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Novel valsartan-loaded solid dispersion with enhanced bioavailability and no crystalline changes

Yi-Dong Yan[a], Jun Ho Sung[a], Kun Kook Kim[a], Dong Wuk Kim[b], Jong Oh Kim[a], Beom-Jin Lee[c], Chul Soon Yong[a,**], Han-Gon Choi[b,*]

[a] College of Pharmacy, Yeungnam University, 214-1 Dae-Dong, Kyungsan, Kyungbuk 712-749, South Korea
[b] College of Pharmacy, Hanyang University, 55, Hanyangdaehak-ro, Sangnok-gu, Ansan 426-791, South Korea
[c] College of Pharmacy, Kangwon National University, Chuncheon 200-701, South Korea

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ABSTRACT

With the aim of developing a novel valsartan-loaded solid dispersion with enhanced bioavailability and no crystalline changes, various valsartan-loaded solid dispersions were prepared with water, hydroxypropyl methylcellulose (HPMC) and sodium lauryl sulphate (SLS). Effects of the weight ratios of SLS/HPMC and carrier/drug on both the aqueous solubility of valsartan and the drug-release profiles of solid dispersions were investigated. The physicochemical properties of solid dispersions were characterized using scanning electron microscope (SEM), differential scanning calorimetry (DSC) and X-ray diffraction (XRD). The bioavailability of the solid dispersions in rats was evaluated compared to valsartan powder and a commercial product (Diovan®). Unlike the conventional solid dispersion system, the valsartan-loaded solid dispersion had a relatively rough surface and did not change the crystalline form of the drug. It was suggested that the solid dispersions were formed by attaching hydrophilic carriers to the surface of the drug, thus changing from a hydrophobic to a hydrophilic form without changing the crystalline form. The drug-loaded solid dispersion composed of valsartan/HPMC/SLS at a weight ratio of 3/1.5/0.75 improved the drug solubility by about 43-fold. It gave a higher AUC, C_{max} and shorter T_{max} compared to valsartan powder and the commercial product. The solid dispersion improved the bioavailability of the drug in rats by about 2.2 and 1.7-fold in comparison with valsartan powder and the commercial product, respectively. Thus, the valsartan-loaded solid dispersion would be useful for delivering poorly water-soluble valsartan with enhanced bioavailability and no crystalline changes.

1. Introduction

Valsartan [(S)-N-valeryl-N-{[2′-(1H-tertrazol-5-yl)biphenyl-4-yl]-metyl}-valine] is an orally active angiotensin II type 1 receptor-specific blocker effective at lowering blood pressure in hypertensive patients (Markham and Goa, 1997). However, this drug has low aqueous solubility and high membrane permeability, belonging to class 2 of the Biopharmaceutical Drug Classification system (Brunella et al., 2006). Its bioavailability is relatively low after oral administration since it is almost totally insoluble in water (Dressman and Reppas, 2000).

A well-established method for increasing the solubility and bioavailability of poorly water-soluble drugs is the solid dispersion system (Chiou and Riegelman, 1971). Drugs in solid dispersion systems can exist in an amorphous form in polymeric carriers. Such a system improves the solubility and dissolution of a drug compared to the crystalline material, since dispersal in polymeric carriers may lead to high levels of particle size reduction and surface area enhancement (Craig, 2002; Taylor and Zografi, 1997). Several conventional methods such as melting, solvent evaporation and solvent wetting were previously reported for the preparation of solid dispersions (Leuner and Dressman, 2000; Yamashita et al., 2003). However, the use of the melting method at a high temperature might chemically decompose the drug (Miller et al., 2007; Newa et al., 2008). In the case of solvent evaporation and solvent wetting, the drug could change to an amorphous form in the solid dispersion, meaning that the drug might then be unstable (Joe et al., 2010; Oh et al., 2011). Furthermore, large amounts of hydrophilic carriers are required in these conventional solid dispersions in order to improve the solubility of poorly water-soluble drugs.

In order to solve the problems associated with conventional solid dispersions and to improve the bioavailability of poorly water-soluble valsartan without any crystalline changes, the valsartan-loaded solid dispersions in this study were prepared with

* Corresponding author. Tel.: +82 31 400 5802; fax: +82 31 400 5958.
** Co-corresponding author. Tel.: +82 53 810 2812; fax: +82 53 810 4654.
E-mail addresses: csyong@yu.ac.kr (C.S. Yong), hangon@hanyang.ac.kr (H.-G. Choi).

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Table 1
Aqueous solubility of valsartan.

Carrier	Aqueous solubility of valsartan (μg/ml)
Water	3.08 ± 0.2
Hydrophilic polymers[a]	
Sodium carboxymethyl cellulose	49.4 ± 1.9
Polyvinylpyrrolidone	12.6 ± 1.1
Hydroxypropyl cellulose	22.1 ± 3.1
Hydroxypropylmethyl cellulose	53.2 ± 6.1
Surfactants[b]	
Poloxamer 188	504.1 ± 105.7
Poloxamer 407	839.3 ± 71.1
Sodium lauryl sulphate	1458.2 ± 95.2
Span 20	80.0 ± 18.0
Span 80	27.3 ± 6.7
Tween 20	418.1 ± 17.4
Tween 80	624.8 ± 56.3

Each value represents the mean ± S.E. ($n = 3$).
[a] Each value means the solubility of valsartan in distilled water containing 1% hydrophilic polymer.
[b] Each value means the solubility of valsartan in distilled water containing 10% surfactant.

water, hydroxypropyl methylcellulose (HPMC) and sodium lauryl sulphate (SLS) using a spray drying technique. This allowed a relatively low ratio of carrier to drug and no organic solvent. The formulation of the drug-loaded solid dispersion was optimized by investigating the effects of SLS and HPMC on the aqueous solubility of valsartan and the dissolution profiles of solid dispersions. The physicochemical properties of the optimal solid dispersion were then investigated using scanning electron microscope (SEM), differential scanning calorimetry (DSC) and X-ray diffraction (XRD). Furthermore, a comparative study of bioavailability in rats was carried out to gain further insights into the absorption potential of valsartan via the solid dispersion.

2. Materials and methods

2.1. Materials

Valsartan was supplied by Hanmi Pharm. Co. (Suwon, Korea). Hydroxypropyl methylcellulose (HPMC), hydroxypropyl cellulose, polyvinylpyrrolidone and poloxamer series were purchased from BASF Chemical Co. (Ludwigshafen, Germany). Sodium lauryl sulphate (SLS), sodium carboxylmethyl cellulose (Na-CMC), polysorbate 20 (Tween 20), polysorbate 80 (Tween 80), sorbitan monolaurate 20 (Span 20) and sorbitan monooleate 80 (Span 80) were purchased from Duksan Chemical Co. (Ansan, Korea). The commercial product (Diovan®; in a tablet form) was purchased on the market. All other chemicals were of reagent grade and were used without further purification.

2.2. Solubility of valsartan

An excess of valsartan powder (about 1 g) was added to 10 ml of 1% or 10% of the carrier, as shown in Table 1. Excess amounts of the solid dispersions (about 1 g) were added to 10 ml of water. They were shaken in a water bath at 25 °C for 7 days, centrifuged at 3000 × *g* for 10 min (Eppendorf, USA) and filtered through a membrane filter (0.45 μm). The concentration of valsartan in the resulting solution was analysed by HPLC as described below.

2.3. Preparation of the valsartan-loaded solid dispersion

A Buchi 190 nozzle-type mini spray dryer (Flawil, Switzerland) was used to prepare the valsartan-loaded solid dispersion. Various amounts of SLS and HPMC were dissolved in water. Then, 10 g of valsartan, pre-sieved through a 60-mesh screen, was dispersed in this solution. Details of the composition of the valsartan-loaded solid dispersion are given in Table 2. The resulting dispersion was delivered to the nozzle (0.7 mm diameter) at a flow rate of 5 ml/min using a peristaltic pump, and spray-dried at an inlet temperature of 120 °C and an outlet temperature of 65–70 °C. The spray pressure was 4 kg/cm^2. The flow rate of drying air was maintained at the aspirator setting of 10, which indicated that the pressure in the aspirator filter vessel was −25 mbar. The direction of the air flow was the same as that of the sprayed products (Lee et al., 1999; Li et al., 2008).

Table 2
Compositions of valsartan-loaded solid dispersions.

Ingredients (g)	I	II	III	IV	V	VI	VII
Valsartan	3	3	3	3	3	3	3
HPMC	1.5	1.25	1	0.75	0.5	1.5	2
SLS	0	0.25	0.5	0.75	0.25	0.75	1

2.4. Dissolution

The valsartan-loaded solid dispersions and commercial product (equivalent to 80 mg of valsartan powder) were placed in a basket that in turn was placed in a dissolution tester (Shinseang Instrument Co., South Korea). The dissolution tester was equipped with an outer water bath in order to maintain a constant temperature and sink conditions. The dissolution test was performed at 36.5 °C using the basket method at 50 rpm with 900 ml of each dissolution medium: distilled water, 0.1 N HCl (pH 1.2), acetate buffer solution (pH 4.0) and phosphate buffer solution (pH 6.8). At a predetermined interval, 1 ml of the medium was sampled and filtered through a membrane filter (0.45 μm). Then, the concentration of valsartan in the supernatant layer was analysed by HPLC as described below.

2.5. Shape and surface morphology

The shape and surface morphology of the valsartan powder and the valsartan-loaded solid dispersion were examined using a scanning electron microscope (S-4100, Hitachi, Japan). The powders were fixed to a brass specimen club using double-sided adhesive tape and were made electrically conductive by coating with platinum (6 nm/min), in a vacuum (6 Pa), using a Hitachi Ion Sputter (E-1030) for 300 s at 15 mA (Windbergs et al., 2009).

2.6. Thermal and structural characterization

The thermal characteristics of valsartan powder, ingredients, the physical mixture and the valsartan-loaded solid dispersion were investigated using a differential scanning calorimeter (DSC-2010, TA Instruments, USA). The physical mixture was prepared by physically mixing valsartan, HPMC and SLS at the weight ratio of 3/1.5/0.75. Samples of about 2 mg were placed in sealed aluminium pans before being heated under a nitrogen flow (25 ml/min) at a heating rate of 10 °C/min from 20 to 130 °C. Furthermore, the powder crystallinity of the valsartan-loaded solid dispersion was assessed by X-ray powder diffraction (D/MAX-2500, Rigacu, Japan) at room temperature using monochromatic Cu K_α-radiation ($\lambda = 1.54178$ Å) at 100 mA and 40 kV in the region of $10^\circ \leq 2\theta \leq 50^\circ$ with an angular increment of 0.02° per second (Li et al., 2008; Venkateswarlu and Manjunath, 2004).

2.7. Pharmacokinetics

2.7.1. In vivo experiments

Male Sprague-Dawley rats weighing 280 ± 20 g were fasted for 24 h prior to the experiments but allowed free access to water.

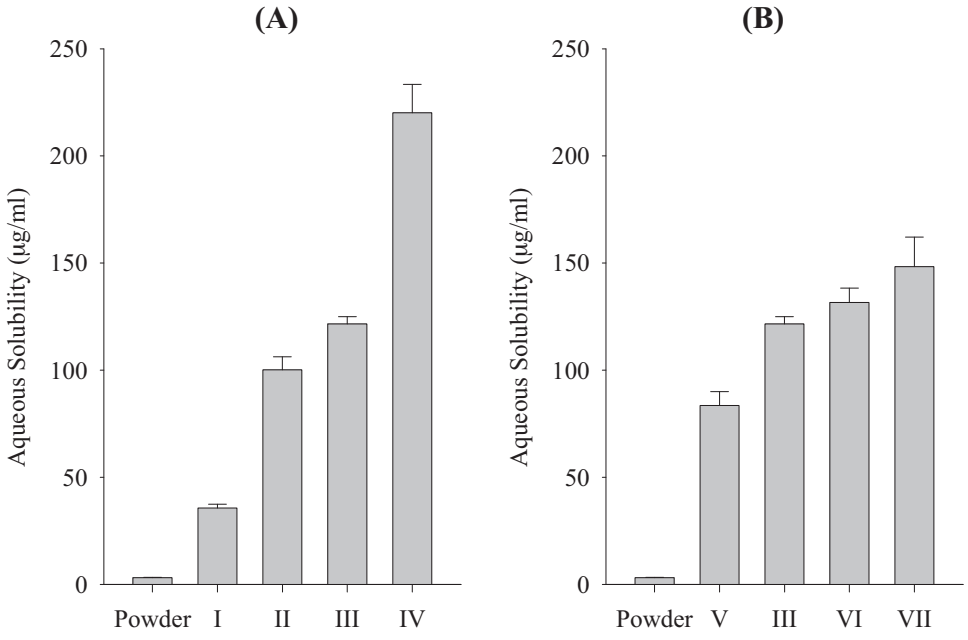

Fig. 1. Effect on the solubility of valsartan: (A), HPMC/SLS ratio; (B) amount of carrier with a constant ratio of HPMC/SLS (2:1). Each value represents the mean ± S.D. ($n = 3$).

Twelve rats were divided into three groups. The rats were administered with the drug powder, commercial product or solid dispersion at a dosages of 10 mg/kg valsartan (Li et al., 2010). All animal care 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). Furthermore, the protocols for the animal studies were approved by the Institute of Laboratory Animal Resources of Yeungnam University.

2.7.2. Administration and blood collecting

Each rat, anaesthetized in an ether-saturated chamber, was secured to a surgical board in the supine position by a thread. A polyethylene tube was inserted into the right femoral artery of the rat. The drug powder and valsartan-loaded microcapsules were placed in small hard capsules (#9, Suheung Capsule Co.; Seoul, South Korea), the commercial product was cut as a capsule-type form for conventional oral administration, and they were orally administered to the rats in each group. Then, 0.4 ml of blood was collected from the right femoral artery at predetermined time intervals and centrifuged at 3000 × *g* for 10 min using a 5415C centrifuge (Eppendorf; Hauppauge, NY, USA) (Li et al., 2008; Newa et al., 2008).

2.7.3. Blood sample analysis

Plasma (0.2 ml) was mixed with 1.5 ml acetonitrile solution containing flurbiprofen (1 μg/ml) as an internal standard. It was then vortexed for 10 min and centrifuged at 4500 × *g* for 10 min. Then, the supernatant layer (1.4 ml) was evaporated using a vacuum dryer (Modul 3180C; Buchon, South Korea) at 60 °C for 1 h. The residue was reconstituted in 60 μl of mobile phase, vortexed for 10 min and centrifuged at 4500 × *g* for 10 min. Then, 20 μl of the supernatant layer was analysed by HPLC (Varian Prostar 210/215; Richmond, CA, USA) equipped with an Inertsil ODS-3 C_{18} column (GL science, 0.5 μm, 15 cm × 0.46 cm i.d.) and a UV detector (Varian Prostar 210/215; Richmond, CA, USA). The mobile phase consisted of acetonitrile and distilled water (6:4, volume ratio), and the pH was adjusted to pH 3.0 with 10% phosphoric acid. The effluent was monitored at a UV absorption wavelength of 247 nm and a flow rate of 1.0 ml/min (Li et al., 2010).

2.7.4. Pharmacokinetic data analysis and statistical analysis

The area under the drug concentration–time curve from zero to infinity (AUC), the elimination rate constant (K_{el}) and half-life ($t_{1/2}$) were calculated using a non-compartmental analysis (WinNonlin; professional edition, version 2.1; Pharsight Co., 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. Levels of statistical significance ($P < 0.05$) were assessed using the ANOVA test among three means for unpaired data. All data are expressed as mean + standard deviation (S.D.) or as the median (ranges) for T_{max}.

3. Result and discussion

3.1. Optimization of valsartan-loaded solid dispersion

A novel solid dispersion system was prepared using a spray drying technique with water, a hydrophilic polymer and a surfactant, without an organic solvent. In order to select a suitable hydrophilic polymer and surfactant as carriers for the valsartan-loaded solid dispersion, the solubility of valsartan in distilled water containing 1% of different hydrophilic polymers or 10% of different surfactants was assessed (Table 1). The aqueous solubility of valsartan is about 3.08 μg/ml, indicating that this drug is poorly water soluble in nature. Among the hydrophilic polymers tested, HPMC showed the maximum drug solubility. Among the surfactants tested, the highest solubility of valsartan was seen in SLS, at about 1500 μg/ml. Thus, HPMC and SLS were selected as carriers for development of the valsartan-loaded solid dispersion.

In conventional solid dispersion systems, the poorly water-soluble drug exists in an amorphous form in polymeric carriers since the drug and polymeric carriers are soluble in the organic solvents that are subsequently eliminated. Furthermore, drugs dispersed in polymeric carriers may achieve high levels of particle size reduction and surface area enhancement, leading to improved solubility and dissolution of the drug (Craig, 2002; Taylor and Zografi, 1997). However, in the novel solid dispersion prepared in this study, relatively small amounts of HPMC and SLS were dissolved in water and the poorly water-soluble valsartan was

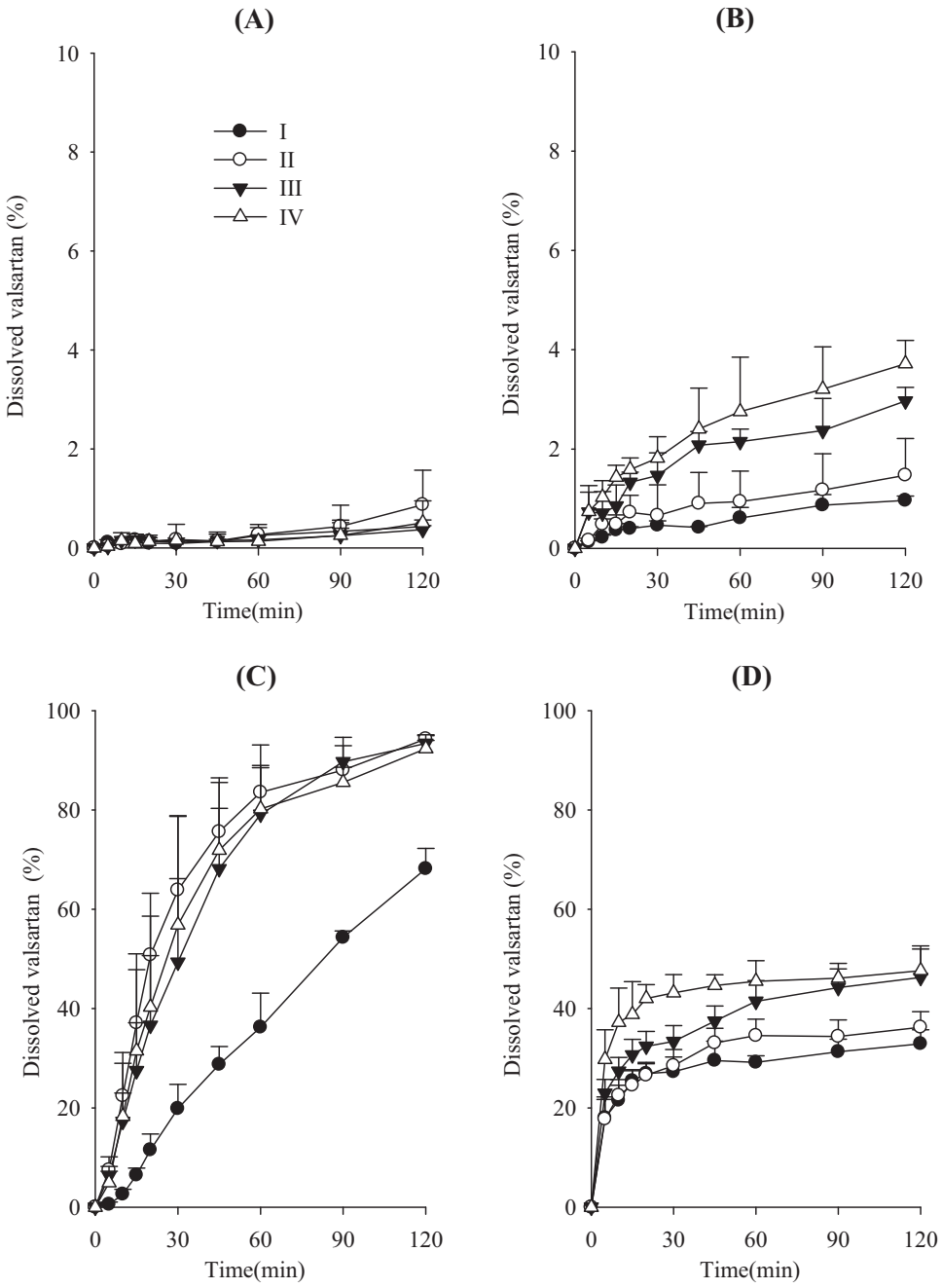

Fig. 2. Effect of the HPMC/SLS ratio on the dissolution of valsartan from the solid dispersions at pH 1.2 (A), pH 4.0 (B), pH 6.8 (C) and in distilled water (D). Each value represents the mean ± S.D. ($n = 6$).

dispersed in this solution (Chutimaworapan et al., 2000; Joe et al., 2010; Oh et al., 2011). The resulting suspension was spray-dried, resulting in a valsartan-loaded solid dispersion. In this novel solid dispersion, the dissolved carriers (hydrophilic polymer and surfactant) were attached to the surfaces of dispersed drug particles. This solid dispersion might convert the hydrophobic drug to a hydrophilic form, resulting in increased solubility and dissolution of the poorly water-soluble drug. Moreover, since water was used as a solvent in this study, unlike in the conventional solid dispersion method, this novel method has several advantages over other methods at an industrial scale, such as the relatively low ratio of carriers to the drug, the lack of crystalline changes, not having to remove an organic solvent and the lack of toxicity or potential explosion of the organic solvent (Kachrimanis et al., 2000; Kaur et al., 2008).

The effect of the ratio of SLS/HPMC with a constant carrier to drug ratio of 1/2 (Table 2, formulations I–IV) on the aqueous solubility of the drug in the solid dispersion is shown in Fig. 1A. The solid dispersions (formulations I–IV) significantly increased the solubility of the drug compared to valsartan powder, irrespective of the ratio of SLS/HPMC. Furthermore, the aqueous solubility of valsartan in the solid dispersion was found to be increased as the ratio of SLS/HPMC increased. Moreover, the effect of the amount of carriers on the aqueous solubility of the drug at a constant ratio of SLS/HPMC (1:2) was investigated by varying the ratio of total carrier to the drug from 0.25 to 1 (Table 2, formulations III and V–VII).

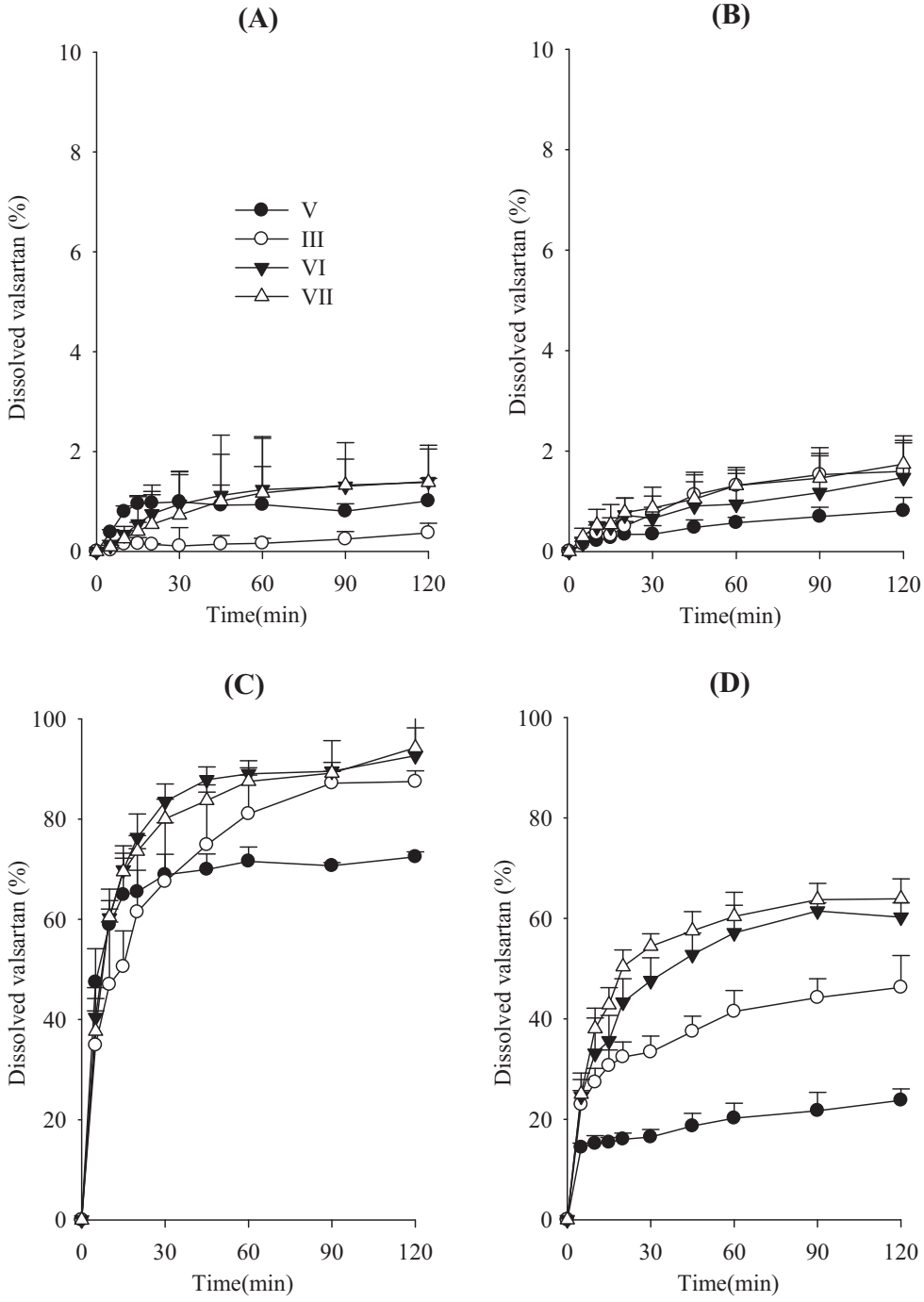

Fig. 3. Effect of amount of carrier with a constant ratio of HPMC/SLS (2:1) on the dissolution of valsartan from the solid dispersions at pH 1.2 (A), pH 4.0 (B), pH 6.8 (C) and in distilled water (D). Each value represents the mean ± S.D. ($n = 6$).

As the ratio of total carrier to the drug increased, the aqueous solubility of valsartan also improved (Fig. 1B, formulations III, V–VII). However, formulations VI and VII showed no significant differences in drug solubility in distilled water.

In order to evaluate the effect of the ratio of SLS/HPMC on the dissolution of the drug in the solid dispersion, dissolution studies on the formulations with various SLS/HPMC ratios from 0 to 1.0, but with a fixed constant ratio of carrier/drug (1/2) (Table 2, formulations I–IV), were performed in various dissolution media (Fig. 2). The dissolution rate of valsartan in the solid dispersion was in the order of pH 1.2 < pH 4.0 < distilled water < pH 6.8. In general, the amount of valsartan released from the solid dispersion was very low for all formulations, which could be explained by the weak acidity of the drug. At pH 1.2, the dissolution rate of valsartan rarely changed within 120 min, irrespective of the ratio of SLS/HPMC (Fig. 2A). As a result, at both pH 4.0 and in distilled water, the dissolution rate of valsartan within 120 min improved with an increased ratio of SLS/HPMC. However, formulations I–IV gave similar dissolution profiles with no significant differences among the formulations tested (Fig. 2B and D).

On the other hand, at pH 6.8, the dissolution rate of the drug was higher in response to the increased ratio of SLS/HPMC (Fig. 2C), suggesting that SLS greatly affected dissolution of the drug. However, interestingly, formulation IV showed a greater aqueous solubility

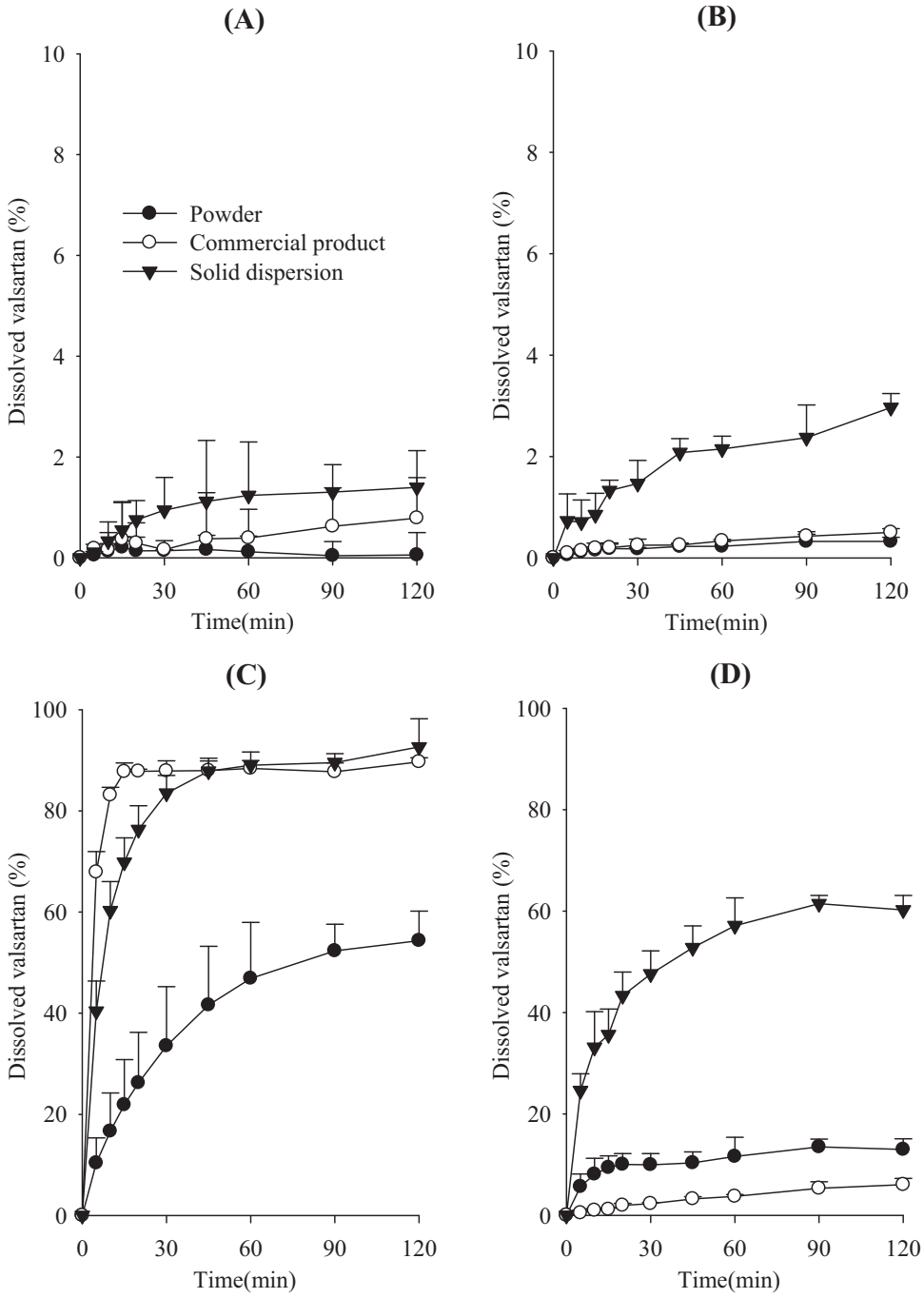

Fig. 4. Dissolution profiles of the drug from capsules containing valsartan powder, the solid dispersion and the commercial product at pH 1.2 (A), pH 4.0 (B), pH 6.8 (C) and in distilled water (D). The solid dispersion was composed of valsartan/HPMC/SLS at a weight ratio of 3/1.5/0.75. Each value represents the mean ± S.D. ($n = 6$).

of valsartan than formulation III although the dissolution rates of these two formulations at both pH 6.8 and in distilled water were not significantly different. Thus, a SLS/HPMC ratio of 1/2 was selected due to its ability to increase both the solubility and dissolution rate of the drug while having the benefit of a lower amount of surfactant.

The effect of the amount of carriers with a constant ratio of SLS/HPMC (1/2) on drug dissolution was evaluated (Table 2, formulations III and V–VII). At both pH 1.2 and pH 4.0, the solid dispersions showed a very limited drug release (Fig. 3A and B). Furthermore, at pH 6.8 (Fig. 3C) and in distilled water (Fig. 3D), the drug dissolution rate of the solid dispersion also increased as the amount of the carrier increased. However, there were no significant differences in the dissolution rates of the drug between formulations VI and VII.

Based on the above results, formulation VI with valsartan/HPMC/SLS at a weight ratio of 3/1.5/0.75, was considered to be the most suitable formulation for the valsartan-loaded solid dispersion since it contained a relatively lower amount of carrier and the highest solubility and dissolution of valsartan.

3.2. Evaluation of valsartan-loaded solid dispersion

The dissolution of the solid dispersion (formulation VI) in each dissolution medium was evaluated in comparison with the drug

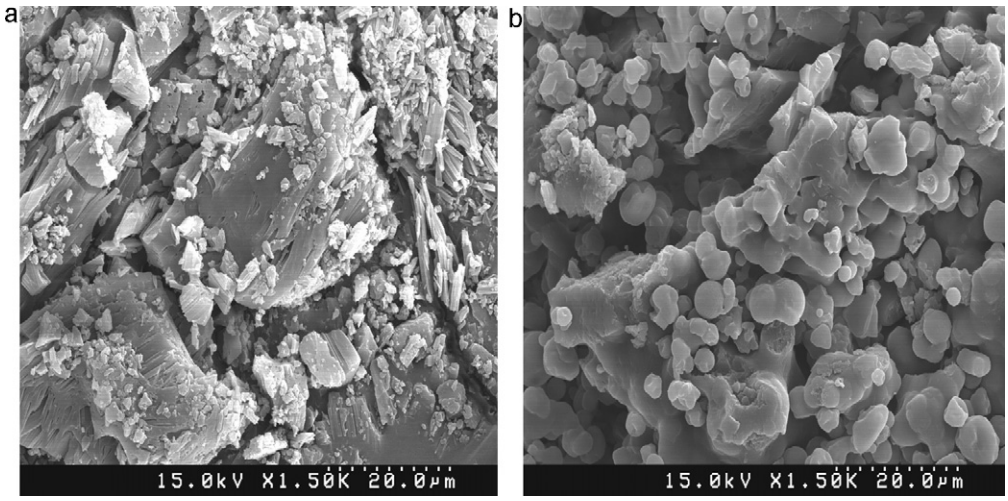

Fig. 5. Scanning electron micrographs (1500×): (A) valsartan powder and (B) solid dispersion.

powder and a commercial product of Diovan®. The solid dispersion gave a higher dissolution rate compared to the drug powder and the commercial product in both pH 1.2 and pH 4.0 buffers. However, these differences were not considered to be meaningful, since the overall amount of drug released within 120 min was extremely low (less than 3.0%) and great intra-individual variations were observed (Fig. 4A and B). The solid dispersion gave a higher initial dissolution rate of the drug compared to the commercial product at pH 6.8 (Fig. 4C), although the difference was not significant. However, from 30 min onwards, the amounts of valsartan dissolved from the former did not significantly differ from those of the latter. Both the dissolution rate in the solid dispersion and commercial product were similar and higher than those of the drug powder after 120 min. In contrast, the dissolution rate of the drug in the solid dispersion in distilled water was significantly higher than the powder or the commercial product (Fig. 4D). After 120 min there were about a 10-fold and 5-fold increase in the rate of drug release from the solid dispersion compared to the commercial product and valsartan powder (60.2 ± 2.9 vs. 6.1 ± 1.2 and 13.0 ± 2.1%), respectively. Thus, this solid dispersion was useful for improving the dissolution rate of the poorly water-soluble valsartan.

The scanning electron micrographs of valsartan powder, the physical mixture and the solid dispersion are shown in Fig. 5. The valsartan-loaded solid dispersion was composed of valsartan/HPMC/SLS at the weight ratio of 3/1.5/0.75. The valsartan powder (Fig. 5A) had a smooth surface and was rectangular and crystalline in shape (Joe et al., 2010; Oh et al., 2011). However, the solid dispersion (Fig. 5B) had a relatively rough surface, suggesting that the hydrophilic polymer and surfactant were attached to the surface of the drug.

The thermal behaviours of the drug powder, ingredients, physical mixture and solid dispersion are shown in Fig. 6. The DSC curve shows that a sharp endothermic peak appeared at about 110 °C for valsartan, corresponding to its melting point and indicating its crystalline nature (Fig. 6A). There were no specific peaks for HPMC from 20 to 130 °C (Fig. 6B). A broad endothermic peak was observed at about 80 °C for SLS (Fig. 6C). Furthermore, unlike in conventional solid dispersions, a sharp peak corresponding to the drug and SLS was also observed in both the physical mixture (Fig. 6D) and solid dispersion (Fig. 6E). Thus, in the DSC curve of the solid dispersion and physical mixture, the characteristic peaks of valsartan were unchanged, indicating the absence of strong interactions between the drug and the carriers during preparation of the solid dispersion. Our results suggest that valsartan was present in an unchanged crystalline state in the solid dispersion (Shrivastava et al., 2009; Walser et al., 1997).

The powder X-ray diffractometry patterns are shown in Fig. 7. Valsartan showed intrinsic peaks at the diffraction angles, showing a typical crystalline pattern (Fig. 7A). No intrinsic peaks were found for HPMC (Fig. 7B), but SLS gave sharp peaks (Fig. 7C). Furthermore, all major characteristic crystalline peaks for the drug and SLS were observed in the solid dispersion and the physical mixture (Fig. 7D and E). Thus, like the DSC results, these result showed that valsartan was present in an unchanged crystalline state in the solid dispersion (Joe et al., 2010; Oh et al., 2011). Our results suggest that the enhanced solubility of valsartan was not due to the transformation of the crystalline form into an amorphous state, but instead were due to the attachment of the carriers to the surface of poorly water-soluble valsartan, converting the hydrophobic drug to hydrophilic form in this solid dispersion.

The pharmacokinetic parameters of valsartan were determined after oral administration of the commercial product, valsartan powder and the solid dispersion. The valsartan-loaded solid dispersion was composed of valsartan/HPMC/SLS at a weight ratio of

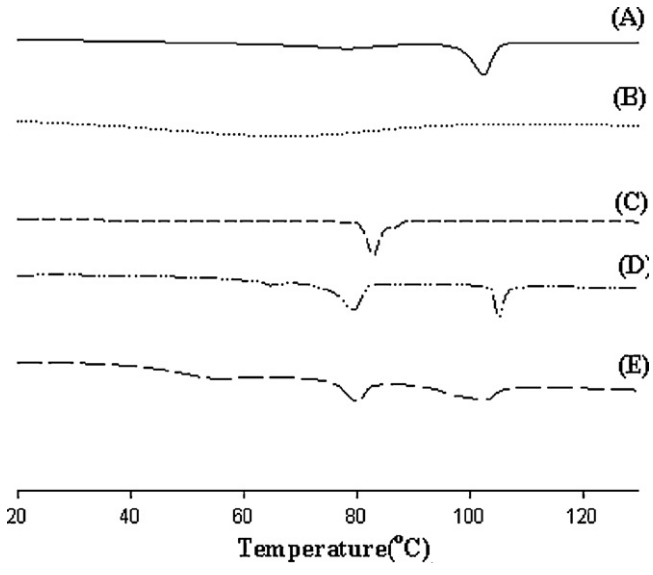

Fig. 6. Differential scanning calorimetric thermograms: (A) valsartan powder; (B) HPMC; (C) SLS; (D) physical mixture; and (E) solid dispersion.

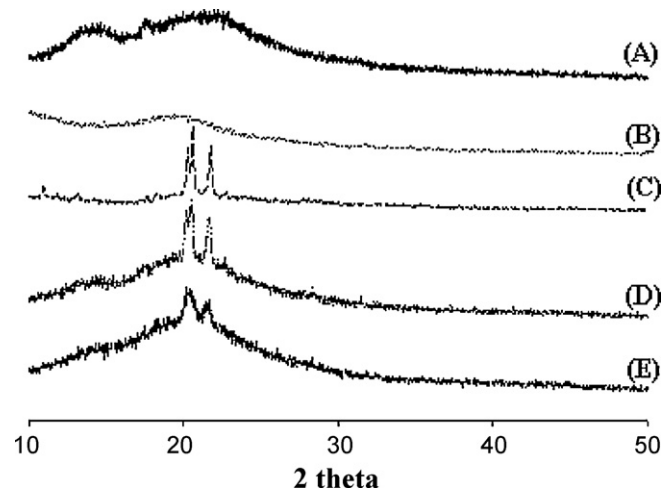

Fig. 7. X-ray powder diffraction: (A) valsartan powder; (B) HPMC; (C) SLS; (D) physical mixture; and (E) solid dispersion.

3/1.5/0.75. Fig. 8 shows the change in mean plasma concentrations of valsartan after oral administration to rats at a dose of 10 mg/kg. The total plasma concentrations of the drug from the solid dispersion were higher than those from the commercial product and valsartan powder. In particular, up to 2 h, the solid dispersion gave significantly higher initial plasma concentrations than the other preparations. Our results suggest that the higher initial plasma concentrations of valsartan might have been due to the increased initial dissolution rate of the drug in the solid dispersion (Oh et al., 2011).

The pharmacokinetic parameters are shown in Table 3. The solid dispersion gave a significantly higher AUC, T_{max} and C_{max} of the drug than valsartan powder or the commercial product ($P < 0.05$). In particular, the AUC of the drug from the solid dispersion was about 1.7- and 2.2-fold higher than from the commercial

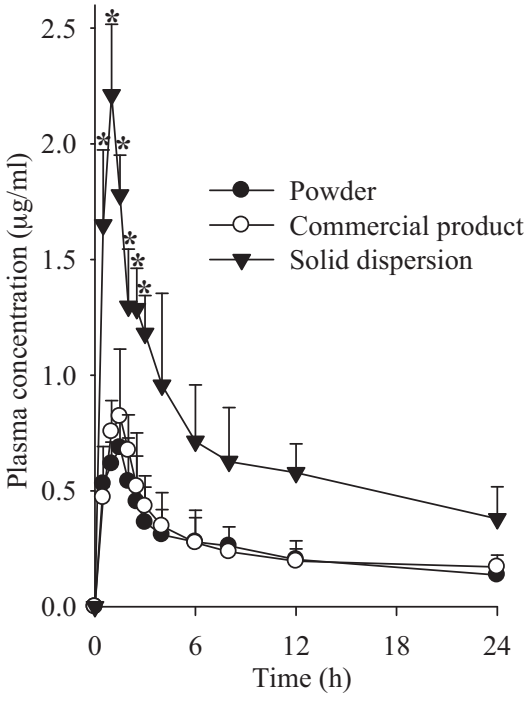

Fig. 8. Plasma concentration–time profiles of the drug after oral administration of the commercial product, pure powder and valsartan-loaded solid dispersion at a dose of 10 mg/kg to rats. Each value represents the mean ± S.D. ($n = 6$). *$P < 0.05$, compared to the powder and commercial product.

Table 3
Pharmacokinetic parameters of valsartan after oral administration of the powder, commercial product and solid dispersion to rats.

Parameters	Powder	Commercial product	Solid dispersion
C_{max} (μg/ml)	0.67 ± 0.10	0.81 ± 0.12	2.54 ± 0.16*
T_{max} (h)	1.05 ± 0.18	1.19 ± 0.11	0.68 ± 0.05*
AUC (h μg/ml)	10.60 ± 0.84	13.66 ± 2.87	23.57 ± 2.61*
$t_{1/2}$ (h)	4.73 ± 1.09	4.69 ± 0.57	5.56 ± 1.49
K_{el} (h^{-1})	0.15 ± 0.03	0.15 ± 0.01	0.12 ± 0.06

Each value represents the mean ± S.D. ($n = 6$).
The solid dispersion was composed of valsartan/HPMC/SLS at the weight ratio of 3/1.5/0.75.
* $P < 0.05$, compared to the powder and commercial product.

product and valsartan powder, respectively. Thus, the enhanced oral bioavailability of valsartan in the solid dispersion might be partly due to the marked increase in the absorption rate of valsartan due to the increased dissolution rate of the drug in the solid dispersion in rats. However, the K_{el} and $t_{1/2}$ values of the drug from the solid dispersion did not significantly differ from those of the commercial product.

Taken together, the significant differences in the plasma concentration–time course of valsartan between the solid dispersion and the commercial product after oral administration might have been associated with the improved aqueous solubility and faster initial dissolution rate in the pH 6.8 buffer or an overall faster dissolution rate in distilled water. Thus, in order to better predict the correlation between the in vitro dissolution performance and pharmacokinetic behaviour in vivo, dissolution studies of the valsartan-loaded solid dispersion should be performed in different types of media. Nevertheless, our results suggest that the valsartan-loaded solid dispersion could be useful for delivering valsartan in a manner that allows fast absorption in the initial phase, leading to better overall absorption.

4. Conclusion

In this study, a novel valsartan-loaded solid dispersion composed of valsartan/HPMC/SLS at a weight ratio of 3/1.5/0.75 was prepared by the spray drying method. Unlike conventional solid dispersion systems, this system took advantage of the relatively low ratio of carrier to drug, where no environmental pollutants were produced and there were no changes to the crystalline form of the drug, which, in return, could help overcome the physical instabilities of phase separation and recrystallization of the amorphous phase associated with conventional solid dispersions. Furthermore, this valsartan-loaded solid dispersion gave higher AUC and C_{max} and shorter T_{max} values compared to the commercial product and drug powder, indicating that it might improve the oral bioavailability of valsartan in rats. Thus, the valsartan-loaded solid dispersion could be useful for delivering poorly water-soluble valsartan with enhanced bioavailability and without crystalline changes.

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