Quetiapine Free Base Complexed with Cyclodextrins to Improve Solubility for Parenteral Use

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Quetiapine, an antipsychotic drug used for schizophrenia treatment, is poorly water soluble, and therefore, administration of the more water-soluble quetiapine fumarate is preferred. Absorption of quetiapine through biological membranes may be improved by enhancing the solubility of the quetiapine base, the non-ionic form. In this study, the currently used salt form was converted into the free base (oily material). We employed cyclodextrins (CDs) as pharmaceutical additives to improve the solubility of the quetiapine base. The formation of quetiapine–β-cyclodextrin (β-CD) complexes was studied by phase solubility studies, continuous variation method, NMR spectroscopy, and powder X-ray diffraction. The formation of a poorly water-soluble complex was confirmed by the phase solubility study, and the interaction between quetiapine and β-CD in water was confirmed by NMR spectroscopy. In addition, the effects of β-CD derivatives (glucosyl-β-CD, maltosyl-β-CD, 2-hydroxypropyl-β-CD, dimethyl-β-CD, and trimethyl-β-CD) on the solubility of the quetiapine base were studied. The findings indicated that the aforementioned hydrophilic β-CD derivatives could be used as pharmaceutical additives of quetiapine for parenteral formulations as a result of the improved solubility of the quetiapine base because of inclusion complexation. Therefore, converting the currently used salt form into the free base, investigating the free base as a candidate for CD inclusion, and converting the oily material such as the free base into a powder by forming an inclusion complex that is easy to deal with is considered a worthwhile approach that may lead to novel formulations of the drug in question.

Key words quetiapine; cyclodextrin; parenteral administration; inclusion compound; solubility enhancement; antipsychotic drug

Schizophrenia is a chronic illness, and poor compliance is a major limitation in achieving the goal of continuous treatment.1) Sustained delivery of an atypical antipsychotic in a controlled manner can offer schizophrenic patients a greater opportunity to experience symptom remission while improving their quality of life.2)

Quetiapine is used in the treatment of schizophrenia and mania associated with bipolar disorders. This drug is reported to have affinity for serotonin, histamine, adrenergic receptors, and dopamine D2 receptors. Therefore, it improves positive and negative symptoms. Moreover, compared with conventional antipsychotic drugs, quetiapine is associated with fewer extrapyramidal side effects, agranulocytosis, and hyperprolactinemia.3–7)

Quetiapine is marketed in tablet and fine particle formulations; fumarate salt (Fig. I(I)) is the principal agent.8–11) Quetiapine fumarate exhibits better solubility in water than the free base. However, absorption of quetiapine through biological membranes could be improved by enhancing the solubility of the quetiapine base because this base is more hydrophobic than quetiapine fumarate. Therefore, in this study, we converted the currently used salt form into the free base (oily material). We utilized cyclodextrins (CDs) as pharmaceutical additives to improve the solubility of the quetiapine base.

CDs are cyclic, non-reducing oligosaccharides composed of 6, 7, or 8 α-glucose units (α-, β-, and γ-CD, respectively) linked through α-1,4 glycosidic bonds. CDs form inclusion complexes with various drug molecules both in solution and solid state. They have been used to improve drug properties such as solubility, stability, and bioavailability.12,13)

In the present study, we converted the currently used salt form into the free base and investigated the free base as a candidate for CD inclusion to modify the solubility of the drugs and improve their applicability and converted the oily material such as the free base into a powder by forming an inclusion complex that is easy to deal with and well suited for application leading to novel formulations of the drug in question. Therefore, the physicochemical characteristics of quetiapine–β-cyclodextrin (β-CD: Fig. I(II)) complexes were studied by phase solubility studies; continuous variation method; 1H-, 13C-, and two-dimensional NMR spectroscopy; and powder X-ray diffraction (PXRD). Furthermore, solubility of the quetiapine base in the presence of β-CD derivatives was studied to elucidate its applicability in parenteral administration.

Experimental

Materials Quetiapine fumarate (quetiapine hemifumarate) was purchased from Toronto Research Chemicals Inc. (Ontario, Canada). β-CD was purchased from Nihon Shokuhin Kako Co., Ltd. (Tokyo, Japan) in a hydrate form (β-CD10.5 H2O); the water content of β-CD was confirmed to be 10.5 H2O by thermogravimetry (data not shown). The solubility of β-CD in water is 1.85×10–2 g/mL at room temperature, as previously reported by Szejtli.14) Methanol, acetonitrile (HPLC grade), phosphoric acid, sodium hydroxide, deuterium oxide (D2O) and deuterated dimethyl sulfoxide (DMSO-d6; NMR measurement grade) were purchased from Wako Pure Chemical Industries, Ltd. (Osaka, Japan). Glucosyl-β-CD (GI-β-CD)
Phase Solubility Studies Phase solubility studies were conducted according to the method of Higuchi and Connors. The quetiapine base (oily material) was dissolved in methanol, and the quetiapine/methanol solution was added to a glass tube at the specific volume needed to include 10 mg quetiapine base. Methanol was evaporated from the glass tube. Five milliliters of β-CD solutions (1–10 mM) were added to an excess of the quetiapine base (10 mg), and the mixture was mechanically shaken (120 strokes/min) for 7 days at 25°C. The equilibrium-attained system was filtered (pore size, 0.45 µm) and used for UV spectrophotometric determinations and the estimation study of the stoichiometric ratio of quetiapine/β-CD complexes.

Continuous Variation Method Using UV data, quetiapine base–β-CD complexes were evaluated by the continuous variation method. The total molar concentrations of quetiapine and β-CD were kept constant at 0.5 mM, but their molar fractions (quetiapine)/(quetiapine) + (β-CD) were varied. The solutions were mechanically shaken (120 strokes/min) for 7 days at 25°C. The equilibrium-attained system was filtered (pore size, 0.45 µm) and used for UV spectrophotometric determination of stoichiometry. The absorbance difference ΔA = A₀ − A was determined by measuring the absorbance of quetiapine with (A) and without (A₀) cycloexextrin at 254 nm. The product ΔA × (quetiapine) was plotted against the molar fraction of the two components to determine the stoichiometry of the complex which was 1:1 when ΔA × (quetiapine) reached its maximum for (quetiapine)/(quetiapine) + (β-CD) = 0.50.18–20 The spectra were obtained using a V-560 UV/VIS spectrophotometer (JASCO Corporation, Tokyo, Japan).

Study of the Interaction between Quetiapine and β-CD in Aqueous Solution by NMR Quetiapine hemifumarate, β-CD, and the mixture samples of quetiapine hemifumarate and β-CD prepared at 1:1 and 1:2 m ratios were dissolved in D₂O and ¹H, ¹³C, and two-dimensional NMR (¹H-²H correlation spectroscopy (¹H–¹H COSY), ¹H–¹³C correlation spectroscopy (¹H–¹³C COSY)), heteronuclear multiple quantum coherence (HMQC), rotating frame Overhauser nuclear effect
spectroscopy (ROESY)) measurements were performed. The mixture samples were prepared by freeze-drying solutions of quetiapine hemifumarate and β-CD dissolved at 1:1 and 1:2 m ratios in purified water, giving a quetiapine concentration of 1 mg/mL. The concentration of β-CD and the mixture samples was 10 mg/mL and that of quetiapine fumarate was 2 mg/mL. Because the aqueous solubility of the quetiapine base is extremely low, the spectra had to be recorded using quetiapine hemifumarate. The NMR spectra were recorded at 30°C on a JNM Lambda 500 spectrometer. Tetramethylsilane was used as an external standard.

**PXRD Measurements** PXRD measurements were recorded on RINT-1400 (Rigaku Corporation, Tokyo, Japan). The experimental conditions were as follows: graphite-monochromated CuKα radiation (λ=1.54178 Å); 60 kV and 150 mA; scanning interval of 3–35° (2θ); scanning speed of 2°/min.

**Estimation of Stoichiometric Ratio of Quetiapine/β-CD Complex** Quetiapine base, β-CD, and precipitated powder were dissolved in DMSO-d₆ and ¹H, ¹³C-, and two-dimensional NMR (¹H–¹H COSY, ¹H–¹³C COSY, HMQC, and heteronuclear multiple bond connectivity (HMBC)) measurements were performed to determine the structure assignment. The concentration of β-CD and the precipitated complex was 10 mg/mL and that of the quetiapine base was 8 mg/mL. The NMR spectra were recorded at 25°C on a JNM Lambda 500 spectrometer. Tetramethylsilane was used as an external standard.

**Solubility Studies of the Quetiapine Base with β-CD Derivatives** The prepared quetiapine base was diluted in methanol, and the quetiapine/methanol solution was added to a glass tube at the specific volume needed to include a certain amount of the quetiapine base. Methanol in the glass tube was evaporated. Five milliliters of β-CD derivative solutions (G1-β-CD, G2-β-CD, HP-β-CD, DM-β-CD, and TM-β-CD) were added to an excess of the quetiapine base and the mixture was mechanically shaken (120 strokes/min) for 7 d at 25°C. The solubility of quetiapine hemifumarate in distilled water was also studied by the same method; water was added to an excess of quetiapine hemifumarate and the mixture was mechanically shaken for 7 d at 25°C. The equilibrium attained system was filtered (0.45 μm) and the quetiapine concentration was determined by HPLC, as described for the phase solubility studies. ¹⁰

**Results and Discussion**

**Phase Solubility Studies** The complexing behavior of quetiapine with β-CD in water was studied by the phase solubility method. The phase solubility curve of the quetiapine base–β-CD complex is shown in Fig. 2. The quetiapine/β-CD system displayed Bs-type solubility curves according to the classification system of Higuchi and Connors. ¹⁵ In the Bs-type curves, an initial ascending portion is followed by a plateau region and a decrease in the total quetiapine concentration with the precipitation of a microcrystalline complex. In this study, the phase solubility diagram could not be explained on the basis of a simple stoichiometric relationship. For example, a shoulder was observed at a β-CD concentration of approximately 6 mM in the descending curve of the diagram. Kurihara et al. reported a similar phenomenon using β-CD and nocloprost, a prostaglandin derivative. ²¹ They reported that according to an examination of the Corey–Pauling–Koltun (CPK) model, the molecular dimension of nocloprost appeared to be too large to be entirely included within one CD cavity. Therefore, it is reasonable to assume that at least one complex with a stoichiometry of more than 1:1 may be formed, particularly at higher CD concentrations. ²¹ In this study, quetiapine also appeared to be too large to be entirely included within one β-CD cavity. Thus, quetiapine is also assumed to form inclusion complexes with different stoichiometries, particularly at higher β-CD concentrations.

The apparent stability constant (K’) of the quetiapine–β-CD complex was calculated according to Eq. 1 using the data of the initial ascending portion of the solubility diagram in which the 1:1 complex may be formed predominantly. The K’ value of the quetiapine–β-CD complex was calculated using at least four values obtained in the β-CD concentration range of 0.0–3.0 mM. Using the slope and S₀ (0.92 mM) calculated using Eq. 1, the stability constant was calculated to be 3638 M⁻¹. The high apparent stability constant suggests strong affinity between the guest and host in aqueous phase and high stability of the complexes.

**Continuous Variation Method** In this study, UV spectroscopy was used for the preparation of Job’s plots to determine the stoichiometry of the inclusion complex. As a result, when the value of ΔA×(quetiapine) reached a maximum at the stoichiometric point, (quetiapine)=(β-CD)] was 0.5 (Fig. 3), thus suggesting that the quetiapine base–β-CD inclusion complex exhibited a 1:1 stoichiometry in a water-based solution under this condition (the total molar concen-
The result suggested that the quetiapine base/β-CD complex with a stoichiometry of 1:1 may be formed at lower β-CD concentrations in water.

Study of the Interaction between Quetiapine and β-CD in Aqueous Solution by NMR

Several techniques such as differential scanning calorimetry (DSC), infrared spectroscopy, and UV spectroscopy can establish whether guest molecules form an inclusion complex with CDs; however, they cannot provide information about the structural configuration of the complex. It has been reported that NMR is the best method to accurately confirm the formation of a CD–guest molecule inclusion complex in solution. The inclusion of a guest molecule in the hydrophobic cavity of a CD molecule generally modifies the environment of the protons of the guest moiety and the host cavity. Therefore, 1H-NMR can provide direct information regarding the complex structure via comparisons of the proton chemical shifts observed for the host–guest mixture with those observed for individual species.

Figures 4(II) and 4(III) show the 1H-NMR spectra of quetiapine hemifumarate, β-CD, and the mixture samples at molar ratios of 1:1 and 1:2 ratios. Figure 4(I) shows the chemical structure of quetiapine hemifumarate. The β-CD resonance assignments were based on a report by Schneider et al. and the quetiapine hemifumarate resonance assignments (Figs. 4(IIb), (IIIb)) were based on reports by Bharathi et al. and Stolarczyk et al. The NMR peaks of quetiapine in the presence of β-CD were assigned by 1H, 13C, and two-dimensional NMR measurements. In Fig. 4(II), a slight upfield shift was observed for β-CD H-4 in both mixture samples, whereas no shift was observed for β-CD H-2' compared with β-CD (Figs. 4(IIa, c, d)). In addition, upfield shifts were observed for β-CD H-3' and H-5' in both mixture samples, which indicated that quetiapine formed an inclusion complex with β-CD. These upfield shifts were observed for both H-3' and H-5' because they were located inside the β-CD cavity. As the molar ratio of quetiapine was increased (β-CD:quetiapine=1:0.25, 1:0.5, 1:1, and 1:2), upfield changes in the chemical shift were observed for the resonances of β-CD H-3' and H-5' inside the cavity (data not shown). Cruz et al. reported an interaction between doxepin, a tricyclic antidepressant, and β-CD using NMR. They also indicated that upfield changes in the chemical shift were observed for the resonances of β-CD H-3' and H-5' as the molar ratio of doxepin was increased.

Several changes in the resonances of quetiapine were also observed in the 1H-NMR spectra of both mixture samples (Figs. 4(II), (III)). The resonances of H-1, H-2, and H-3 (the ethoxyethanol group) of quetiapine in mixture samples shifted and this shift was affected by changes in the molar ratio of β-CD and quetiapine. H-3 of quetiapine is considered to be inside the β-CD cavity when the β-CD concentration is high because upfield shifts occur when the molar ratio is 1:2 (quetiapine:β-CD). It is well known that chemical shifts supply information about the magnetic and chemical environment of the nucleus. In Fig. 4(III), H-18 and H-19 of quetiapine shifted upfield, whereas H-12, H-13, H-14, H-17, and H-20 of quetiapine shifted downfield. These observations suggested that the protons of the aromatic ring composed of C16–C21 were significantly shifted compared with those of the aromatic ring composed of C10–C15, which indicated that the ring of C16–C21 is easily included in the β-CD cavity relative to the ring of C10–C15. The upfield shift (H-18 and H-19) was considered to be caused by forces inside the β-CD cavity and the downfield shift (H-12, H-13, H-14, H-17, and H-20) was con-
considered to be caused by changes in the magnetic and chemical environment of the nucleus. The peaks of aromatic rings were broadened in both mixture samples, which were considered to be caused by a larger distribution of chemical environments or a significant change in molecular dynamics.

The ROESY spectrum of quetiapine with β-CD (molar ratio=1:1) is shown in Fig. 5. ROE cross peaks were typically observed between β-CD H-3’ and H-5’ inside the cavity and nearby protons of the included guest. As shown in Fig. 5, the protons of the quetiapine aromatic rings had strong cross peaks with β-CD H-3’, H-5’, and H-6’, which are typical aromatic protons in the ring of C10–C15 and C16–C21. This suggests that the quetiapine aromatic rings are inserted into the β-CD cavity. Furthermore, cross peaks between the resonances of the quetiapine aromatic rings and β-CD H-4’ on the external surface of the β-CD molecule were observed. These cross peaks suggested that there may be a minor population of complexes in which quetiapine inserts one ring into the narrow end of the β-CD cavity, thus leaving the other ring to interact with the external β-CD H-4’. Similar ROESY cross peaks have been observed for inclusion complexes formed between doxepin and β-CD, salbutamol and β-CD, and between dexamethasone sodium phosphate and γ-CD. Meanwhile, cross peaks between β-CD and fumaric acid have not been observed. Therefore, it was suggested that fumaric acid was not included in the β-CD cavity.

**PXRD Measurements**

The PXRD patterns of β-CD and the precipitated powder are shown in Fig. 6. The precipitate powder (Fig. 6b) displayed some specific peaks that were markedly different from those observed for β-CD (Fig. 6a). Because the quetiapine base is an oily material, the PXRD pattern of quetiapine base could form a halo. The PXRD pat-

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**Fig. 5.** ROESY Spectrum of the Mixture Sample in D₂O at a 1:1 M Ratio, 30°C

**Fig. 6.** PXRD Patterns of β-CD (a) and the Precipitated Powder (b) (3–35°)

**Fig. 7.** ¹H-NMR Spectrum of the Quetiapine/β-CD Complex in DMSO-d₆ at 25°C (a) Protons in the hydroxyl group of β-CD; (b) protons in quetiapine.
terns for the parent crystalline CDs are reported to be useful references in cases in which no inclusion occurs on reacting hosts and guests by Caira.\textsuperscript{30} The PXRD pattern of the precipitated powder obtained in the present study (Fig. 6b) is different from that of β-CD, the parent crystalline CD (Fig. 6a). And the precipitated powder in this study displayed novel peaks as indicated by arrows, which suggested that a β-CD–quetiapine base complex could be formed (Fig. 6b).

Although it is difficult to determine the precise structure of the quetiapine–β-CD complex in the precipitated powder, β-CD packing in this powder is assumed to be β-CD inclusion complex.

Estimation of the Stoichiometric Ratio of Quetiapine/β-CD Complex To estimate the stoichiometry of the complex prepared in the phase solubility studies, we measured the $^1$H-NMR spectrum of the precipitated powder after dissolving the solid complex in DMSO-$d_6$.\textsuperscript{31} Under the present experimental conditions, information regarding only the stoichiometry of the complex but not the formation of the complex can be obtained because the β-CD molecules should dissociate from the complex. Figure 7 shows the $^1$H-NMR spectrum of the quetiapine–β-CD complex in DMSO-$d_6$ at 25°C. The proton signals belonging to the H atoms attached to C1 of β-CD (Fig. 7a) and signals belonging to the H atoms attached to C1 (a part of the ethoxylated group) of quetiapine (Fig. 7b) were observed at approximately 4.8 and 3.46 ppm, respectively. These peak integrations were used to calculate the stoichiometry of the complex. The peak integration of protons in the H atoms attached to C1 of β-CD was 13.99 (Fig. 7a) and that of protons attached to C1 of quetiapine was 2.0 (Fig. 7b). As the β-CD comprises seven glucopyranose units, seven H atoms attached to seven C1 atoms in a β-CD molecule. In case of quetiapine, two H atoms attached to C1 in a molecule. Therefore, the number of β-CD molecules encapsulating a quetiapine molecule in the precipitated powder was estimated to be 2.0. The result suggested that β-CD and quetiapine base could form an inclusion complex exhibiting a 2:1 stoichiometry (host:guest).

Solubility Studies of the Quetiapine Base with β-CD Derivatives According to the phase solubility study, a poorly water-soluble quetiapine base–β-CD complex (precipitated powder) was obtained because of the limited solubility of β-CD in water ($1.85 \times 10^{-3}$ g/mL at room temperature).\textsuperscript{10} To employ quetiapine base in drug delivery systems, particularly for parenteral administration, hydrophilic β-CD derivatives are considered useful because an aqueous interaction between quetiapine and β-CD was confirmed by NMR (Fig. 5). Hydrophilic CDs such as HP-β-CD, sulfobutyl ether-β-CD (SBE-β-CD), and branched β-CD have been used in drug delivery systems because their toxicity is very low and aqueous solubility is very high, permitting parenteral use.\textsuperscript{22} Methyalted β-CDs are also reported to be useful for solubility enhancement; however, these CDs are reported to exhibit surface and hemolytic activities in a concentration-dependent manner and their use is limited to oral, dermal, and mucosal applications.\textsuperscript{33,34}

G1-β-CD, G2-β-CD, HP-β-CD, DM-β-CD, and TM-β-CD were used for the solubility studies of the quetiapine base. Figure 8 shows the effect of β-CD derivatives on the solubility of the quetiapine base. Furthermore, the solubilities of quetiapine hemifumarate and the quetiapine base in water were evaluated. The water solubilities of quetiapine hemifumarate and the quetiapine base were 9.7 and 0.92 mM, respectively. In presence of the β-CD derivatives, the solubility of the quetiapine base increased depending on the β-CD derivative concentration. HP-β-CD, G1-β-CD, G2-β-CD, and DM-β-CD increased the solubility of the quetiapine base by approximately 7-fold at a CD concentration of 10 mM, and TM-β-CD increased the solubility of the quetiapine base by approximately 12-fold. The solubility of the quetiapine base in the presence of 10 mM TM-β-CD was higher than that of quetiapine hemifumarate (9.7 mM). The efficacy of TM-β-CD over the other β-CD derivatives is considered to be a result of its higher surface active property. In this study, we used DM-β-CD and TM-β-CD as methylated β-CDs. Methylated β-CDs are known to interact with stratum corneum components of rat skin and improve drug absorption and are reported to be useful as penetration enhancers for transdermal delivery systems.\textsuperscript{35,36} However, parenteral (intravenous) use of DM-β-CD and TM-β-CD is not possible because of their high cytotoxicity. Uekama has improved the bioadaptability and physicochemical properties of DM-β-CD through a chemical modification.\textsuperscript{31} Therefore, using improved derivatives such as heptakis(2,6-di-O-methyl-3-O-acetyl)-β-CDs, which are highly water soluble and maintain certain inclusion ability comparable to that of TM-β-CD with superior bioadaptability, the quetiapine base could be useful for parenteral administration.\textsuperscript{29} Branched β-CDs are highly water soluble and exhibit low toxicity. In this study, we used G1-β-CD and G2-β-CD as model branched CDs. The solubilities of the quetiapine base in the presence of 25 mM G1-β-CD and G2-β-CD were 14.7 and 14.1 mM, respectively, which indicated that further enhancement of the solubility of the quetiapine base is expected with higher β-CD derivative concentrations. Therefore, the hydrophilic β-CD derivatives could be used as pharmaceutical additives for parenteral formulations because of the improved solubility of the quetiapine base as a result of inclusion complexation.

Conclusion At lower β-CD concentrations, the quetiapine base and β-CD formed inclusion complexes with a 1:1 stoichiometry according to the Job’s plot. According to the data of phase
solubility study, inclusion complexes (quetiapine base–β-CD) of different stoichiometries were assumed to be formed at higher β-CD concentrations. The result of PXRD studies of the precipitated powder formed at higher β-CD concentration suggested that β-CD and the quetiapine base could form an inclusion complex. And the result of the estimation of stoichiometric ratio of the β-CD/quetiapine complex suggested that β-CD and the quetiapine base could form an inclusion complex exhibiting a 2:1 stoichiometry (host:guest).

Furthermore, according to NMR measurements, the aromatic ring of quetiapine is inserted into the β-CD cavity, facilitating the formation of an inclusion complex in aqueous solution. In the presence of β-CD derivatives, the solubility of the free base, investigating the free base as a candidate for base because of inclusion complexation. Therefore, hydrophilic β-CD derivatives could be used as pharmaceutical additives for parenteral formulations as a result of the improved solubility of the quetiapine base because of inclusion complexation.

In conclusion, converting the currently used salt form into the drug in question, a worthwhile approach that may lead to novel formulations of β-CD derivatives, the solubility of the β-CD/quetiapine complex suggested a Chiometric ratio of the β-CD and the quetiapine base could form an inclusion complex in aqueous solution. And the result of the estimation of stoichiometric ratio of the β-CD/quetiapine complex suggested that β-CD and the quetiapine base increased depending on the concentration. Therefore, hydrophilic β-CD derivatives could be used as pharmaceutical additives for parenteral formulations as a result of the improved solubility of the quetiapine base because of inclusion complexation.

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