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Characterization, stability, and pharmacokinetics of sibutramine/β-cyclodextrin inclusion complex

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ABSTRACT

β-Cyclodextrin (β-CD) is widely used to increase the stability, solubility, and bioavailability of poorly soluble drugs because of the appropriate size of its cavity. Sibutramine is a neurotransmitter reuptake inhibitor that has been investigated as an oral anorexiant. Here we report the complexation of sibutramine base with β-CD and the stability, dissolution, and pharmacokinetic properties of the sibutramine/CD complex. The formation of sibutramine/β-CD inclusion complexes is confirmed using differential scanning calorimetry, X-ray diffractometry, and ^{1}H nuclear magnetic resonance. The thermal and photochemical stability of sibutramine is significantly improved by the complexation with β-CD, and the pharmacokinetic parameters (e.g., the plasma concentration, area under the curve, and maximum concentration of two active metabolites) for humans are comparable with those of the commercialized standard product (Reductil®). Our study suggests that sibutramine/β-CD complexation can be of great use to increase the stability and biological efficacy of sibutramine base.

1. Introduction

Cyclodextrins (CDs) are cyclic oligosaccharides composed of 6, 7, 8, or 9 glucopyranose units (α-, β- γ- or δ-CDs, respectively) with a relatively hydrophobic central cavity and a hydrophilic surface [1]. Because CDs can form complexes with a great variety of organic molecules, they have been widely used to increase the stability, solubility, and bioavailability of poorly soluble drugs [2]. Accordingly, more than 35 different drugs are currently marketed as solid or solution-based CD complex formulations, including alprostadil, meloxicam, nicotine, omeprazole, itraconazole, aripiprazole, and insulin [3,4]. CDs having less than six units cannot be formed due to steric hindrance while the higher homologs with more than nine glucose units are very difficult to purify. The cavity size of α-CD is insufficient for many drugs, γ-CD is expensive, and δ-CD has weaker complex forming ability than conventional CDs [5]. Among them, β-CD is widely used for pharmaceutical applications because of the appropriate size of its cavity [1]. As for the regulatory status, β-CD is listed in a number of pharmacopoeia sources including the US Pharmacopoeia/National Formulary (USP/NF), European Pharmacopoeia (Ph.Eur.) and Japanese Pharmaceutical Codex (JPC) [6].

The International Obesity Task Force reported that more than 300 million individuals worldwide are obese, and an additional 800 million are overweighted [7]. Obese patients have higher risks for coronary artery disease, hypertension, hyperlipidemia, diabetes mellitus, certain cancers, cerebrovascular accident, osteoarthritis, obstructive pulmonary disease, and sleep apnea [8]. Sibutramine, introduced as an anti-obesity drug in 1997, is a potent inhibitor of the reuptake of noradrenaline and serotonin [9,10] and may stimulate thermogenesis through the activation of β_3-adrenoceptors in brown adipose tissue [11,12]. Sibutramine hydrochloride monohydrate, a salt form, has been used in a commercial product (Reductil®) because of its improved solubility and stability [12]. The sibutramine salt has a solubility of about 3 mg mL^{-1} in water at pH 5.2 while the solubility of sibutramine base is only 0.01 mg mL^{-1} [13]. In addition to the investigation on other salt forms of sibutramine [14–16], the solid dispersion technique has been suggested with aiming to increase the solubility of sibutramine base in aqueous formulations [17,18].

This report describes the first investigation on the inclusion complex of sibutramine with β-CD and the stability and pharmacokinetic properties of the complex. The stability studies under the stress conditions were performed in comparison with sibutramine hydrochloride monohydrate as a stable salt form. The

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dissolution and pharmacokinetics in humans of sibutramine/β-CD formulation were evaluated compared to a commercialized standard – Reductil®, which is based on a formulation using sibutramine hydrochloride monohydrate.

2. Experimental

2.1. Materials

Sibutramine base and sibutramine hydrochloride monohydrate were supplied from Cipla (India) and DaeHe Chemical (Republic of Korea), respectively. β-CD (Cavamax® W7 Pharma, Ph.Eur. grade) was purchased from ISP (Cologne, Germany). Lactose monohydrate, citric acid anhydrous, sodium starch glycolate, sodium stearyl fumarate and gelatin capsule were of Ph.Eur. grade and obtained from DMV International, Merck, DMV International, JRS Pharma and Suheung capsule, respectively. Reductil® was purchased from Abbott Korea Co. (Republic of Korea). All other reagents were of analytical grade and used without further purification.

2.2. Preparation of inclusion complexes

The inclusion complexes of sibutramine/β-CD were prepared as follows. Briefly, 28.0 g sibutramine base was clearly dissolved at a concentration of 100 mM in aqueous hydrochloride solution (6 L, 200 mM), and an excessive amount of β-CD (256 g) was added to the solution. The sibutramine/β-CD solution was magnetically stirred at 35 °C for 3 h and cooled down to room temperature. Sodium hydroxide was then added in a molar ratio of 1:2 versus hydrochloride, and the solution was shaken for 3 h to precipitate the sibutramine/β-CD inclusion complex. After filtering and vacuum drying, the content of sibutramine base in the resulting white powder was assayed to calculate the actual stoichiometry ratio of the complex.

2.3. Characterization of sibutramine/β-CD complex

The formed complex was examined using differential scanning calorimetry (DSC), X-ray powder diffraction (XRD), and ^{1}H nuclear magnetic resonance (NMR). DSC analysis was carried out using a Perkin Elmer DSC-7 System (Perkin Elmer, MA, USA) equipped with a computerized data station (Pyris series). The thermal behavior was studied by heating the samples (1–2 mg) in a sealed aluminum pan from 20 to 200 °C at a rate of 10 °C min^{-1} and under nitrogen purge, using an empty pan sealed as reference. X-ray powder diffraction patterns were obtained at room temperature with MAC Science, model M18XHF22 diffractometer system equipped with copper (Cu) as anode material and a graphite monochromator using a voltage of 45 kV and a current of 300 mA. The diffractograms were recorded in the 2θ angle range between 5° and 60° and the process parameters were set at: scan step size of 0.02°; scan step time of 5 s. ^{1}H NMR spectra were obtained from Varian Gemini NMR (300 MHz) at room temperature. The samples were dissolved in dimethylsulfoxide (DMSO)-d6.

2.4. Stability studies

The effect of inclusion complexation on the stability of sibutramine base was examined under the following stress conditions. The thermal stability of sibutramine powder samples was examined using a thermostatically controlled stability chamber (PSC022, SANYO Gallenkamp, UK) maintained at 60 °C/75% relative humidity (RH) for 7 days. Thermal stability of sibutramine samples in aqueous solution was also examined using the same chamber. The solutions equivalent to 1 mg mL^{-1} sibutramine in 0.038 M sodium acetate buffer (pH 5.2) were prepared in a sealed glass vial and stored at 60 °C for 2 weeks [19]. The photochemical stability was investigated by spreading the powder samples in a transparent Petri dish with a thickness of less than 3 mm. The samples were then exposed to UV or visible light at 25 °C in accordance to ICH guideline [20]. The light source with an overall illumination of about 1.2 million lux h and an integrated near ultraviolet energy of about 200 Wh m^{-2} was used in a photostability chamber (PSC062, SANYO Gallenkamp, UK).

2.5. High performance liquid chromatography (HPLC)

At predetermined time intervals, samples were taken and dissolved with methanol, filtered through 0.45 μm membrane filters and analyzed by HPLC. The HPLC system (Waters, Milford, MA, USA) composed of 2695 separation module, 2695 auto sampler, 2996 PDA detector, and Empower 2 chromatography manager for processing data. A C18 column (Hypersil BDS, 250 mm × 4.5 mm i.d., 5 μm particle size, Thermo Hypersil-Keystone, Germany) was used at 35 °C with a flow rate of 1.0 mL min^{-1}. The mobile phase was a 35:65 (v/v) mixture of phosphate buffer (pH 6.0) and acetonitrile, and the elution of sibutramine was detected at 225 nm.

2.6. Formulation of sibutramine/β-CD inclusion complex

The composition of the capsule dosage form containing sibutramine/β-CD inclusion complex was determined based on compatibility screening between sibutramine/β-CD and candidate excipients. Citric acid was used to adjust the pH because sibutramine base is very soluble in acidic solution. In addition, citric acid is known to increase the aqueous solubility of sibutramine base in solid dispersion systems [17,18]. The composition of the sibutramine/β-CD complex formulation includes sibutramine/β-CD inclusion complex, lactose monohydrate, citric acid, sodium starch glycolate and sodium stearyl fumarate in size 2 hard gelatin capsules. The capsule dosage form was manufactured through dry granulation process using a roller compactor under KGMP condition. The amount of sibutramine base per capsule was 12.55 mg.

2.7. In vitro dissolution testing

In vitro dissolution tests were performed using Ph.Eur 7.0, dissolution apparatus II with 900 mL buffer (pH 1.2, 4.0, and 6.8) as a dissolution medium at 37.0 ± 0.5 °C. The speed of the paddle was fixed to 50 rpm. The sibutramine/β-CD complex formulation and Reductil® containing the equivalent dose of 12.55 mg sibutramine base were inserted into a sinker and placed in a dissolution tester (VK 7025, Vankel, USA). At predetermined time intervals, 5 mL of the medium was centrifuged at 13,000 rpm, and the drug concentration in the supernatant was then analyzed using the same HPLC system as described above. A C18 column (Capcellpak UG120, 150 mm × 4.5 mm i.d., 5 μm particle size, Shiseido, Japan) was used at 35 °C at a flow rate of 1.5 mL min^{-1}. The mobile phase was a 64:35:10 (v/v/v) mixture of phosphate buffer (pH 3.0), acetonitrile, and tetrahydrofuran.

2.8. Pharmacokinetics

A single-center, randomized, open-label, 2-period, comparative crossover study was conducted with 2 week washout period in accordance with ethical principles and standards described in the Declaration of Helsinki and the International Conference on Harmonization (ICH)/Good Clinical Practice (GCP) and with the approval of the institutional review board of Asan Medical Center,

Seoul, Republic of Korea. All subjects received a single 12.55 mg oral dose of sibutramine base (sibutramine/β-CD formulation) and 15 mg oral dose of sibutramine hydrochloride monohydrate (the commercial product) equivalent to sibutramine base 12.55 mg. All subjects were admitted to the study center on the evening before the day of drug administration. The next morning, they received a single oral dose of the sibutramine/β-CD complex formulation or Reductil® according to the randomized schedule. An indwelling angiocatheter with a normal saline lock was inserted into a brachial vein. Blood samples were collected immediately before drug administration (baseline) and at 0.5, 1, 2, 3, 4, 5, 6, 8, 10, 12, 24, 48 and 72 h after drug administration. After 1 mL blood from the angiocatheter was discarded, 6 mL blood was collected in a heparinized tube. The plasma was separated by centrifugation at 1800 × *g* at a temperature of 4 °C within 10 min of collection and was stored at −70 °C until analysis [21,22].

2.9. Blood sample analysis

Plasma concentrations of two active metabolites (denoted M1 and M2) were analyzed using a modified high-performance liquid chromatographic mass spectrometric (LC–MS-MS) method [22–24] validated according to ICH guideline [25] and in accordance with Good Laboratory Practice (GLP) environment. For the analysis, 4 mL *tert*-butylmethylether and 30 μL desipramine methanol solution (50 ng mL^{-1}) as the internal standard were sequentially added to 0.5 mL plasma. After vigorous vortexing for 20 min in a mixer (C-SGM, JISCO, Republic of Korea), the mixture was centrifuged, and the organic phase was transferred to a clean glass tube and dried under a flow of nitrogen gas (MG-2100, Eyela, Japan). The dried residue was reconstituted with 300 μL of 50% acetonitrile, and 10 μL aliquot of this solution was injected into the Thermo Finningan LC–MS-MS system (Thermo Electron, Japan). The compounds were separated on a Capcell pak C18 column (150 mm × 2.0 mm, 5 μm, Shiseido, Japan) with a 45:55 (v/v) mixture of acetonitrile and water (adjusted to pH 4.0 with trifluoroacetic acid) as a mobile phase. The column was heated to 30 °C, and the mobile phase was eluted at 0.2 mL min^{-1}. The mass spectrometer with an electrospray source was run in the positive ion mode, and *m*/*z* 266, 252, and 267 were monitored M1, M2, and internal standard, respectively.

2.10. Pharmacokinetic data analysis and statistical analysis

The concentrations of M1 and M2 in plasma and their pharmacokinetic characteristics were compared in two sibutramine formulations because the metabolites of sibutramine were pharmacologically active compared with the parent drug, sibutramine [26]. The area under the drug concentration–time curve from zero to the last measurement (AUC_{last}) or infinity (AUC_{inf}) and the half-life ($t_{1/2}$) were calculated using a noncompartmental analysis (WinNonlin Pharsight Corporation, US). Values for C_{max} and T_{max} were estimated directly from the observed plasma concentration–time data [27]. Levels of statistical significance ($p < 0.05$) were assessed using the Student-*t*-test between the two means for unpaired data. All data are expressed as the mean ± standard deviation (S.D.) or as the median (ranges) for T_{max}.

3. Results and discussion

3.1. Characterization of sibutramine/CD complex

The ^{1}H NMR spectrum of the sibutramine/β-CD complex is shown in Fig. 1. The characteristic peaks of the aromatic ring of sibutramine base were found at 7–8 ppm, and β-CD has the characteristic proton peaks at 4–6 ppm. The theoretical peak ratio

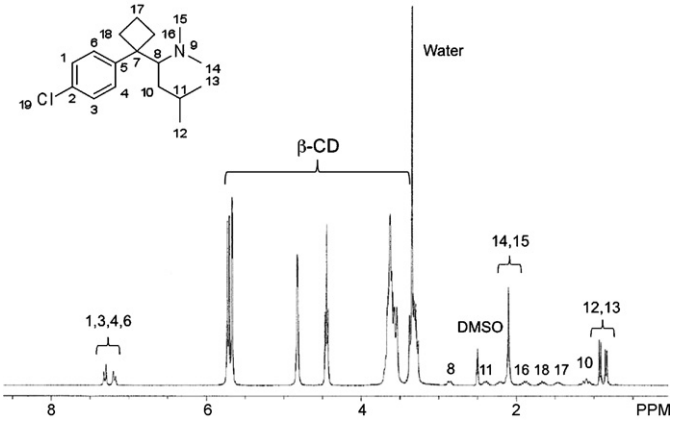

Fig. 1. ^{1}H NMR spectrum of sibutramine/β-CD inclusion complex in DMSO-d6.

was 1:7 for a 1:1 complex. From the ^{1}H NMR spectra for the optimized sibutramine/β-CD inclusion complex, the molar ratio of sibutramine base and β-CD in inclusion complex was expected to be 1:2. The DSC thermograms of sibutramine base, β-CD, a 1:2 mixture of sibutramine base and β-CD, and the sibutramine/β-CD inclusion complex were shown in Fig. 2. Crystalline powder of sibutramine base appeared a sharp endothermic melting peak around 53 °C. The broad endothermic peak of β-CD was observed around 120 °C. This peak was likely to be associated with the loss of bound water. Their physical mixture clearly exhibited two endothermic peaks corresponding to sibutramine base and β-CD, though the bound water peak slightly decreased. This result indicates that there was no strong interaction between sibutramine base and β-CD in the mixture. Interestingly, the sibutramine/β-CD complex has no apparent endothermic peaks, indicating the effective inhibition of crystalline phases of individual molecules through the formation of inclusion complex between sibutramine and β-CD. The XRD patterns of sibutramine base, β-CD, a 1:2 mixture of sibutramine base and β-CD, and the sibutramine/β-CD inclusion complex are shown in Fig. 3. The presence of intense and sharp peaks in the XRD of sibutramine base (2θ = 14.2, 20.4, and 24.3°), and β-CD (2θ = 9.1, 12.8, 23.1, 27.1, and 34.9°) indicates that these compounds existed in a crystalline form. Their physical mixture exhibited the superposition of the individual components. The sibutramine/β-CD complex showed distinctive peak patterns

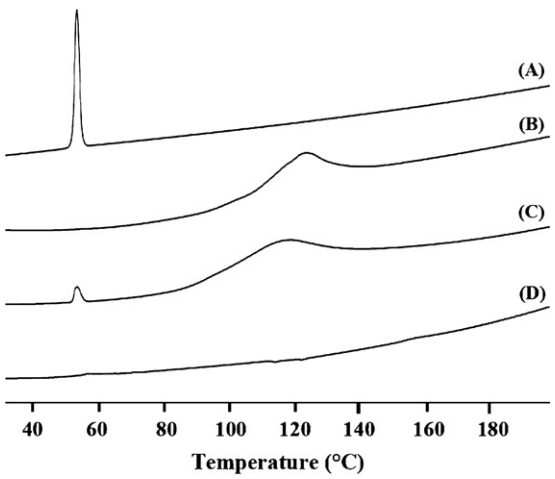

Fig. 2. DSC thermograms of sibutramine base (A), β-CD (B), the physical mixture (C), and the inclusion complex of sibutramine and β-CD (D).

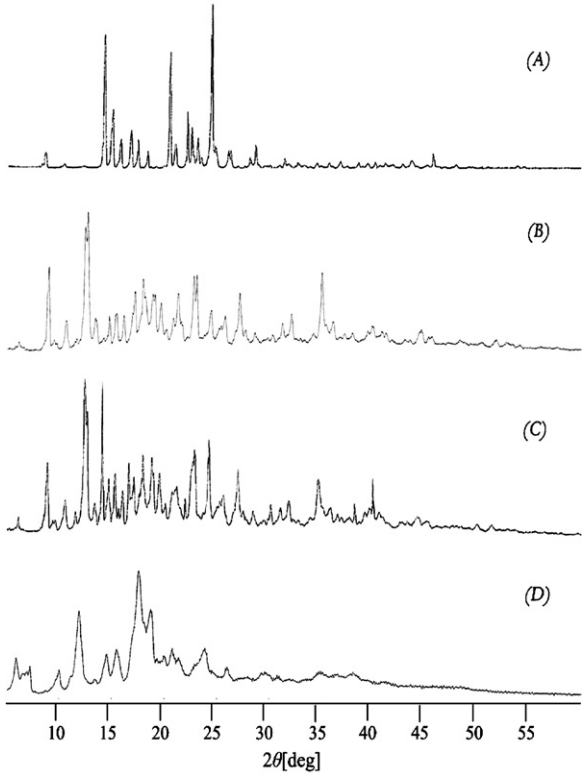

Fig. 3. X-ray powder diffraction spectra of sibutramine base (A), β-CD (B), the physical mixture (C), and the inclusion complex of sibutramine and β-CD (D).

with relatively broad bands, indicating the structural changes of sibutramine and β-CD as they form an inclusion complex.

3.2. Thermal and photochemical stability

The inclusion complexation with β-CD can affect the physical and chemical properties of guest molecules (e.g., aqueous solubility and stability). Although it can negatively affect the chemical stability of guest molecules, the formation of an inclusion complex usually leads to the retardation of degradation processes [28–31]. As shown in Fig. 4, the effect of the elevated temperature on the degradation of sibutramine powder was examined at 60 °C for 7 days. All of the samples showed excellent stability in the form of powder. Particularly, there was no obvious change of the sibutramine/β-CD complex, whereas the degradation products of sibutramine base increased by about 0.13% in a week. The thermal

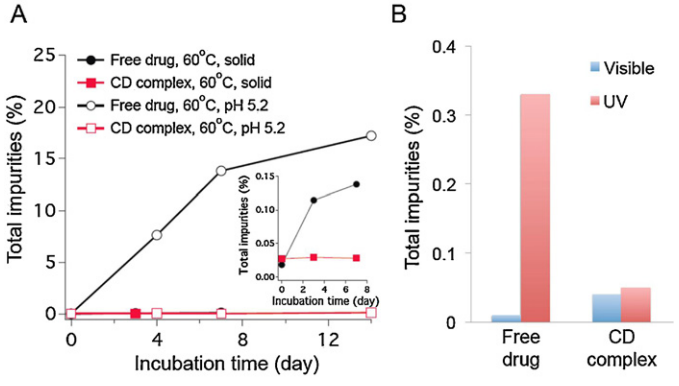

Fig. 4. Thermal and photochemical stability of sibutramine powder at 60 °C and 75% RH and sibutramine solution in acetate buffer (pH 5.2) at 60 °C (A), and UV or visible light at 25 °C (B).

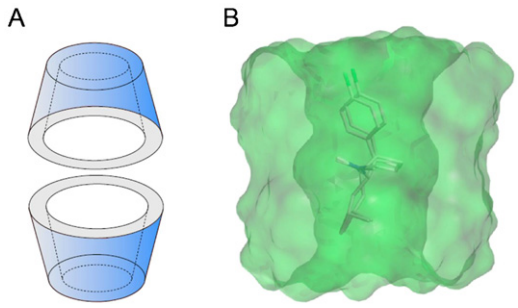

Fig. 5. Schematic representations of a β-CD dimer (A) and the 2:1 inclusion complex between β-CD and sibutramine (B).

stability of sibutramine was also investigated in aqueous solution (acetate buffer at pH 5.2). Although sibutramine base had a dramatic degradation of more than 15%, the sibutramine/β-CD inclusion complex showed no significant change for 2 weeks at 60 °C. Extended stability test showed that there was no further change in the sibutramine/β-CD inclusion complex for 2 months. Sibutramine/β-CD inclusion complex was very stable against UV illumination though sibutramine itself quickly degrades when exposed to UV light. From the HLPC chromatograms from the stability studies, the main degradation product was identified to be desmethyl sibutramine (M1). It is likely that the dimethylamino group of sibutramine was positioned in the cavity of β-CD and thus protected from chemical and photochemical stresses. The stability of sibutramine against elevated temperature, hydrolysis, and light was effectively increased through its complexation with β-CD.

Molecular modeling was performed using the X-ray structure of β-CD as an initial conformation [32]. As mentioned above, β-CD and sibutramine form complexes at a molar ratio of 2:1, making three possible types of β-CD dimers. Molecular mechanical analysis on both of the (R) isomer and (S) isomers of sibutramine were carried out to obtain the energetically favorable conformation. The Surflex-Dock in SYBYL8.1.1 was used to perform docking studies to obtain the complex structure between β-CD dimer and sibutramine. The complex formation of one sibutramine molecule with face-to-face β-CD dimers showed the optimal docking mode (Fig. 5A). In addition, the docking modes of the (R) and (S) forms of sibutramine were similar to each other. The molecular structure of the 2:1 inclusion complex between β-CD and sibutramine is shown in Fig. 5B.

3.3. In vitro dissolution study

The in vitro release profiles of the sibutramine/β-CD complex formulation and Reductil® were compared (Fig. 6) using the difference factor (f_1) and similarity factor (f_2), as defined by the following equation [33,34]: $f_1 = [\sum(R_t - T_t)/\sum R_t] \times 100$ and $f_2 = 50 \times \log\{[1 + \sum(R_t - T_t)^2]^{-0.5} \times 100\}$, where n is the number of time points, and T_t and R_t are percentage releases at time point (t) for the sibutramine/β-CD complex and Reductil®, respectively. In general, to ensure a similar correlation between the profiles, f_1 should be in the range of 0–15, and f_2 in the range of 50–100. As shown in Table 1, f_1 values between the sibutramine/β-CD complex and Reductil® were 5.02, 5.50, 19.83 and 18.32, at pH

Table 1
Difference and similarity factors between the sibutramine/β-CD complex formulation and Reductil®.

Dissolution medium	pH 1.2	pH 4.0	pH 6.8	Water
Difference factor (f_1)	5.02	5.50	19.83	18.32
Similarity factor (f_2)	59.63	66.57	45.35	40.51

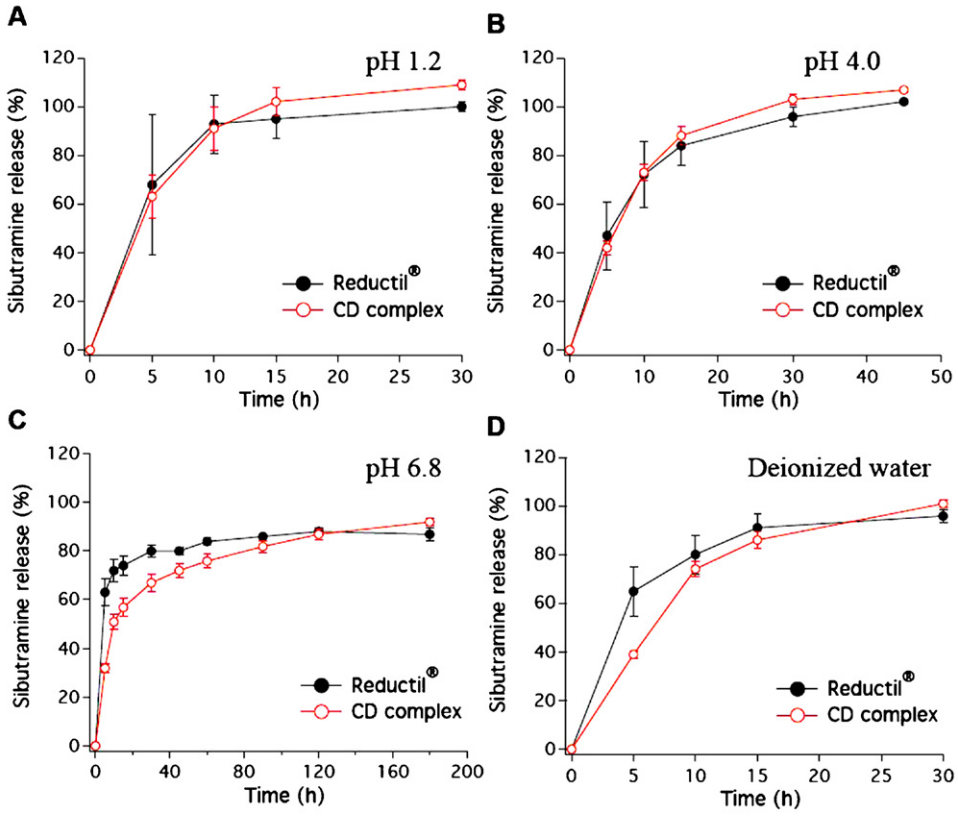

Fig. 6. Dissolution profiles of sibutramine from the sibutramine/β-CD complex formulation and Reductil® at pH 1.2 (A); pH 4.0 (B); pH 6.8 (C); deionized water (D). Each value represents the mean ± S.D. (n = 6).

1.2, 4.0, 6.8 and water, respectively. Furthermore, they had f_2 values of 59.63, 66.57, 45.35 and 40.51 at pH 1.2, 4.0, 6.8 and water, respectively. Thus, the sibutramine/β-CD complex and Reductil® showed a similar correlation of dissolution profiles at pH 1.2 and 4.0 but a different correlation at pH 6.8 and deionized water, caused by the difference of dissolution rate during the first 10 min. The different correlation at pH 6.8 and deionized water seems to result from the decreased micro-environmental pH, which is caused by free hydrochloride released from Reductil®, around sibutramine in dissolution medium.

3.4. Pharmacokinetics

Fig. 7 shows the mean plasma concentration–time profiles for M1, M2, and M1 + M2 following the oral administration of the sibutramine/β-CD complex and Reductil® at an equivalent dose of 12.55 mg sibutramine base in humans. The pharmacokinetic parameters for M1, M2 and M1 + M2 are summarized in Table 2. The in vivo effects of sibutramine are predominantly the results of the action of these two metabolites [12,22,26,35]. In human subjects, sibutramine is rapidly metabolized to an *N*-monodesmethyl compound (desmethylsibutramine, M1) and an *N*,*N*-didesmethyl compound (didesmethylsibutramine, M2). The AUC and C_{max} values of M1 and M2 for the sibutramine/β-CD complex were not significantly different from those for Reductil®. The mean log-transformed ratios of the parameters and their confidence intervals were all within the predefined bioequivalence range of 80–125% [36]. The pharmacokinetic parameters calculated for the active moiety by the summation of M1 and M2 concentrations were also found to be biologically equivalent in considering that the effects of sibutramine are predominantly the result of the actions of M1 and M2 [11,37]. Sibutramine hydrochloride monohydrate and sibutramine base may have different pharmacokinetic characteristics as a result of potentially different

Table 2
Pharmacokinetic properties of desmethylsibutramine (M1), didesmethylsibutramine (M2) and the summation of desmethylsibutramine and didesmethylsibutramine (M1 + M2) after oral administration of the sibutramine/β-CD complex and Reductil® in 22 healthy male humans. Each value represents the mean ± S.D.

Parameters	AUC_{last} (ng h mL^{-1})	AUC_{inf} (ng h mL^{-1})	C_{max} (ng mL^{-1})	T_{max} (h)	$t_{1/2}$ (h)
M1					
Complex	40.6 ± 17.8	43.62 ± 19.42	2.81 ± 1.02	3.5 ± 1.1	17.4 ± 3.85
Reductil®	38.12 ± 17.44	40.9 ± 18.87	2.69 ± 1.06	3.28 ± 1.06	17.39 ± 3.37
Ratio (90% CI)	1.07 (96.2–118.4)	1.07 (96.0–118.7)	1.06 (97.2–115.5)		
M2					
Complex	127.5 ± 31.55	137.11 ± 35.46	7.36 ± 2	3.63 ± 1	18.98 ± 3.42
Reductil®	113.73 ± 22.58	122.68 ± 24.89	6.58 ± 1.6	3.37 ± 1.21	19.07 ± 3.75
Ratio (90% CI)	1.11 (107.6–114.6)	1.11 (106.8–114.5)	1.11 (105.0–117.2)		
M1 + M2					
Complex	168.24 ± 38.76	180.52 ± 45.29	10.12 ± 2.2	3.5 ± 0.91	18.52 ± 3.32
Reductil®	151.97 ± 29.61	163.33 ± 34.41	9.1 ± 1.83	3.42 ± 1.21	18.49 ± 3.3
Ratio (90% CI)	1.10 (105.5–114.6)	1.10 (104.8–114.7)	1.11 (105.3–116.4)		

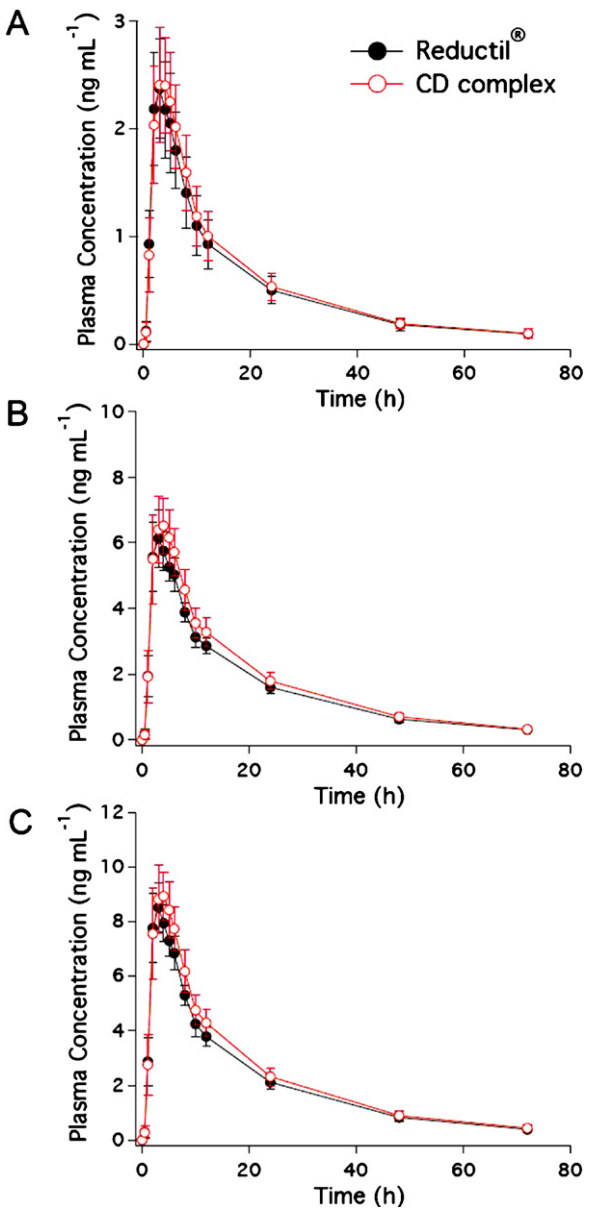

Fig. 7. Plasma concentration–time profiles of the active metabolites of sibutramine after oral administration of the sibutramine/β-CD complex and Reductil® in 22 healthy male humans: (A) desmethylsibutramine (M1); (B) didesmethylsibutramine (M2); (C) the summation of desmethylsibutramine and didesmethylsibutramine (M1 + M2). Each value represents the mean ± S.D.

solubility and dissolution characteristics [38]. However, the AUC, C_{max} and T_{max} for M1, M2, and the active moiety of the two sibutramine formulations were biologically equivalent, suggesting that the two formulations have the similar exposure and absorption patterns.

4. Conclusion

This study introduced the complexation of sibutramine base with β-CD and characterized the structure, stability, dissolution, and pharmacokinetic properties. The stability studies indicated β-CD can greatly improve the chemical stability of sibutramine base in the form of inclusion complex, equal to sibutramine hydrochloride monohydrate, a commercially stable salt form. Furthermore, the formulation of sibutramine base/β-CD inclusion complex showed in vitro dissolution profiles and biological equivalence in humans compared with Reductil®, a commercial product based on sibutramine hydrochloride monohydrate. Thus, the inclusion complexation with β-CD is a promising method to develop a sibutramine base-loaded product with improved stability and bioequivalence.

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