Enhanced Solubility and Bioavailability of Sibutramine Base by Solid Dispersion System with Aqueous Medium

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To develop a novel sibutramine base-loaded solid dispersion with improved solubility bioavailability, various solid dispersions were prepared with water, hydroxypropylmethyl cellulose (HPMC), poloxamer and citric acid using spray-drying technique. The effect of HPMC, poloxamer and citric acid on the aqueous solubility of sibutramine was investigated. The physicochemical properties of solid dispersion were investigated using scanning electron microscopy (SEM), differential scanning calorimetry (DSC) and X-ray powder diffraction. The dissolution and pharmacokinetics in rats of solid dispersion were evaluated compared to the sibutramine hydrochloride monohydrate-loaded commercial product (Reductil®). The sibutramine base-loaded solid dispersion gave two type forms. Like conventional solid dispersion system, one type appeared as a spherical shape with smooth surface, as the carriers and drug with relatively low melting point were soluble in water and formed it. The other appeared as an irregular form with relatively rough surface. Unlike conventional solid dispersion system, this type changed no crystalline form of drug. Our results suggested that this type was formed by attaching hydrophilic carriers to the surface of drug without crystal change, resulting from changing the hydrophobic drug to hydrophilic form. The sibutramine-loaded solid dispersion at the weight ratio of sibutramine base/HPMC/poloxamer/citric acid of 5/3/3/0.2 gave the maximum drug solubility of about 3 mg/ml. Furthermore, it showed the similar plasma concentration, area under the curve (AUC) and Cmax of parent drug, metabolite I and II to the commercial product, indicating that it might give the similar drug efficacy compared to the sibutramine hydrochloride monohydrate-loaded commercial product in rats. Thus, this solid dispersion system would be useful to deliver poorly water-soluble sibutramine base with enhanced bioavailability.

Key words solid dispersion; water; sibutramine base; solubility; pharmacokinetics

Sibutramine [1-(4-chlorophenyl)-N,N-dimethyl-a-(2-methylpropyl)cyclobutane methane amine] is a newer anti-obesity drug with a novel mechanism of action.1,3) It contains a potent inhibitor of the reuptake of noradrenaline (NA), serotonin (5-HT) and may stimulate thermogenesis by its activation of ß3-adrenoceptors in brown adipose tissue.2—4) In human subjects, sibutramine is rapidly metabolized to an N-mono-desmethyl metabolite (desmethylsibutramine [Metabolite I]) and an N,N-didesmethyl metabolite (didesmethylsibutramine [Metabolite II]). The in vivo effects of sibutramine are predominantly the results of the action of the above 2 metabolites.4—7)

Sibutramine hydrochloride monohydrate is the commercially available formulation of sibutramine with the relatively high solubility of 2.9 mg/ml at pH 5.2 and melting point of 190 °C.5,8) However, sibutramine base has not been used in commercial formulation. Various oral formulations of sibutramine such as other salt form such as sibutramine mesylate9,10) and sibutramine tartrate, 11) solid dispersions with poloxamer12—14) and inclusion complex.15)

One of the well established method for increasing the solubility and bioavailability of poorly water-soluble drugs is solid dispersion.16) Several conventional methods such as melting, solvent evaporation and solvent wetting were reported to prepare solid dispersions.17,18) However, the solid dispersion prepared by melting method with high temperature might chemically decompose the drugs.19,20) In the case of solvent evaporation and solvent wetting method, the drug in the solid dispersions changed to amorphous form, resulting that the drug might be unstable.18) Furthermore, a large amount of hydrophilic carriers against drug in these conventional solid dispersions must be needed to improve the solubility of poorly water-soluble drugs.21,22)

In this study, to improve the bioavailability of poorly water-soluble sibutramine base, various sibutramine base-loaded solid dispersions were prepared with water, hydroxypropylmethyl cellulose (HPMC), poloxamer and citric acid using spray-drying technique. The effect of HPMC, poloxamer and citric acid on the aqueous solubility of sibutramine was then investigated. The physicochemical properties of solid dispersion were investigated using scanning electron microscope (SEM), differential scanning calorimetry (DSC) and X-ray powder diffraction. The dissolution and pharmacokinetics in rats of solid dispersion were evaluated compared to the sibutramine hydrochloride monohydrate-loaded commercial product (Reductil®). This commercial product is a conventional capsule which contains 100 mg sibutramine hydrochloride monohydrate and is usually taken multiple times a day. Poloxamer has been employed to enhance the solubility and bioavailability of poorly water-soluble drugs.19,23) HPMC is frequently used in the preparation of conventional pharmaceutical oral dosage form due to its hydrophilic and soft property.24,25)
**MATERIALS AND METHODS**

**Materials**  Sibutramine base was supplied from Cipla Co. (India). Poloxamer 407 was purchased from BASF Chemical Co. (Ludwigshafen, Germany). Commercial product (Reductil®) was purchased from Abbott Korea Co. (Seoul, South Korea). Citric acid and hydroxypropylmethyl cellulose (HPMC) were of USP grade. All other chemicals were of reagent grade and used without further purification.

**Preparation of Sibutramine Base-Loaded Solid Dispersion**  A Büchi 190 nozzle type mini spray dryer (Flawil, Switzerland) was used for the preparation of sibutramine-loaded solid dispersion. Various amounts of poloxamer, HPMC and citric acid were dissolved in water, and 5 g sibutramine base pre-sieved through 60 mesh screen was dispersed in this solution. The detailed formulae of spray-drying solutions for the preparation of sibutramine-loaded solid dispersion are given in Table 1. The resulting suspension was prewarmed to 30 °C, delivered to the nozzle (0.7 mm diameter) at a flow rate of 5 ml/min using a peristaltic pump and spray-dried at 100—115 °C inlet temperature. The pressure of spray air was 4 kg/cm² and the flow rate of drying air was maintained at the aspirator setting of 10 which indicated the pressure of aspirator filter vessel —30 mbar. The direction of air flow was the same as that of sprayed products.16,27

**Effects of Carriers on Aqueous Solubility of Sibutramine Base in the Solid Dispersions**  To investigate the effects of carriers on aqueous solubility of sibutramine base in the solid dispersions, excessive amount of solid dispersions (about 100 mg) were added to 10 ml of water, shaken in water bath for 3 d and centrifuged at 3000 g for 10 min (Eppendorf, U.S.A.). The supernatants were filtered through a membrane filter (0.45 μm) to obtain a clear solution.27—29) The concentration of sibutramine in the resulting solution was then analyzed by UV (Model U-2800, Hitachi, Tokyo, Japan) at 225 nm.30)

**Shape and Surface Morphology**  The shape and surface morphology of sibutramine base and sibutramine-loaded solid dispersion were examined using a scanning electron microscope (S-4100, Hitachi, Japan). The powders were fixed on a brass specimen club using double-side adhesive tape and made electrically conductive by coating in a vacuum (0.1 ml of mobile phase containing domperidone (80 U/ml) to prevent blood clotting. Sibutramine base, commercial product (Reductil®) and solid dispersion at the equivalent dose of 10 mg sibutramine base were inserted into the basket and placed in a dissolution tester (Shinseang Instrument Co., South Korea), respectively. At 10, 15, 30, 45, 60, 90 and 120 min, 3 ml of the medium was sampled and filtered through membrane filter (0.45 μm).19,32,33) The concentration of sibutramine in the filtrate was then analyzed by UV at 225 nm.30

**Thermal Characteristics and Crystallinity**  The thermal characteristics of sibutramine base, ingredients, physical mixture and sibutramine-loaded solid dispersion were investigated using a differential scanning calorimeter (DSC Q-1000, TA Instrument, Leatherhead, U.K.). The physical mixture was prepared by physically mixing sibutramine base, HPMC, poloxamer and citric acid at the weight ratio of 5 : 3 : 3 : 0.2. About 5 mg of samples were placed in sealed aluminum pans, before heating under nitrogen flow (20 ml/min) at a heating rate of 10 °C/min from 0 to 200 °C. Moreover, their powder crystallinity were assessed by X-ray powder diffraction (D5005, Bruker, Germany) conducted at room temperature using monochromatic CuKα-radiation (λ=1.5406 Å) at 40 mA and 40 kV in the region of 2θ=2θ±40° with an angular increment of 0.02° per second.27,31

**Dissolution**  Dissolution test was performed using USP XXIV, dissolution apparatus II with 900 ml water as a dissolution medium at 37±0.5 °C. The speed of the basket was adjusted to 50 rpm. Sibutramine base, conventional product and solid dispersion at the equivalent dose of 10 mg sibutramine base were inserted into the basket and placed in a dissolution tester (Shinseang Instrument Co., South Korea), respectively. At 10, 15, 30, 45, 60, 90 and 120 min, 3 ml of the medium was sampled and filtered through membrane filter (0.45 μm).19,32,33) The concentration of sibutramine in the filtrate was then analyzed by UV at 225 nm.30

**Pharmacokinetics. In Vivo Experiments**  Male Sprague-Dawley rats weighing 280±20 g were fasted for 12 h prior to the experiments but allowed free access to water. Eighteen rats were divided into three groups. The rats in each group were administered with sibutramine base, commercial product (Reductil®) and solid dispersion at a dose of sibutramine base 10 mg/kg, respectively. All animals care and procedures were conducted according to the Guiding Principles in the Use of Animals in Toxicology, as adopted in 1989 and revised in 1999 by the Society of Toxicology.34

**Administration and Blood-Collecting**  Each rat, anesthetized in an ether-satured chamber, was secured on a surgical board in the supine position with a thread. A polyethylene tube was inserted into the right femoral artery of the rat, all of the incisions were covered with wet cotton and the cannula was flushed with 0.2 ml of heparinized normal saline (80 U/ml) to prevent blood clotting. Sibutramine base, commercial product and solid dispersion were filled in small hard gelatin capsules (No. KN-346-2, 4.3 mm×2.65 mm i.d., Natsume Co., Tokyo, Japan), and orally administered to rats in each group, respectively. At predetermined time intervals, 0.4 ml of blood was collected from the right femoral artery and centrifuged at 3000 g for 10 min using a centrifuge 5415C (Eppendorf, U.S.A.).15,35

**Blood Sample Analysis**  Plasma (0.1 ml) was mixed with 0.1 ml of mobile phase solution containing domperidone (100 ng/ml), as an internal standard. Then, 0.01 ml of 1 M NaOH was added and followed by liquid–liquid extraction for 10 min with 1.5 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., Ltd., 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.30

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Table 1. Composition of Spraying Solution for the Preparation of Sibutramine Base-Loaded Solid Dispersion

<table>
<thead>
<tr>
<th>Ingredients</th>
<th>I</th>
<th>II</th>
<th>III</th>
<th>IV</th>
<th>V</th>
<th>VI</th>
<th>VII</th>
<th>VIII</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sibutramine (g)</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>HPMC (g)</td>
<td>4.8</td>
<td>3.6</td>
<td>3</td>
<td>1.5</td>
<td>0.75</td>
<td>3</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Poloxamer (g)</td>
<td>1.2</td>
<td>2.4</td>
<td>3</td>
<td>1.5</td>
<td>0.75</td>
<td>3</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Citric acid (g)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0.1</td>
<td>0.2</td>
</tr>
<tr>
<td>Water (ml)</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
</tr>
</tbody>
</table>
**RESULTS AND DISCUSSION**

**Preparation of Sibutramine-Loaded Solid Dispersion**
A novel solid dispersion system was prepared using spray drying technique with water, hydrophilic polymer and surfactant without organic solvent. In this study, HPMC and poloxamer were used as a hydrophilic polymer and surfactant, respectively. Relatively small amounts of HPMC and poloxamer were dissolved in water and a poorly water-soluble sibutramine base was dispersed in this solution. The resulting suspension was spray-dried, resulting in producing the sibutramine-loaded solid dispersion.

In the conventional solid dispersion systems, the poorly water-soluble drug may exist as an amorphous form in polymeric carriers, and improved the solubility and dissolution of drug compared with crystalline material. Furthermore, the drugs dispersed in polymeric carriers may achieve the highest levels of particle size reduction and surface area enhancement, resulting in improved dissolution rates. However, in the novel solid dispersion prepared in this study, the dissolved hydrophilic polymer and surfactant might be attached to the surface of dispersed drug particles. It might change the hydrophobic drug to hydrophilic form, resulting in increased solubility of the poorly water-soluble drug. Thus, since water is used as a solvent in this study unlike conventional solid dispersion method, this solid dispersion method has several advantages over other methods in an industry scale, such as the relatively lower ratio of carriers to drug, no necessity to remove organic solvent and no toxicity or explosion of organic solvent.

**Effects of Aqueous Solubility of Sibutramine Base in the Solid Dispersions**
To select an optimal formula of sibutramine base-loaded solid dispersion which increased the drug solubility with the minimum amount of carriers, the effect of the ratio of HPMC/poloxamer (Table 1, formula I—III) on the aqueous solubility of sibutramine was shown in Fig. 1A. The solid dispersion gave more increased drug solubility that did sibutramine base. The aqueous solubility of sibutramine was significantly increased with decreased ratio of HPMC/poloxamer. Our results suggested that the more hydrophilic carrier, poloxamer improved the drug solubility compared to less hydrophilic carrier, HPMC. Furthermore, the effect of the amount of carriers with constant ratio of HPMC/poloxamer (1:1) on aqueous solubility of sibutramine was investigated (Table 1, formula III—V). The formula III improved more the drug solubility than did the formula IV and V (Fig. 1B). Therefore, the more increased the carrier was, the more increased the drug solubility was. The effect of citric acid on aqueous solubility of drug was investigated (Table 1, formula III, VI—VIII). Citric acid was used as a solubilizer for sibutramine formulation. The formula VI—VIII with citric acid greatly improved the solubility of drug compared to the formula III without citric acid (Fig. 1C). However, the formula VIII with 0.3 g citric acid hardly improved the solubility of drug compared to the formula VII with 0.2 g citric acid. Among the formulae tested, formula VII with the most increased drug solubility improved about 300-fold solubility of sibutramine base (3120±210 vs. 10.0±1.2 μg/ml). Thus, the formula VII with the minimum amounts of carrier and maximum drug solubility was chosen for further studies.

**Shape, Thermal Characteristics and Crystallinity**
The scanning electron micrographs of sibutramine base and
solid dispersion were shown in Fig. 2. The solid dispersion was composed of sibutramine base/HPMC/poloxamer/citric acid at the weight ratio of 5/3/3/0.2. Sibutramine base (Fig. 2A) appeared as rectangular crystalline in shape. However, the solid dispersion (Fig. 2B) gave two type forms. Like conventional solid dispersion system, one type appeared as a spherical shape with smooth surface. Furthermore, the other appeared as an irregular form with relatively rough surface unlike conventional solid dispersion system.

Thermal behavior of drug powder, carriers, physical mixture and solid dispersion were shown in Fig. 3. The DSC curve showed that sibutramine appeared a sharp endothermic peak at about 50 °C corresponding to its melting, indicating its crystalline nature (Fig. 3A). The endothermic peaks of citric acid and poloxamer were observed between 50 and 60 °C (Figs. 3D, E). The intrinsic peak appeared in the drug was appeared with reduced intensity in physical mixture, indicating that the drug could not interact with other carriers (Fig. 3B). However, not a sharp but broad peak was also observed in solid dispersion at about 50 °C (Fig. 3C), indicating that this solid dispersion might change the crystallinity of drug like other conventional solid dispersion.

The powder X-ray diffractometry patterns are presented in Fig. 4. Sibutramine showed intrinsic peaks at diffraction angles showing a typical crystalline pattern (Fig. 4A). All major characteristic crystalline peaks appeared in drug were observed in physical mixture (Fig. 4B). However, among major characteristic crystalline peaks appeared in drug, some were observed and the others were not observed in the solid dispersion (Fig. 4C). Thus, unlike conventional solid dispersion, the sibutramine base might be present together as a changed amorphous form and no changed crystalline form in this solid dispersion.

From these findings, this sibutramine base-loaded solid dispersion had two type forms. Like conventional solid dispersion system, one type appeared as a spherical shape with smooth surface. This spherical type might be formed by spraying the soluble carriers and drug with low melting point of 50 °C in water at high inlet temperature. Furthermore, the other appeared as an irregular form with relatively rough surface. Our results suggested that, unlike conventional solid dispersion system, this type might be formed by attaching hydrophilic carriers to the surface of undissolved drug, resulting in changing the hydrophobic drug to hydrophilic property in this solid dispersion.

Thus, the enhanced solubility of sibutramine base in the solid dispersion was not only due to the transformation of the crystalline form into the amorphous state, but also due to the attachment of the hydrophilic carriers to the surface of poorly water-soluble sibutramine base.

**Dissolution** The dissolution test on the solid dispersion was carried out compared to the sibutramine hydrochloride
monohydrate-loaded commercial product (Reductil®) and sibutramine base. The sibutramine base-loaded solid dispersion was composed of sibutramine base/HPMC/poloxamer/citric acid at the weight ratio of 5/3/3/0.2. The dissolution profiles of three preparations are shown in Fig. 5. The dissolution rate of drug from solid dispersion is very high as compared to the powder. The amounts of drug dissolved from solid dispersion for 60 min increased about 18-fold compared to the powder. The amounts of drug dissolved from solid dispersion were not significantly different from those from the commercial product. In particular, the amounts of drug dissolved from solid dispersion for 120 min was similar to commercial product (82.3±2.8 vs. 78.5±3.9%). Furthermore, about 80% of sibutramine base dissolved from this solid dispersion and sibutramine hydrochloride dissolved from commercial product were maximum amounts due to their limited solubility. Thus, this solid dispersion was very useful for improving the initial dissolution rate of sibutramine, since it gave two type forms together.

Pharmacokinetics Figure 6 shows the change of mean plasma concentration of sibutramine (a), metabolite I (b) and metabolite II (c) after oral administration of solid dispersion and commercial product (Reductil®) at the dose of 10 mg/kg sibutramine base in rats. However, the total plasma concentrations of parent drug, metabolite I and II in solid dispersion were not significantly different from those from the commercial product. From the pharmacokinetic view, this solid dispersion system might give the similar drug efficacy compared to the commercial product in rats. For the development of novel sibutramine-loaded solid dispersion, the further study on bioequivalence test in human subjects will be performed.

The pharmacokinetic parameters are shown in Table 2. The solid dispersion gave significantly higher AUC and C_{max} of parent drug, metabolite I and II than did sibutramine base. Our results suggested that the enhanced oral relative bioavailability of sibutramine in the solid dispersion was contributed by the marked increase in the absorption rate of drug due to improved dissolution of drug. The AUC, C_{max} and T_{max} of parent drug, metabolite I and II from the solid dispersion were not significantly different from those from commercial product, respectively. Thus, the solid dispersion might be bioequivalent to commercial product in rats. Furthermore, the K_{el} and t_{1/2} values of parent drug, metabolite I and II from the solid dispersion were not significantly different from those from commercial product.

From the pharmacokinetic view, this solid dispersion system might give the similar drug efficacy compared to the commercial product in rats. For the development of novel sibutramine-loaded solid dispersion, the further study on bioequivalence test in human subjects will be performed.

![Figure 6](image-url)  
**Figure 6.** Plasma Concentration–Time Profiles of Drug after Oral Administration of Commercial Product and Solid Dispersion to Rats  
The solid dispersion was composed of sibutramine base/HPMC/poloxamer/citric acid at the weight ratio of 5/3/3/0.2. Each value represents the mean±S.D. (n=6).

<table>
<thead>
<tr>
<th>Parameters</th>
<th>AUC (h·ng/ml)</th>
<th>T_{max} (h)</th>
<th>C_{max} (μg/ml)</th>
<th>K_{el} (h^{-1})</th>
<th>t_{1/2} (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sibutramine base</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Commercial product</td>
<td>50.68±23.45</td>
<td>0.83±0.47</td>
<td>17.66±8.92</td>
<td>0.67±0.23</td>
<td>1.16±0.49</td>
</tr>
<tr>
<td>Solid dispersion</td>
<td>54.07±21.02</td>
<td>1.02±0.72</td>
<td>19.24±3.02</td>
<td>0.43±0.32</td>
<td>2.55±1.76</td>
</tr>
<tr>
<td>Metabolite I</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Commercial product</td>
<td>364.86±199.36</td>
<td>2.68±2.09</td>
<td>34.56±19.50</td>
<td>0.09±0.05</td>
<td>10.85±8.37</td>
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<tr>
<td>Solid dispersion</td>
<td>363.60±134.02</td>
<td>5.23±4.74</td>
<td>33.83±29.55</td>
<td>0.09±0.05</td>
<td>10.89±7.06</td>
</tr>
<tr>
<td>Metabolite II</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Commercial product</td>
<td>11408.21±10208.61</td>
<td>4.42±4.60</td>
<td>637.28±549.22</td>
<td>0.10±0.06</td>
<td>10.62±7.17</td>
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<tr>
<td>Solid dispersion</td>
<td>11804.42±5982.62</td>
<td>6.52±5.01</td>
<td>668.82±507.81</td>
<td>0.10±0.06</td>
<td>10.32±7.71</td>
</tr>
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</table>

Each value represents the mean±S.D. (n=6). The plasma concentrations of drug after oral administration of sibutramine base were not detected due to its very small absorption in rats. The solid dispersion was composed of sibutramine base/HPMC/poloxamer/citric acid at the weight ratio of 5/3/3/0.2.
CONCLUSION

Unlike conventional solid dispersion systems, this solid dispersion prepared with water, HPMC, poloxamer and citric acid gave relatively lower ratio of carrier to drug, no changed crystalline form of drug and no environmental pollution. Furthermore, the sibutramine-loaded solid dispersion at the weight ratio of sibutramine base/HPMC/poloxamer/citric acid of 5/3/3/0.2 gave the maximum drug solubility of about 3 mg/ml. It gave the similar AUC, C_{max}, T_{max}, K_{el} and t_{1/2} values of parent drug, metabolite I and II compared to the commercial product, indicating that it might give the similar drug efficacy compared to commercial product in rats. Thus, this solid dispersion system would be useful to deliver poorly water-soluble sibutramine base with enhanced bioavailability.

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