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Development of novel sibutramine base-loaded solid dispersion with gelatin and HPMC: Physicochemical characterization and pharmacokinetics in beagle dogs

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ABSTRACT

To develop a novel sibutramine base-loaded solid dispersion with enhanced solubility and bioavailability, various solid dispersions were prepared using a spray drying technique with hydrophilic polymers such as gelatin, HPMC and citric acid. Their solubility, thermal characteristics and crystallinity were investigated. The dissolution and pharmacokinetics of the sibutramine base-loaded solid dispersion were then compared with a sibutramine hydrochloride monohydrate-loaded commercial product (Reductil®). The solid dispersions prepared with gelatin gave higher drug solubility than those prepared without gelatin, irrespective of the amount of polymer. The sibutramine base-loaded solid dispersions containing hydrophilic polymer and citric acid showed higher drug solubility compared to sibutramine base and sibutramine hydrochloride monohydrate. Among the formulations tested, the solid dispersion composed of sibutramine base/gelatin/HPMC/citric acid at the weight ratio of 1/0.8/0.2/0.5 gave the highest solubility of 5.03 ± 0.24 mg/ml. Our DSC and powder X-ray diffraction results showed that the drug was present in an altered amorphous form in this solid dispersion. The difference factor (f_1) values between solid dispersion and commercial product were 2.82, 6.65 and 6.31 at pH 1.2, 4.0 and 6.8, respectively. Furthermore, they had the similarity factor (f_2) value of 65.68, 53.43 and 58.97 at pH 1.2, 4.0 and 6.8, respectively. Our results suggested that the solid dispersion and commercial product produced a similar correlation of dissolution profiles at all pH ranges. The AUC, C_{max} and T_{max} of the parent drug and metabolite I and II from the solid dispersion were not significantly different from those of the commercial product, suggesting that the solid dispersion might be bioequivalent to the commercial product in beagle dogs. Thus, the sibutramine base-loaded solid dispersion prepared with gelatin, HPMC and citric acid is a promising candidate for improving the solubility and bioavailability of the poorly water-soluble sibutramine base.

1. Introduction

Obesity is a chronic, multifactorial disorder that has reached epidemic proportions in most industrialized countries and is threatening to become a global epidemic (Popkin, 1998). The risks of morbidity and mortality increase with increasing body weight and waist circumference (an index of the visceral localization of fat). Obese patients have higher risks for coronary artery disease, hypertension, hyperlipidemia, diabetes mellitus, certain cancers, cerebrovascular accident, osteoarthritis, obstructive pulmonary disease, and sleep apnea (Rippe et al., 1998). Efforts to develop innovative anti-obesity drugs have intensified, and there have been calls for medically based outcome measures for obesity treatments that are more appropriate than those currently used (Clapham et al., 2001; Halpern and Mancini, 2003).

Sibutramine, an anti-obesity drug, is a potent inhibitor of the reuptake of noradrenaline and serotonin (Carek and Dickerson, 1999), and may stimulate thermogenesis by its activation of β_3-adrenoceptors in brown adipose tissue (Connoley et al., 1999; McNeely and Goa, 1998). Sibutramine base has not been used in commercial products due to its poor water-solubility and instability. It has a solubility of about 0.01 mg/ml and a melting point of about 55 °C (Li et al., 2010). However, sibutramine hydrochloride monohydrate, a salt form, has been used in a commercial product (Reductil®) because of its improved solubility and stability (McNeely and Goa, 1998). It has a solubility of about 3 mg/ml at pH 5.2 and a melting point of about 190 °C (Fang et al., 1999). Recently, considerable attention has been focused on the improvement of drug solubility by synthesizing different salt forms. Sibutramine

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mesylate (Kim et al., 2005) and sibutramine tartrate (HPC, 2006) have been synthesized, and showed an increase in solubility to 2500 and 500 mg/ml at pH 5.2, respectively. However, in order to use these new synthesized materials as commercial products, clinical tests must be carried out. Another oral formulation of sibutramine base, a solid dispersion prepared with poloxamer, was developed but showed little improvement in solubility (Li et al., 2010; Sheen et al., 1995).

Thus, in this study, in order to develop a novel sibutramine base-loaded solid dispersion with enhanced solubility and bioavailability, various solid dispersion systems were prepared using a spray drying technique with hydrophilic polymers such as gelatin, HPMC and citric acid. Their solubility, thermal characteristics and crystallinity were investigated. The dissolution and pharmacokinetics of the sibutramine base-loaded solid dispersion were compared with a sibutramine hydrochloride monohydrate-loaded commercial product.

2. Materials and methods

2.1. Materials

Sibutramine base, HPMC 2910 (hydroxypropylmethylcellulose 2910) and gelatin were obtained from Cipla Co. (India), Shin-Etsu Co. (Tokyo, Japan) and Sammi Co. (Anyang, South Korea), respectively. Citric acid was provided by Yung-Jin Pharm. Co. (Anyang, South Korea) and was of USP grade. The commercial product (Reductil®; in capsule form) was purchased from Abbott Korea Co. (Seoul, South Korea). All other chemicals were of reagent grade and were used without further purification.

2.2. Animals

All animal care and procedures were conducted according to the Guiding Principles in the Use of Animals in Toxicology, as adopted in 1989, revised in 1999 and amended in 2008 by the Society of Toxicology (SOT, 2008). The protocols for the animal studies were also approved by the Institute of Laboratory Animal Resources of Yeungnam University. Six male beagle dogs weighing 12.6–13.2 kg were fasted for 16 h prior to the experiments with free access to water and were allowed access to water and food 4 h after drug administration.

2.3. Preparation of sibutramine base-loaded solid dispersions

A Büchi 190 nozzle type minispray dryer was used for the preparation of sibutramine base-loaded solid dispersions. Various amounts of sibutramine base, gelatin, HPMC and citric acid were dissolved or dispersed in 30% ethanol. The detailed formulae of sibutramine base-loaded solid dispersions are given in Table 1. The resulting solution was delivered to the nozzle at a flow rate of 5 ml/min using a peristaltic pump and thereafter spray-dried at an inlet temperature of 120 °C. The pressure of the spray air was 4 kg/cm^2. The flow rate of the drying air was maintained at the aspirator setting of 10, corresponding to a pressure in the aspirator filter vessel of −30 mbar. The direction of air flow was the same as that of the sprayed products. The diameter of the nozzle was 0.7 mm (Li et al., 2008, 2010).

2.4. Aqueous solubility

Excessive amounts of sibutramine base-loaded solid dispersions (about 300 mg) were added to 5 ml of water, shaken in a water bath for 3 days and centrifuged at 3000 × *g* for 10 min (Eppendorf, USA). The supernatants were filtered through a membrane filter (0.45 μm) to obtain a clear solution. The concentration of sibutramine in the resulting solution was then analysed by UV (Model U-2800, Hitach, Tokyo, Japan) at 225 nm (Li et al., 2010).

2.5. Thermal characteristics and crystallinity

The thermal characteristics of the sibutramine base, ingredients, physical mixture and sibutramine base-loaded solid dispersion were investigated using a differential scanning calorimeter (DSC-823, Mettler Toledo; Imlangacher, Greifensee, Toledo, Switzerland). The physical mixture was prepared by simply mixing 1 g sibutramine base, 0.8 g gelatin, 0.2 g HPMC and 0.5 g citric acid. About 2 mg of samples were placed in sealed aluminium pans, before heating under nitrogen flow (20 ml/min) at a heating rate of 5 °C/min from 0 to 200 °C. Their powder crystallinity was assessed by X-ray powder diffraction (D5005, Bruker, Germany) conducted at room temperature using monochromatic Cu K_α-radiation (λ = 1.5406 å) at 40 mA and 40 kV in the region of $2^\circ \leq 2\theta \leq 40^\circ$ with an angular increment of 0.02° per second (Newa et al., 2007).

2.6. Dissolution

The dissolution test was performed using a USP XXIV dissolution apparatus II with 900 ml 0.1 N HCl (pH 1.2), acetate buffer solution (pH 4.0) and phosphate buffer solution (pH 6.8) as the dissolution mediums at 37 ± 0.5 °C. The speed of the basket was adjusted to 50 rpm. Capsules containing sibutramine base, sibutramine base-loaded solid dispersion or sibutramine HCl-loaded conventional product at the equivalent dose of 12.56 mg sibutramine base were

Table 1
Composition and aqueous solubility of sibutramine base solid dispersion.

No.	Sibutramine base (g)	Gelatin (g)	HPMC (g)	Citric acid (g)	Solubility (mg/ml)
Drug					0.01 ± 0.00
1	1	1.0	–	–	0.04 ± 0.01
2	1	–	1.0	–	0.02 ± 0.01
3	1	2.0	–	–	0.04 ± 0.01
4	1	–	2.0	–	0.03 ± 0.01
5	1	1.5	0.5	–	0.03 ± 0.01
6	1	1.0	–	0.5	3.17 ± 0.12
7	1	–	1.0	0.5	2.54 ± 0.08
8	1	2.0	–	0.5	3.19 ± 0.04
9	1	–	2.0	0.5	2.26 ± 0.18
10	1	1.5	0.5	0.5	3.20 ± 0.03
11	1	0.8	0.2	0.5	5.03 ± 0.24
12	1	0.8	0.2	0.25	3.10 ± 0.26
13	1	0.8	0.2	0.75	4.99 ± 0.31

Each value represents the mean ± S.D. (n = 3).

inserted into a sinker and placed in a dissolution tester (Shinseang Instrument Co.; Hwasung, South Korea). At predetermined time intervals, 3 ml of the medium was sampled and filtered through a membrane filter (0.45 μm). The concentration of drug in the filtrate was then analysed by UV at 225 nm (Li et al., 2010).

2.7. Oral administration

Beagle dogs, divided into two groups, were fasted overnight and restrained by means of a dog sling (Alice King Chatham Medical Arts, Los Angeles, CA) during the 48 h experimental period. The dogs were administered with capsules containing the sibutramine base-loaded solid dispersion (31.4 mg/kg) or a sibutramine HCl-loaded conventional product (15 mg/kg) equivalent to sibutramine base 12.56 mg/kg. About 1 ml of blood was collected from the cephalic vein of the hind leg at predetermined time intervals. These samples were immediately centrifuged at 3000 × *g* at 4 °C for 15 min using a centrifuge (5415C; Eppendorf, Hamburg, Germany) and stored at −80 °C prior to analysis. To assess the individual variance in the pharmacokinetic profile, a pharmacokinetic study was conducted with an open two-way crossover design with a 2-week washout period (Schulze et al., 2005).

2.8. Blood sample treatment

Plasma (200 μl) was mixed with 200 μl of mobile phase solution containing domperidone (100 ng/ml) as an internal standard. Then, 0.02 ml of 1 M NaOH was added, followed by liquid–liquid extraction for 10 min with 3 ml of diethyl ether/n-hexane (4:1, v/v). The organic layer was separated and removed at 40 °C in a heated centrifugal evaporator (EYELA CVE-200D; Tokyo Rikakikai Co., Tokyo, Japan). The residue was reconstituted in 50 μl of the mobile phase by vortex-mixing for 15 s, and 5 μl of this solution was injected onto the column.

2.9. HPLC–MS–MS conditions

The plasma concentrations of the parent drug and metabolite I and metabolite II were quantified using an API 4000 LC/MS/MS system (Applied Biosystems, Foster City, CA, USA) equipped with an electrospray ionization interface that was used in the positive ion mode ($[M+H]^+$). The compounds were separated on a chiral stationary-phase column (Chiralcel AGP, 100 × 2.0 mm internal diameter, 5 μm particle size; ChromTech Ltd., Congleton, Cheshire, UK) with a mobile phase that consisted of 10 mM ammonium acetate adjusted to pH 4.03 with acetic acid/acetonitrile (94:6, v/v). The column was heated to 22 °C, and the mobile phase was eluted at 0.2 ml/min using an HP 1100 series pump (Agilent, Wilmington, DE, USA). The Turboion spray interface was operated in the positive ion mode at 5500 V and 450 °C. The parent drug, metabolite I, metabolite II and domperidone (internal standard) gave mainly protonated molecules at *m*/*z* 280.2, 266.0, 252.1 and 427.2, respectively. The product ions were scanned in Q3 after collision with nitrogen in Q2 at *m*/*z* 125.2 for the parent drug, metabolite I and metabolite II, and at *m*/*z* 175.1 for domperidone. Quantification was performed by multiple reaction-monitoring (MRM) of the protonated precursor ions and the related product ions, using the ratio of the area under the peak for each solution and a weighting factor of $1/y^2$. The analytical data were processed with Analyst software (version 1.4.1, Applied Biosystems) (Bae et al., 2009; Li et al., 2010).

2.10. Pharmacokinetic data analysis and statistical analysis

The area under the drug concentration–time curve from zero to infinity (AUC), the mean residence time (MRT), the elimination constant (K_{el}) and the half-life ($t_{1/2}$) were calculated using a non-compartmental analysis (WinNonlin; professional edition, version 2.1; pharsiquit, Mountain View, CA, USA). The maximum plasma concentration of drug (C_{max}) and the time taken to reach the maximum plasma concentration (T_{max}) were obtained directly from the plasma data (Gibaldi and Perrier, 1982). 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

In this study, the solid dispersion system was prepared using a spray drying technique with hydrophilic polymers in order to improve the solubility of the poorly water-soluble sibutramine base. Hydrophilic polymers such as gelatin and HPMC were dissolved in 30% ethanol and the poorly water-soluble drug was suspended or dissolved in these solutions. The resulting solutions were spray-dried so that the sibutramine base formed a solid dispersion together with the hydrophilic polymers (Joe et al., 2010). HPMC has been known to be a solubility-friendly hydrophilic polymer to sibutramine base (Li et al., 2010). Moreover, gelatin was used as a carrier in the development of poorly water-soluble drugs (Li et al., 2008; Yong et al., 2006).

The solid dispersion improved the aqueous solubility of the sibutramine base with a solubility of 0.1 mg/ml (Table 1). The solubility was ranked in the following order: sibutramine base < sibutramine base-loaded solid dispersions with hydrophilic polymers < sibutramine base-loaded solid dispersion with hydrophilic polymers and acidifying agent. Furthermore, the sibutramine base-loaded solid dispersions with hydrophilic polymers showed significantly lower increases in drug solubility compared to sibutramine hydrochloride monohydrate. The sibutramine hydrochloride monohydrate had the drug solubility of about 2 mg/ml.

The polymers had little effect on the solubility of the sibutramine base without an acidifying agent, suggesting that the drug did not dissolve well in the polymer solution, irrespective of polymer amounts. Suspended white particles were observed in the polymer/drug mixture, indicating that the sibutramine base was not completely soluble in the pH range of 6.7–8.1. However, complete solubility of the drug was observed when the pH of the drug/polymer mixture was adjusted to pH 4.0 by the addition of an acidifying agent. In this study, citric acid was used as an acidifying agent (Li et al., 2010). The aqueous solubility of the sibutramine base increased dramatically by up to 100-fold, as citric acid was added to the solid dispersions. Moreover, sibutramine base-loaded solid dispersions with hydrophilic polymers and citric acid increased the drug solubility compared to sibutramine hydrochloride monohydrate (2.2–5.0 mg/ml vs. 2.05 ± 0.10 mg/ml).

On the other hand, the solid dispersions prepared with gelatin increased the drug solubility more than the solid dispersions prepared without gelatin, irrespective of the amount of polymer. Furthermore, the solid dispersion with 0.5 mg citric acid showed better drug solubility compared to the solid dispersion with 0.25 mg citric acid, but did not improve the drug solubility compared to the solid dispersion with 0.75 mg citric acid. Thus, more than 0.5 mg citric acid was not required in the development of the sibutramine base-loaded solid dispersion.

Among the formulations tested, the solid dispersion composed of sibutramine base/gelatin/HPMC/citric acid at the weight ratio of 1/0.8/0.2/0.5 gave the highest solubility of 5.03 ± 0.24 mg/ml. Thus, this formulation was selected for further study.

Fig. 1 shows the thermal behavior of the drug powder, carriers, physical mixture and solid dispersion. The DSC curve shows

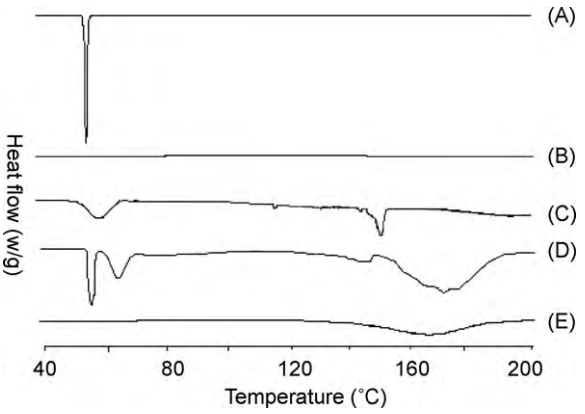

Fig. 1. Differential scanning calorimetric thermograms: (A) sibutramine base; (B) HPMC; (C) citric acid; (D) physical mixture; (E) solid dispersion. The physical mixture was prepared by simply mixing 1 g sibutramine base, 0.8 g gelatin, 0.2 g HPMC and 0.5 g citric acid. The solid dispersion was composed of sibutramine base/gelatin/HPMC/citric acid at the weight ratio of 1/0.8/0.2/0.5.

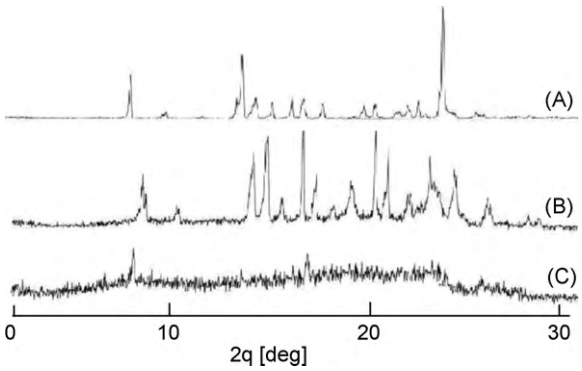

Fig. 2. X-ray powder diffraction: (A) sibutramine base; (B) physical mixture; (C) solid dispersion. The physical mixture was prepared by simply mixing 1 g sibutramine base, 0.8 g gelatin, 0.2 g HPMC and 0.5 g citric acid. The solid dispersion was composed of sibutramine base/gelatin/HPMC/citric acid at the weight ratio of 1/0.8/0.2/0.5.

that the sibutramine base produced a sharp endothermic peak at about 50 °C corresponding to its melting point, indicating its crystalline nature (Fig. 1A). HPMC had no endothermic peaks from 20 to 200 °C (Fig. 1B). The endothermic peaks of citric acid were observed at about 55 and 150 °C (Fig. 1C). The intrinsic peak produced by the drug was observed in the physical mixture, indicating that the drug did not interact with the other carriers (Fig. 1D). However, no sharp peak at about 50 °C corresponding to the melting point of sibutramine base was observed in the solid dispersion, suggesting that this solid dispersion might change the crystallinity of the drug (Joe et al., 2010; Li et al., 2010).

The powder X-ray diffractometry patterns are presented in Fig. 2. Sibutramine produced intrinsic peaks at diffraction angles showing a typical crystalline pattern (Fig. 2A). All major characteristic crystalline peaks produced by the drug were observed in the physical mixture (Fig. 2B). However, some of these were not observed in the solid dispersion (Fig. 2C). Thus, the sibutramine base was present in an altered amorphous form in this solid dispersion (Joe et al., 2010).

To evaluate whether the solid dispersion system affected the dissolution rates of the drug, dissolution studies on the sibutramine base, sibutramine base-loaded solid dispersion and sibutramine hydrochloride monohydrate-loaded commercial product were performed in 0.1 N HCl (pH 1.2), acetate buffer solution (pH 4.0) and phosphate buffer solution (pH 6.8). The dissolution profiles of three preparations are shown in Fig. 3. Sibutramine base, a basic molecule, showed a small amount of dissolution after 1 h at pH 6.8. However, at pH 1.2 and pH 4.0, it showed almost complete dissolution within 30 min.

The solid dispersion gave a higher initial dissolution rate of the drug compared to the drug powder at pH 1.2 (Fig. 3A). However, from 30 min onwards, the amounts of sibutramine dissolved from the solid dispersion did not significantly differ from those from the powder. The amounts of drug dissolved from the solid dispersion after 60 min were similar to the commercial product. As shown in Fig. 3B, there were no significant differences between the amounts dissolved from the three preparations.

At pH 6.8, the dissolution rate of the drug from the solid dispersion was very high compared to the powder (Fig. 3C). After 60 min there was about a 15-fold increase in the dissolution rate of the drug from the solid dispersion compared to the sibutramine base ($82.6 \pm 5.1\%$ vs. $5.6 \pm 0.4\%$). The solid dispersion showed a higher rate of dissolution of sibutramine than the commercial product at pH 6.8, although the difference was not significant. In particular, the amount of drug dissolved from the solid dispersion after 60 min was similar to the commercial product ($82.6 \pm 5.1\%$ vs. $78.5 \pm 4.4\%$). Thus, this solid dispersion was useful for improving the dissolution of the poorly water-soluble sibutramine base.

It is generally well known that a drug in a solid dispersion system often exists in an amorphous form. The amorphous form of a

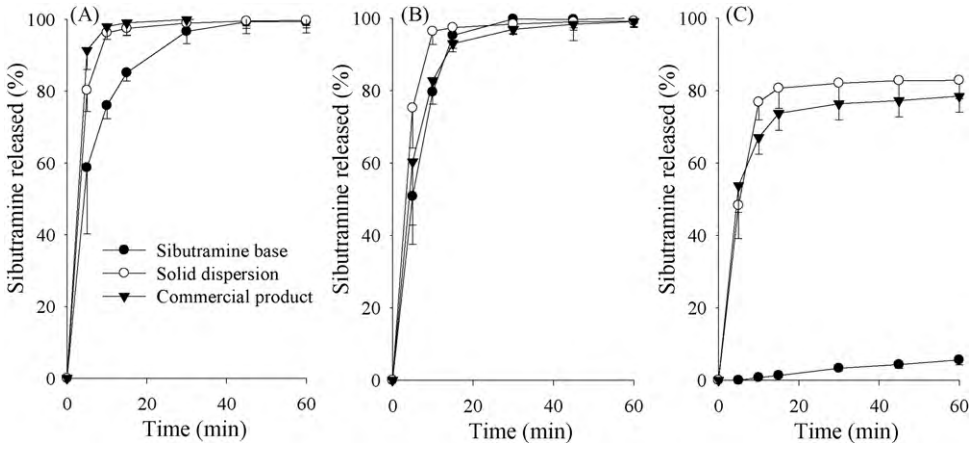

Fig. 3. Dissolution profiles of drug from capsules containing sibutramine base, solid dispersion and conventional product at pH 1.2 (A), pH 4.0 (B) and pH 6.8 (C). Each value represents the mean ± S.D. ($n = 6$). The solid dispersion was composed of sibutramine base/gelatin/HPMC/citric acid at the weight ratio of 1/0.8/0.2/0.5.

Table 2
Difference factor and similarity factor between solid dispersion and commercial product.

Dissolution medium	pH 1.2	pH 4.0	pH 6.8
Difference factor (f_1)	2.82	6.65	6.31
Similarity factor (f_2)	65.98	53.43	58.97

drug has a higher thermodynamic activity than its crystalline form, leading to rapid dissolution (Betageri and Makarla, 1995; Jung et al., 1999). Similarly, such improved solubility and dissolution was due to the change of drug crystallinity to the amorphous form in the sibutramine base-loaded solid dispersion prepared with HPMC and gelatin (Joe et al., 2010; Li et al., 2010). Furthermore, drugs dispersed in these polymeric carriers may achieve the highest levels of particle size reduction and surface area enhancement (Mitchell et al., 1990; Taylor and Zografi, 1997).

The *in vitro* release profiles of the solid dispersion and commercial product were compared using the difference factor (f_1) and similarity factor (f_2), as defined by the following equation (Cao et al., 2005; Hernandez et al., 1994):

$$f_1 = [\sum(R_t - T_t)/\sum(R_t + T_t)/2] \times 100 \quad (1)$$

$$f_2 = 50 \times \log\left\{\left[1 + \frac{1}{n}\sum(R_t - T_t)^2\right]^{-0.5} \times 100\right\} \quad (2)$$

where n is the number of time points, and T_t and R_t are percentage releases at time point (t) for the commercial product and solid dispersion, respectively. In these equations, $0 < f_1 < 15$ and $50 < f_2 < 100$ mean a similar correlation between the dissolution patterns of the two products. As shown in Table 2, the difference factor (f_1) values between solid dispersion and commercial product were 2.82, 6.65 and 6.31, at pH 1.2, 4.0 and 6.8, respectively. Furthermore, they had the similarity factor (f_2) value of 65.68, 53.43 and 58.97 at pH 1.2, 4.0 and 6.8, respectively. Thus, the solid dispersion and commercial product showed a similar correlation of dissolution profiles at all pH ranges.

Fig. 4 shows the change in mean plasma concentration of sibutramine (A), metabolite I (B) and metabolite II (C) after oral administration of the sibutramine base-loaded solid dispersion and sibutramine hydrochloride monohydrate-loaded commercial product (Reductil®) at a dose of 12.56 mg/kg sibutramine base in beagle dogs. In animals, sibutramine is rapidly metabolized to metabolite I (N-mono-desmethyl metabolite, desmethylsibutramine) and metabolite II (N,N-di-desmethyl metabolite, didesmethylsibutramine) (Hind et al., 1999; McNeely and Goa, 1998). The *in vivo* effects of sibutramine are predominantly the result of the actions of these two metabolites (Cheetham et al., 1990; Connoley et al., 1999).

As in rats, the total plasma concentrations of the parent drug, and metabolite I and II after oral administration of the sibutramine base at a dose of 12.56 mg/kg were impossible to detect due to its very low absorption in beagle dogs (Li et al., 2010). The solid dispersion might give higher total plasma concentrations of the drug compared to the sibutramine base (not detected). Thus, the higher plasma concentrations of the parent drug and metabolite I and II in the solid dispersion were contributed to by improved dissolution of the drug. However, the total plasma concentrations of the parent drug and metabolite I and II in the solid dispersion did not significantly differ from those in the commercial product in rats.

The pharmacokinetic parameters are shown in Table 3. The solid dispersion gave a significantly higher AUC and C_{max} of the parent drug, and metabolite I and II than the sibutramine base, the

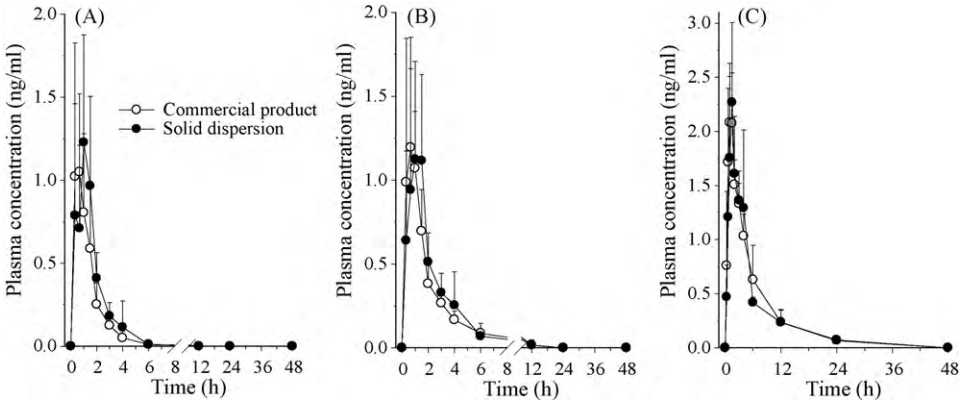

Fig. 4. Plasma concentration–time profiles of drug after oral administration of commercial product and solid dispersion to beagle dogs: (A) parent drug; (B) metabolite I; (C) metabolite II. Each value represents the mean ± S.D. (n = 6). The solid dispersion was composed of sibutramine base/gelatin/HPMC/citric acid at the weight ratio of 1/0.8/0.2/0.5.

Table 3
Pharmacokinetic parameters of parent drug, metabolite I and metabolite II after oral administration of commercial product and solid dispersion to beagle dogs.

Parameters	AUC (ng h/ml)	C_{max} (ng/ml)	T_{max} (h)	$t_{1/2}$ (h)	K_{el} (h^{-1})
Parent drug					
Commercial product	1.67 ± 0.79	1.28 ± 0.57	0.75 ± 0.39	0.85 ± 0.23	0.87 ± 0.24
Solid dispersion	1.95 ± 0.63	1.52 ± 0.52	1.00 ± 0.46	1.32 ± 0.77	0.72 ± 0.44
Metabolite I					
Commercial product	2.47 ± 0.71	1.40 ± 0.54	0.61 ± 0.29	1.79 ± 0.58	0.42 ± 0.13
Solid dispersion	2.68 ± 0.80	1.51 ± 0.59	1.14 ± 0.48	1.86 ± 0.92	0.44 ± 0.17
Metabolite II					
Commercial product	11.83 ± 2.04	2.19 ± 0.47	1.28 ± 0.36	5.19 ± 1.15	0.14 ± 0.03
Solid dispersion	11.04 ± 1.70	2.52 ± 0.77	1.64 ± 1.23	6.23 ± 1.50	0.12 ± 0.03

The solid dispersion was composed of sibutramine base/gelatin/HPMC/citric acid at the weight ratio of 1/0.8/0.2/0.5. Each value represents the mean ± S.D. (n = 6).

plasma concentrations of which were not detected in this study. Our results suggest that the enhanced relative oral bioavailability of sibutramine in the solid dispersion was contributed to by the marked increase in the absorption of the drug. It was due to its improved solubility and dissolution induced by the formation of solid dispersion with HPMC and gelatin (Li et al., 2010). The AUC, C_{max} and T_{max} values of the parent drug, and metabolite I and II for the solid dispersion did not significantly differ from the commercial product. Thus, the solid dispersion might be bioequivalent to the commercial product in beagle dogs. Furthermore, the K_{el} and $t_{1/2}$ values of the parent drug and metabolite I and II from the solid dispersion were not significantly different from those from the commercial product. Thus, from the pharmacokinetic view, this solid dispersion system showed similar drug efficacy compared to the commercial product in beagle dogs.

4. Conclusion

In conclusion, the sibutramine base-loaded solid dispersion composed of sibutramine base/gelatin/HPMC/citric acid at the weight ratio of 1/0.8/0.2/0.5 gave a solubility of 5.03 ± 0.24 mg/ml. Furthermore, it showed similar dissolution to the sibutramine hydrochloride monohydrate-loaded commercial product and was bioequivalent to the commercial product in beagle dogs. Thus, the sibutramine base-loaded solid dispersion prepared with gelatin, HPMC and citric acid is a promising candidate for improving the solubility and bioavailability of the poorly water-soluble sibutramine base. For the development of a novel sibutramine base-loaded solid dispersion, further bioequivalence tests in human subjects will be performed.

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