanol moieties. Quetiapine is marketed in tablet and fine particle formulations in which the principal agent is quetiapine fumaric salt (Ravikumar and Sridhar, 2005, Saller and Salama, 1993) which exhibit better solubility in water than the free base. On the other hand, absorption of quetiapine through biological membranes could be improved by enhancing the solubility of the quetiapine free base because the base is more hydrophobic than quetiapine salt form (Ogawa et al., 2013). In the treatment of schizophrenia, poor treatment compliance is a major problem that cause psychotic relapse (Baweja et al., 2012). Developing parenteral long acting dosage forms of antipsychotic drugs will serve patients' needs and improve compliance. It is expected that using antipsychotic drug base for developing parenteral dosage forms is beneficial if its solubility or absorption through biological membranes is enhanced. We previously converted the currently used salt form (quetiapine hemifumarate) into a free base and utilized cyclodextrins (CDs) as pharmaceutical additives to improve the solubility of quetiapine (Ogawa et al., 2013). CDs are cyclic oligosaccharides comprising 6, 7, or 8 D-glucose units, called α-, β-, and γ-CD, respectively. They have the molecular feature of a hollow, truncated cone with external hydrophilic properties and an internal hydrophobic cavity. CDs form inclusion

complexes with various guest compounds and hence are used in pharmaceutical technology to improve drug properties such as solubility, stability and bioavailability (Hirayama and Uekama, 1999, Jansook et al., 2018, Saenger, 1980). We previously found that β-CD and quetiapine could form an inclusion complex exhibiting a 2:1 stoichiometry (host:guest) in the precipitated powder (Ogawa et al., 2013). However, the three-dimensional structure in the solid state could not be determined and a crystallographic evidence for the β-CD-quetiapine complex remains elusive. It is well known that single crystal X-ray analysis allows us to visualize the three-dimensional structures of molecules in crystals. As the results of the large number of investigations which have been attempted to elucidate the nature of CD inclusion complex formation, numerous crystalline structures of CD inclusion complexes have been reported (Harata, 1998, 1999). In general, the guest molecules are allowed significant degrees of freedom inside the CD cavity because of their weak interactions such as hydrogen bonds, electrostatic interactions, van der Waals force, etc. (Harata, 1999). Therefore, disorder structures of guest molecules have been frequently found, because the high mobility of the guest molecules inside the CD cavity compared to the host molecules. (Aree and Chaichit, 2009; Brett et al., 1999; Christoforides et al., 2015; Clark et al., 2006; Harada and Ogawa, 2009, Ogawa et. al., 2017). To elucidate the characteristics of included guest, it is essential to analyze not only the mean inclusion structure, but also the mobility of the guest molecule in the CD cavity

(Harata, 1999). To clarify the mobility of the guest molecules in the β-CD cavity, we have previously determined the β-CD-fentanyl inclusion complex structure by single crystal analysis and theoretical calculations, focusing on the molecular mobility of the phenylethyl group of fentanyl (Ogawa et al., 2017). The results of theoretical calculation indicated the conformational disordered molecule which had high occupancy was more stable. In the inclusion complex of fentanyl and β-CD, there was a disorder only in the phenylethyl group, but there are many cases in which the entire guest compound has a disorder in the CD cavity, making the structural analysis difficult. Therefore, it is important to consider the conformational calculation of the fully occupied guest molecule embedded in the CD cavity. It is valuable to obtain the crystal structure of the inclusion complex to provide direct insight into the binding mechanism of quetiapine and β-CD and the functional mechanism of the inclusion complex. Furthermore, it might be useful in predicting the drug release from various formulations that contained β-CDs such as tablets, transdermal formulation, and intramuscular injection.

In this study we evaluated the disordered structures of the guest molecule, quetiapine completely contained within the β-CD cavity by theoretical studies in addition to X-ray single-crystal structural analysis.

2. Material and methods

2.1. Materials

Quetiapine fumarate (quetiapine hemifumarate) was purchased from Fuji Film Wako Pure Chemical Co. (Osaka, Japan). β-CD was purchased from Tokyo Chemical Industry Co., Ltd. (Tokyo, Japan) in a hydrate form (β-CD10.5 H_2O). Ultrapure water was supplied by a Milli-Q water system.

2.2 Remove of fumaric acid from quetiapine salt

Quetiapine was prepared by liquid–liquid extraction from quetiapine hemifumarate by using ethyl acetate/sodium hydrogen carbonate saturated solution (Ogawa et al., 2013). The prepared quetiapine was a faint yellow oily material. The removal of fumaric acid was confirmed by ^{1}H- and ^{13}C-NMR measurements (data not shown). The NMR spectra were recorded on a JNM-ECZ400S spectrometer (JEOL Ltd., Tokyo, Japan).

2.3. Single-crystal preparation

To prepare the single crystal of β-CD-quetiapine inclusion complex, the precipitated sample was prepared by mixing quetiapine (0.18 mmol) with 30 mL of β-CD solution (12.6 mM). The mixed solution was shaken (120 strokes/min) for 48 h thus a white precipitate was produced. The precipitate was filtered and dried under vacuum at room temperature for 24 h. Thirty milligrams of precipitate were suspended in 3 mL purified

water and the suspension was heated at 60°C. The suspension was cooled at room temperature and good quality, colorless, needle-shape single crystals were obtained. The obtained acicular crystals were not twins, and crystal polymorphism was not recognized.

2.4. X-ray diffraction experiment

The crystal obtained by the method described in 2.3 was soaked with Parabar10312 (Hampton Research Corporation, California, USA) and mounted in a loop. The crystal with dimensions of 0.140 × 0.100 × 0.030 mm^3 was used and all measurements were made using a XtaLAB Synergy-S DS, Dualflex, HyPix diffractometer (Rigaku Corporation, Tokyo, Japan, Cu Kα radiation; λ = 1.54187 Å). The crystal was kept at 100.00(10) K during data collection. Using OLEX^2 (Dolomanov et al., 2009), the structure was solved with the ShelXT (Sheldrick, 2015) structure solution program using Intrinsic Phasing and refined with the ShelXL (Sheldrick, 2015) refinement package using Least Squares minimization. In the process of the refinement, quetiapine had several constraints with the commands of SHELXL (Sheldrick, 2015) such as AFIX 6 which restraints benzene rings into a regular hexagon, DFIX which restraints interatomic distances, SADI which restraints interatomic distances to be equal between disorder parts of quetiapine, and SIMU and RIGU which restraint the temperature factors. Disordered water molecules were masked with OLEX^2 (Dolomanov et al., 2009). In addition, large

solvent void was removed during the refinement because the void was occurred by water masking. Mercury 4.2.0 software was used for drawing the crystal structures (Bruno et al., 2002; Macrae et al., 2006, 2008, 2020; Taylor and Macrae, 2001).

2.5 Computational methods

Theoretical calculations were carried out using CONFLEX software (version 8 Rev. C; CONFLEX Corporation, Tokyo, Japan). The starting atomic coordinates of the β-CD-quetiapine inclusion complex with the drug in Part 1 and part 2 were extracted from the corresponding X-ray derived structures. Molecular mechanics (MM) calculations with MMFF94s forcefields of quetiapine were performed with β-CD conformation fixed (Goto and Osawa, 1989, 1993; Obata and Goto, 2008a, 2008b). The crystal energy ($E_{crystal}$), the total intramolecular energy (E_{intra}), and the lattice energies ($E_{lattice}$) were calculated as previous reported (Ogawa et. al, 2017). To visualize the crystal structures, GaussView, version 6 (Dennington et al., 2009) packages and Mercury 4.2.0 were used.

3. Results and Discussion

3.1 Single crystal structure analysis

Table 1 shows the summarized crystallographic data. As shown in Figure 2, β-CD and quetiapine form a host-guest inclusion complex at a ratio of 2:1. Figures 3 shows ORTEP

plots of the inclusion complex of β-CD and quetiapine. The β-CD molecules form head-to-head dimers with their secondary hydroxyl groups linked by multiple hydrogen bonds (Figure 4). A head-to-head dimer structure is frequently observed for β-CD in crystalline complexes (Harata, 1998; Mentzafos et al., 1991). The relative setting of the dimeric layers leads to four classes of molecular packing, *i.e*., the channel, chessboard, screw-channel, and intermediated types. The channel-type packing exists in space groups *C*2 or *P*1 and the chessboard, intermediated and screw-channel types in $C222_1$, *P*1 and $P2_1$ space groups, respectively (Mentzafos et al., 1991). Packing of the β-CD molecules in this study was of the screw-channel type. In addition, several hydrogen bonds between water molecules located in the interstices of the inclusion complex and hydroxyl groups of β-CD are found [Figures 4 and S1(I)]: O0AA, O5, O11 and O20 form 3, 2, 2 and 2 hydrogen bonds with hydroxyl groups of β-CD, respectively. These hydrogen bonds are considered to play an important role to stabilize the channel type packing.

It is considered that host-guest interactions are also important for the stability of CD inclusion complexes. Therefore, we subsequently paid attention to intermolecular interactions between quetiapine and β-CD. As shown in Figure S1(I), there is no hydrogen bond between quetiapine and β-CD although there are multiple hydrogen bonds between β-CDs. Inside of the β-CD packing, we can find a water molecule which makes hydrogen bonds with N and OH of quetiapine [Figure S1(I)]. These hydrogen bonds are thought to

participate in the conformational stability of quetiapine in the inclusion complex. Furthermore, there is a CH/π interaction between quetiapine and β-CD in the inclusion complex as shown in Figure S1 (II). The distance between the center of benzene ring B of quetiapine and a secondary carbon of β-CD is 3.699 Å which indicates CH/π interaction has taken place (Hobza and Havlas, 2000). The CH/π interaction is weaker than hydrogen bonding, but it is known that it plays an important role in many fields such as in crystals, organic reactions, conformational analysis and molecular recognition (Gil et al., 2007). Therefore, it is considered that the CH/π interaction occurred between quetiapine and β-CD stabilizes the inclusion complex.

As shown in Figure 3, quetiapine molecule is totally included in the β-CD cavity. The structure of quetiapine is disordered inside the β-CD cavity (Figures 2 and 5). The disordered structures with occupancies of 0.62 and 0.38 are named part 1 and part 2 respectively. The disordered structures of quetiapine inside the β-CDs cavity viewed along the *b* axis and *c* axis are shown in Figures 5A and 5B, respectively. There is a disorder in the OH of β-CD which is indicated by arrows in Figure 5. Quetiapine shows relatively higher thermal motion with equivalent isotropic temperature factors (U_{eq}) of 0.0401(4)-0.0756(13) Å^2 compared to the β-CD structures with U_{eq} of 0.0186(10)-0.081(3) Å^2 (Figure 3). Previously, we reported that quetiapine and β-CD formed an inclusion complex with a 1:1 stoichiometry at lower β-CD concentrations in aqueous

solution and inclusion complexes of different stoichiometries were assumed to be formed at higher β-CD concentration (Ogawa et al., 2013). At a low concentration of β-CD, quetiapine is included in one molecule of β-CD, and in that case, quetiapine is considered to move relatively freely in the β-CD cavity. At higher β-CD concentration, it is considered that quetiapine is included in multiple β-CDs and the β-CD adopts a screw-channel type packing in the solid state.

Focusing on the guest molecule quetiapine, the conformation of the central thiazepine ring in the (6,7,6)-tricyclic ring system can be described as a boat, with the atoms common to the benzene rings (A and B in Figures 1 and 6) as the basal plane, the S atom as the bow and the N=C bridge as the stern (Ravikumar et al., 2005). Ravikumar et al. have reported the crystal structure of quetiapine hemifumarate and discussed its conformation in comparison to related antipsychotic agents, amoxapine, clozapine, loxapine, loxapine succinate monohydrate, clothiapine-modified (8-chloro-11-(4-methypiperazin-1-yl)dibenzo[b,f]-1,4-thiazepine), clothiapine, olanzapine, olanzipinium nicotinate, oxyprothepine, and metitepine maleate (Ravikumar et al., 2005). They reported that the corresponding torsion angles in the related antipsychotics were similar to those of quetiapine fumarate. The data showed a remarkable similarity in the disposition of the molecular fragments for the analyzed compounds and may be useful for postulating receptor interactions for structure activity relationships (Ravikumar et al., 2005). The

comparison of selected conformational parameters (*d*1 to *d*4) of quetiapine included in β-CD and quetiapine fumarate (Ravikumar et al., 2005) is given in Figure 6 and Table 2. As shown in Table 2, all the distances represented by *d*1 to *d*4 of quetiapine included in β-CD are shorter than quetiapine fumarate. Large differences in distances are seen in *d*2 and *d*4 between quetiapine fumarate and quetiapine included in β-CD. However, there is no significant difference in *d*1 to *d*4 between part 1 and part 2 of quetiapine included in β-CD. In the tricyclic framework, the central thiazepine ring has a boat conformation and the dihedral angles (χ) between the planar benzene rings (A and B in Figures 1 and 6) are 108.63, 262.06, 96.74° in quetiapine fumarate, and part 1 and part 2 of the complex, respectively (Table 2). The dihedral angle (χ) of quetiapine part 1 is a reflex angle which indicates more than 180° but less than 360°, therefore remarkably different from those in quetiapine fumarate and quetiapine part 2. It is considered that the conformation of dibenzothiazepine has dramatically changed in quetiapine part 1 as if turned over in the process of inclusion by β-CD. The obtuse angle (360° - χ°) of quetiapine part 1 and the dihedral angle (χ) of quetiapine part 2 included in β-CD are narrow compared to quetiapine fumarate. Since quetiapine fumarate is charged and thus it is difficult to make a uniform comparison, it is considered that quetiapine adopts a more compact conformation by inclusion in β-CDs. For better understanding of the conformational changes upon complexation, we conducted the structural comparisons of quetiapine

conformations (Figure S2), and calculated the root mean square deviation (RMSD). The superposition of quetiapine structures and RMSD calculations were conducted by using CueMol: Molecular Visualization Framework (http://www.cuemol.org/). Figure S2 (I) shows superposition of uncomplexed quetiapine and included ones by β-CD. The uncomplexed quetiapine structure was obtained from the crystal structure of quetiapine fumarate (Ravikumar et al., 2005) and the included quetiapine structures (part 1 and 2) were obtained from X-ray structure. As shown in Figure S2(I), the conformation of quetiapine has extremely changed, especially in part 1 which shows the opposite directions to uncomplexed drug, and RMSD calculated between uncomplexed drug and the included drug part1 (1.968 Å) was higher than that calculated by part 2 (1.482 Å). In comparison of conformations between part 1 and part 2 included in β-CD, the conformations show the opposite directions and RMSD calculated between part 1 and part 2 was 1.843 Å [Figure S2 (II)]. These results show that the inclusion of β-CD significantly changes the conformation of quetiapine molecule, and the large difference between part 1 and part 2 conformations.

As associated with the structure of inclusion complexes of CDs with antipsychotic drug, Aree recently reported the β-CD inclusion complexation with nortriptyline HCl and amitriptyline HCl by single-crystal X-ray diffraction and DFT calculation (Aree, 2020). The study showed that nortriptyline and amitriptyline are less open in the β-CD cavity

than those in free HCl salt forms (Aree, 2020). The result is considered to support our results. In addition, Castiglione et al. reported that amitriptyline forms 1:1 inclusion complex with β-CD in water solution and in the solid state by the studies of NMR, the molecular dynamics simulations and single crystal X-ray diffraction (Castiglione, et. al., 2017). In the solution and the solid state, a benzene ring of amitriptyline is deeply inserted into the β-CD cavity with the seven membered ring, the side chain, and the other benzene ring protruding above the secondary rim of β-CD. They also reported that amitriptyline is present as single conformer in the crystal of amitriptyline β-CD inclusion complex and as two diastereomic conformations in the solution state with β-CD (Castiglione, et. al., 2017). Pietro et al. also reported that amitriptyline forms diastereomeric inclusion complex with β-CD at a ratio of 1:1 in deep eutectic system using a combination of NMR experiments (Pietro, et al., 2020). It is considered that complexation constrains the flexibility of the central cycle of amitriptyline in a single conformation in the solid state (Castiglione, et. al., 2017).

As the results of previous NMR studies in aqueous solution, benzene rings of quetiapine are inserted into the β-CD cavity and the benzene ring B is easily included in the β-CD cavity relative to the benzene ring A (Ogawa et al., 2013). In addition, the ethoxyethanol group of quetiapine is inside the β-CD cavity when the β-CD concentration is high (Ogawa et al., 2013). In aqueous solution, the benzene rings of quetiapine were deeply

included in the β-CD cavity, but in the inclusion complex crystal, quetiapine molecule was totally contained in the β-CD packing and the benzene rings of quetiapine closed to the secondary rim of β-CD. As mentioned above, there is a CH/π interaction between the benzene ring B of quetiapine and a secondary carbon of β-CD in the inclusion complex crystal, that might be associated with the results of NMR studies which indicate the benzene ring B is easily included in the β-CD cavity. It is considered that the benzene ring of quetiapine is included in the β-CD cavity in aqueous solution and that time the CH/π interaction has taken place, and the whole of quetiapine molecule is included in the β-CDs in the process of crystal formation.

From the crystallographic results in this study, quetiapine has two kinds of disorder (parts 1 and 2) in opposite directions within β-CD. The hypothesis is that such disorder is caused by the two stable conformations of quetiapine in β-CD. Therefore, we conducted theoretical calculations by comparing the cases of two or three β-CDs forming the packing as the initial structures, as described in section 3.2.

3.2. Computational analysis

For the conformational searches, the inclusion complex consisted of two β-CD molecules and one quetiapine molecule (Figures 7 and S3), or three β-CD molecules and one quetiapine molecule (Figures 8 and S4) was used for initial structures. The purpose

of these calculations is to compare the conformational and stability differences of quetiapine to evaluate the mechanism of formation of the β-CD-quetiapine complex in the case where β-CD includes the entire molecule of quetiapine (Figures 8 and S4) and the case where quetiapine's tricyclic structure is not included in β-CD (Figures 7 and S3). Two sets of initial structures with different total numbers of conformations of the doubly disordered drug parts 1 and 2 were calculated: 2 β-CD + 1 quetiapine set, 61, 382; and 3 β-CD + 1 quetiapine set, 229, 499. The extracted list of the steric energy and the distribution derived from the conformational search for quetiapine in the β-CD packing is indicated in Table 3. Table 3(A) and (B) represent the most stable five results of conformational search where β-CD packing is composed of two β-CD and three β-CD units as initial structures, respectively.

Figures 7 and S3 show the conformations from No. 1 (the most stable) to No. 4 of quetiapine disorder part 1 and part 2 in the case of two β-CDs and one quetiapine set as the initial structure, respectively. There are multiple conformations in which the quetiapine molecule is rotated more than 90° in β-CD (Figures 7 and S3). The piperazine and ethoxyethanol parts of quetiapine are entirely included in β-CD, whereas the tricyclic benzothiazepine part, which is the most bulky part of the molecule, is not. Therefore, it is considered that the quetiapine tricyclic structure can move freely and there are multiple conformations in β-CD.

Figures 8 and S4 show the conformations from No. 1 (the most stable) to No. 4 of quetiapine disorder part 1 and part 2 in the case of three β-CDs and one quetiapine set, respectively. As shown in Figures 8 and S4, there is almost no conformational difference other than in the ethoxyethanol group of quetiapine for which several stable conformations exist. Therefore, it is considered that the mobility of the quetiapine tricyclic structure is restricted by being covered by β-CD. Significantly, even if the entire quetiapine molecule is included in β-CD, the ethoxyethanol group can move relatively freely in β-CD. The temperature factors for quetiapine were relatively large compared to β-CD as the results of single crystal structure analysis discussed in 3.1. This is caused by the relatively high mobility of quetiapine compared to β-CD, since the guest molecule bound by weakly noncovalent interactions. The results of conformational calculations, which show that several stable conformations exist at the ethoxyethanol part, support the relatively large temperature factors of the ethoxyethanol part of quetiapine determined by X-ray crystallography.

There was little change in quetiapine conformation before and after the crystal optimization as shown in Figures S5 and S6. Actually, RMSDs calculated between original conformation and optimized one were small such as 0.163 and 0.388 Å in part 1 and part 2, respectively. Table 4 indicated that the energies (E_{intra}, E_{lattice}, and E_{crystal}) of the initial and the optimized structure for crystal optimization calculation with disorder

part 1 and part 2 as the initial structure. Making a comparison of the $E_{crystal}$ calculated by disorder parts 1 and 2, the $E_{crystal}$ was lower in part 1. These results indicated that the conformation of disorder which was high in occupancy was more stable. It would be useful to consider more detailed conformations of guest compounds in CD by proposing multiple stable conformations of guest molecules using the theoretical calculation, in case not only a part but also the entire guest compound has a disorder in the CD cavity.

4. Conclusions

In this study, the crystal structure of the inclusion complex of β-CD and quetiapine was determined. The crystal belongs to the monoclinic space group $P2_1$, and the complex comprises one quetiapine and two β-CD molecules. Quetiapine is twofold disordered (with respective occupancies of 0.62 and 0.38 for part 1 and part 2) in the screw-channel formed by stacking of β-CD dimers. As the result of a conformational search of quetiapine by theoretical calculations, the mobility of the quetiapine tricyclic structure was found to be restricted by being covered by β-CD. Even if the entire quetiapine molecule was included in β-CD, the ethoxyethanol group could move relatively freely in β-CD. In addition, the conformation which was high in occupancy by crystal structural analysis (part 1) was more stable from the viewpoint of crystal energy according to the results of the crystal energy calculations. These results are expected to be useful not only for

clarifying the inclusion mechanism of quetiapine by β-CD, but also predicting drug release from the novel formulations which includes β-CD inclusion complex.

5. Supplementary data

Complete crystallographic data for the structural analysis have been deposited with the Cambridge Crystallographic Data Centre (CCDC no. 1958048). Copies of this information may be obtained free of charge from the Director of the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44-1223-336033, e-mail: deposit@ccdc.cam.ac.uk or via: www.ccdc.cam.ac.uk).

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Table legends

Table 1. Crystal data and structure refinement for β-CD-quetiapine inclusion complex.

Table 2. Selected conformational parameters derived from crystal structures of quetiapine fumarate and quetiapine in β-CD.

Table 3. Results of the conformational search of quetiapine molecule in the β-CD packing. The distribution of the top five results of disorder parts 1 and 2, respectively. Calculated β-CD packing is composed of (A) two β-CD and (B) three β-CD molecules.

Table 4. The energies (E_{intra}, $E_{lattice}$, and $E_{crystal}$) of the initial and the optimized structure for crystal optimization calculation with disorder part 1 and part 2 as the initial structure.

Figure captions

Figure 1. Chemical structure of quetiapine.

Figure 2. Column structure of the β-CD-quetiapine complex. For better visibility, quetiapine is displayed in ball and stick model and all H atoms were omitted.

Figure 3. ORTEP drawings (50% probability level) of the β-CD-quetiapine inclusion complex viewed along the *b* axis (I) and *c* axis (II). For better visibility, all H atoms and quetiapine disorder structure (part 2) were omitted.

Figure 4. Dimeric structure of the β-CD-quetiapine inclusion complex formed by multiple hydrogen bonds (blue lines). For better visibility, quetiapine is displayed in ball and stick model, and all H atoms and quetiapine disorder structure were omitted.

Figure 5. Disordered structure of quetiapine (part 1 and part 2) inside the cavity of β-CDs viewed along the *b* axis (A) and *c* axis (B). Arrows indicate the disordered structure of OH in β-CD. For better visibility, quetiapine is displayed in ball and stick model, and all H atoms were omitted.

Figure 6. Selected conformational parameters derived from crystal structures of quetiapine. (I) and (II) indicate the structural parameters *d*1-*d*4 and (III) indicates the dihedral angles (χ) between the planar benzene rings (A and B).

Figure 7. Selected results of the conformational search using quetiapine disorder part 1 in two β-CDs as the initial structure.

Figure 8. Selected results of the conformational search using quetiapine disorder part 1 in three β-CDs as the initial structure.

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Table 1. Crystal data and structure refinement for β-CD-quetiapine inclusion complex.

Crystal name	Quetiapine-β-CD inclusion complex
Molecular Formula	$C_{105}H_{167}N_3O_{76}S$
M_r [g mol^{-1}]	2719.47
Crystal System	Monoclinic
Space Group	$P2_1$
Z	2
a [Å]	15.2184(1)
b [Å]	32.2627 (2)
c [Å]	15.4748(1)
α [º]	90.00
β [º]	102.632(1)
γ [º]	90.00
V [Å^3]	7414.01(9)
ρ_{calcd} [g cm^{-3}]	1.218
F (000)	2884.0
T [K]	100
μ [mm^{-1}]	1.029
Crystal size [mm^3]	0.140 × 0.100 × 0.030
Radiation	CuKα (λ = 1.54184)
2θ range for data collection/°	5.478 to 136.5
Reflections collected	134864
Independent reflections	26829 [R_{int} = 0.0415, R_{sigma} = 0.0298]
Data/restraints/parameters	26829/1250/1885
Goodness-of-fit on F^2	1.034
Final R indexes [I>=2σ (I)]	R_1 = 0.0735, wR_2 = 0.2027
Final R indexes [all data]	R_1 = 0.0750, wR_2 = 0.2048

Table 2. Selected conformational parameters derived from crystal structures of quetiapine fumarate and quetiapine in β-CD.

Conformational parameters		*d*1 (Å)	*d*2 (Å)	*d*3 (Å)	*d*4 (Å)	χ (°)
Quetiapine –fumarate *		6.005	7.727	4.763	6.989	108.63
Complex	Part 1	5.799	6.973	4.596	5.190	262.06
	Part 2	5.910	7.069	4.555	5.287	96.74

*: Ravikumar K. and Sridhar B., 2005. Quetiapine hemifumarate. Acta Crystallogr., Sect. E: Struct. Rep. Online, 61, o3245–o3248.

Table 3. Results of the conformational search of quetiapine molecule in the β-CD packing. The distribution of the top five results of disorder parts 1 and 2, respectively. Calculated β-CD packing is composed of (A) two β-CD and (B) three β-CD molecules.

(A)	**Disorder 1 for initial structure**		**Disorder 2 for initial structure**	
No.	Steric energy (kcal/mol)	Distribution (%)	Steric energy (kcal/mol)	Distribution (%)
1	-83.0632	96.7599	-82.8960	70.1870
2	-80.4787	1.2337	-81.5697	7.4825
3	-80.1949	0.7641	-81.4313	5.9246
4	-79.7724	0.3746	-81.3912	5.5362
5	-79.6173	0.2883	-80.6421	1.5637
(B)	**Disorder 1 for initial structure**		**Disorder 2 for initial structure**	
No.	Steric energy (kcal/mol)	Distribution (%)	Steric energy (kcal/mol)	Distribution (%)
1	-88.3945	75.6570	-84.9727	22.8923
2	-87.0464	7.7754	-84.8944	20.0586
3	-86.5464	3.3433	-84.5815	11.8290
4	-86.4965	3.0735	-84.4656	9.7262
5	-85.9314	1.1842	-84.3366	7.8233

Table 4. The energies (E_{intra}, $E_{lattice}$, and $E_{crystal}$) of the initial and the optimized structure for crystal optimization calculation with disorder part 1 and part 2 as the initial structure.

Initial structure	**The energies**	E_{intra} **(kcal/mol)**	$E_{lattice}$ **(kcal/mol)**	$E_{crystal}$ **(kcal/mol)**
Part 1	The energies of the initial structure	2954.4662	-75.1472	2879.3190
	The energies of the optimized structure	2956.0944	-93.7634	2862.3310
Part 2	The energies of the initial structure	2961.6275	-20.8953	2940.7322
	The energies of the optimized structure	2963.3241	-93.8868	2869.4373

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Highlights

β-CD and quetiapine form an inclusion complex at a ratio of 2:1.

The crystal of quetiapine-β-CD belongs to the monoclinic space group $P2_1$.

Quetiapine is disordered inside the dimeric cavity of the β-CD complex.

The conformation, which was high in occupancy, was more stable in crystal energy.