In vitro dissolution and physicochemical characterizations of novel PVP-based solid dispersions containing valsartan prepared by a freeze-drying method

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Abstract: Valsartan (VAL) shows poor oral bioavailability mainly as a result of its low water solubility at low pH. This study is designed to investigate the dissolution properties and physicochemical characteristics of novel PVP-based solid dispersions (SDs) containing VAL. The SDs were prepared with polyvinylpyrrolidone (PVP-K30) as a hydrophilic polymer, sodium hydroxide (NaOH) as an alkalizer, and poloxamer 188 (F68) as a surfactant, without using any organic solvents by a freeze-drying method. The dissolution study was carried out and the physicochemical properties of SDs were also characterized by using differential scanning calorimetry (DSC), fourier transform-infrared (FT-IR) spectroscopy, X-ray diffractometry (XRD) and scanning electron microscopy (SEM). The dissolution rates of SDs were significantly improved at pH1.2 and pH6.8 compared to that of pure drug. The results of physicochemical properties suggested that some interactions between VAL and carriers had occurred in the molecular level and the drug presented in the SDs was amorphous. It was concluded that the novel PVP-based SDs has been successfully prepared by a freeze-drying method, resulting in significant dissolution improvement of VAL.

Keywords: Valsartan, solid dispersion, freeze-drying, dissolution, physicochemical property.

INTRODUCTION

Valsartan (VAL) is an orally effective antihypertensive drug which was angiotensin II receptor antagonist, and it also exhibited high affinity for the type I (AT1) angiotensin receptor (Criscione *et al*., 1993). However, it shows about 23-39 % bioavailability in humans (Israili, 2000), which is mainly due to its low water solubility at low pH (Mbah, 2005). Therefore, it needs to develop a very productive technology for enhancing the solubility of VAL.

Solid dispersion (SD) technology can be used to raise the dissolution rate of poor water soluble drugs thereby enhance their bioavailability (Lee *et al*., 2005). The mechanism of improved dissolution rate has been considered to be the transformation of the drug's crystal lattice, smaller drug particles resulted in enlarging surface area available for drug dissolution and a better wettability exerted by the hydrophilic carrier (Dai *et al*., 2007). Although various methods such as the melting method (Miller *et al*., 2007), the solvent-evaporation method (Yamashita *et al*., 2003) and the solvent-wetting method (Joe *et al*., 2010) have been widely reported for the preparation of SDs, there are still some limitations of using these methods such as the degradation of drug due to the requirement of relatively high preparation temperatures, and the toxicity associated with the use of organic solvents.

Freeze-drying is an industrial method, which can keep the physical and chemical characters and biological activity of products and preserve the long-term stability (Tsinontides *et al*., 2004). Moreover, the drying process has clear influence on the surface of SD powders, which results in enhanced water uptake and wettability. However, few researches on the crystal changes of drug and the molecular interactions between drug and excipients have been reported for the SDs prepared by the freeze-drying technology.

In addition, some drugs whose solubility are dependent on pH can be used in combination with pH modifiers. This process is a common effective tactic to improve the dissolution rate of basic or weakly acidic drug (Riis *et al*., 2007). These pH modifiers can convert the micro-environmental pH and also change the crystal of drug and the drug amorphous form due to the interactions of intermolecular hydrogen bonding (Tran *et al*., 2008). More importantly, pH modifiers such as an alkalizer can enhance the solubility of VAL at high pH, which avoid the use of organic solvent during the preparing process.

In this study, novel PVP-based SDs containing VAL were prepared with polyvinylpyrrolidone K30 (PVP K30) as a hydrophilic polymer, NaOH as an alkalizer, and poloxamer 188 as a surfactant, without using any organic solvents by a freeze-drying method. The dissolution rates of drug from SDs were investigated in simulated gastric fluid (pH 1.2) and intestinal fluid (pH 6.8), respectively. The physicochemical properties of SDs were also characterized using differential scanning calorimetry (DSC), fourier transform-infrared (FT-IR) spectroscopy, X-ray diffractometry (XRD) and scanning electron microscopy (SEM).

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MATERIALS AND METHODS

Materials

Valsartan (VAL) was provided by Eura Pharm Co. (Suwon, Korea). Sodium hydroxide (NaOH) and Monopotassium phosphate were purchased from Sinopharm Chemical Reagent Co. (Shanghai, China). Polyvinylpyrrolidone K30 (PVP K30, Povidone® K30) was supplied by BASF (Shanghai, China). Poloxamer 188 (Lutrol®F68) was kindly provided by Chineway Pharmaceutical Tech. Co. (Shanghai, China). All reagents were of analytical grade except methanol and acetonitrile of chromatographic grade.

Preparation of solid dispersions (SDs) and their physical mixtures (PMs)

The SDs of VAL were prepared using a freeze-drying technique. VAL, PVP K30, and poloxamer 188 were dissolved in 0.8moL/mL NaOH solution with a continuous stirring. The solution was frozen in vials at −70°C and then lyophilized using a lyophilizer (Christ Alpha 1-4, Germany). After the lyophilization, the solid mass was grinded and sieved to obtain a particle size fraction of 125-500 μm. The detailed compositions of SDs are shown in table 1. On the other hand, the PMs were prepared by using a mortar until VAL and excipients well mixed.

Drug content analysis

The SDs equivalent to 80 mg of VAL were dissolved in methanol and filtered through PTFE (0.45μm) membrane filter. The VAL content was determined with high performance liquid chromatography (HPLC, Shimadzu LC-20A, Kyoto, Japan) equipped with UV detection on a Phenomenex® C_{18} (4.6×150 mm, 5μm) column. The separation was use acetonitrile /water/acetic acid (60:40:0.1; v/v) as mobile phase at a flow rate of 1.4mL/min (Cao *et al*., 2012). UV detection wavelength was at 265 nm and column temperature was 35°C. The injection volume was 20 μL.

Scanning electron microscopy (SEM)

Samples were detected by S-4700 (Hitachi, Japan) scanning electron microscope in high vacuum mode. Samples were coated with gold for 180s using a JEOL JFC-1100 sputter coater (Jeol, Japan) under argon atmosphere and then imaged at ambient temperature at 15 kV and observed at magnifications of 500×.

In vitro dissolution study

Dissolution study was conducted using the USP paddle method at 37°C in a RCZ-6B2 dissolution tester (Shanghai, China) at 50 rpm with 900mL of simulated gastric (pH1.2) and intestinal (pH6.8) fluids as dissolution media. The SDs and pure drug (equivalent to 80 mg of VAL) were filled into the hard gelatin capsules respectively and then exposed to the dissolution media for 2h. The samples were taken out at predetermined time points (10, 20, 30, 45, 60, 90 and 120 min) and then filtered through a membrane filter (0.45μm). In order to maintain the constant volume of dissolution media, an equivalent amount of fresh medium was added after each sample (5mL) collection. HPLC method as described above was used for the determination of release quantities *in vitro*.

Differential scanning calorimetry (DSC)

The glass transition temperatures of SDs and other samples were determined by a TA Instruments differential scanning calorimeter (DSC) (SDT2960, Model2010, U.S.A.). All samples (1-2 mg) were accurately weighted and placed in perforated aluminium pans. The samples were heated under nitrogen gas purge from 20 to 200°C at a rate of 10°C/min. The reference pan was left empty and sealed in the same way.

X-ray diffraction (XRD)

XRD patterns were recorded using a X Pert-Pro MPD diffractometer (PANalytical B.V., Netherlands) with a copper anode (Cu Ka radiation, 40 kV, 40 mA). Samples of powder were placed into channeled stages, and the diffraction profiles were measured from 5° to 50° with a scanning speed of 4 °/min in a 2 theta range.

Fourier transform infrared spectroscopy (FT-IR)

FT-IR spectra of VAL and SDs were obtained on a ProStar LC240 spectrophotometer (Thermo Electron Corporation, Waltham, USA). Samples were compressed into KBr disks in a hydraulic press in order to prepare sample-KBr-blends. KBr pellets were characterized from 400 to 4000 cm^{-1} and with a resolution of 2 cm^{-1}.

RESULTS

Preparation and morphology of SDs

The drug contents in SDs were analyzed by HPLC. As shown in table 2, the content of VAL in SD1 and SD2 were 100.45±0.78% and 100.3±1.85%, which indicating that the composition of formulation and preparation process had almost no impact on the drug content in SDs. The SEMs of VAL and SDs are shown in fig. 1. It could be found that VAL alone displayed a fine crystalline structure. Compared to the pure drug, the resulting SDs gave relatively regular shapes with no crystalline powders, suggesting that VAL had already been incorporated into the PVP-based SDs during the freezing-drying process.

In vitro dissolution study

In order to assess the dissolution rate of VAL from SDs, the dissolution study was carried out in two different media. Fig. 2 shows the drug-releasing curve from the pure drug, SD1 and SD2 in simulated gastric (pH 1.2) and intestinal (pH 6.8) fluids, respectively. Both SD1 and SD2

showed remarkably higher dissolution rates of VAL than the pure drug in both media. For the pure drug, the dissolution rates of VAL was around 9% and 55% at 2 h in two different media, showing higher values at pH6.8 than at pH 1.2. On the contrary, both SD1 and SD2 exhibited significantly higher drug release compared to the pure drug. At pH 1.2, dissolution rates reached up to 42% and 58% for SD1 and SD2, respectively (fig. 2A). However, SD1 and SD2 presented similar release profiles with dissolution rates of over 90 % at pH6.8 (fig. 2B).

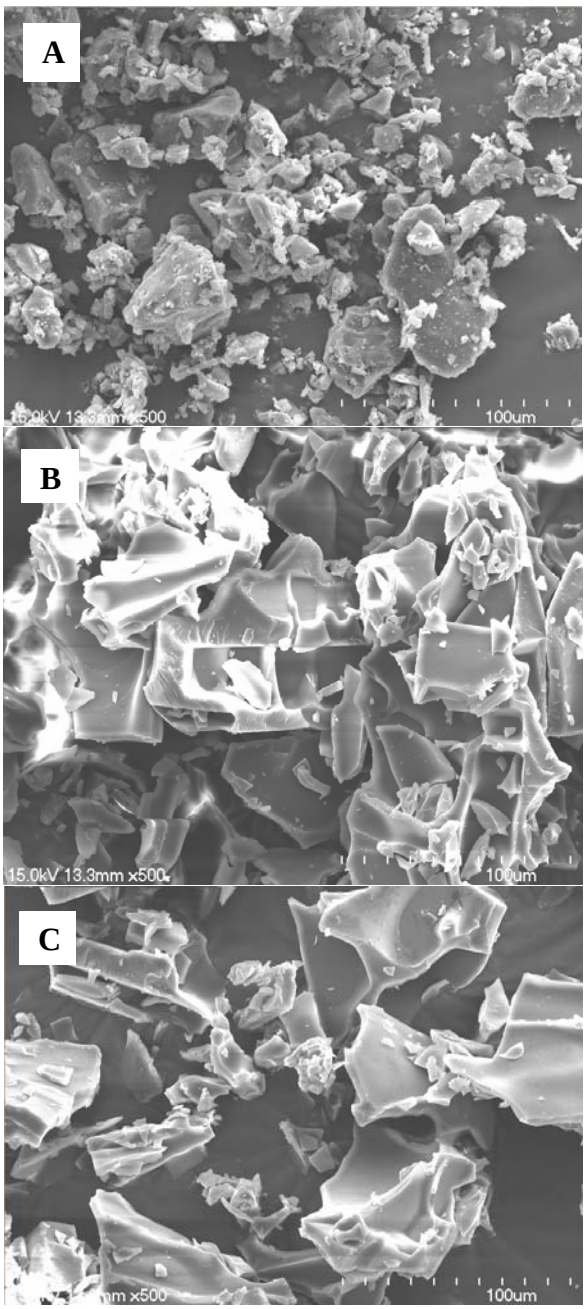

Fig. 1: SEM micrographs of VAL and SDs. (A) VAL, (B) SD1, (C) SD2; each sample is shown at 500× magnification.

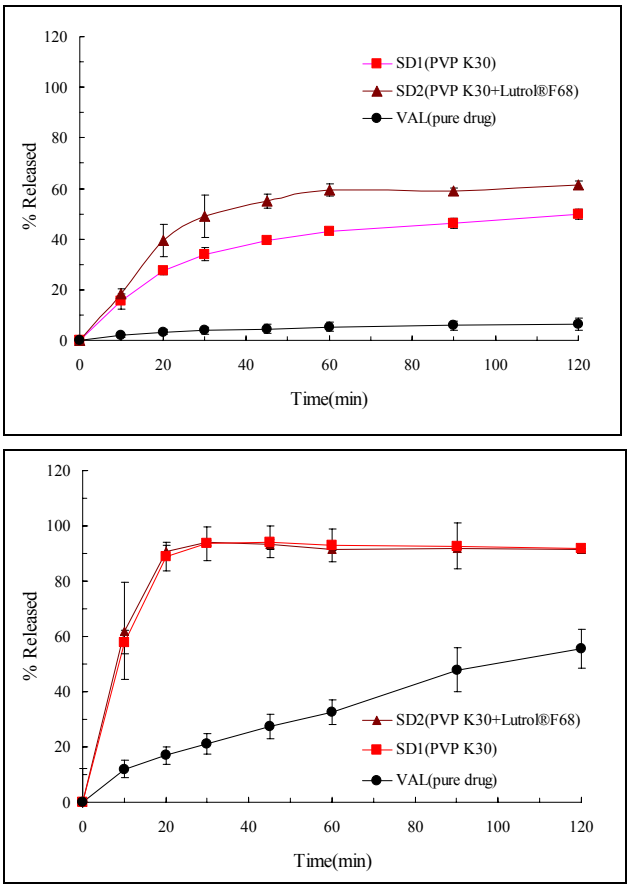

Fig. 2: Dissolution profiles of VAL and SDs at pH1.2 (A) and pH 6.8 (B). Each point represents the mean ± SD (n=3).

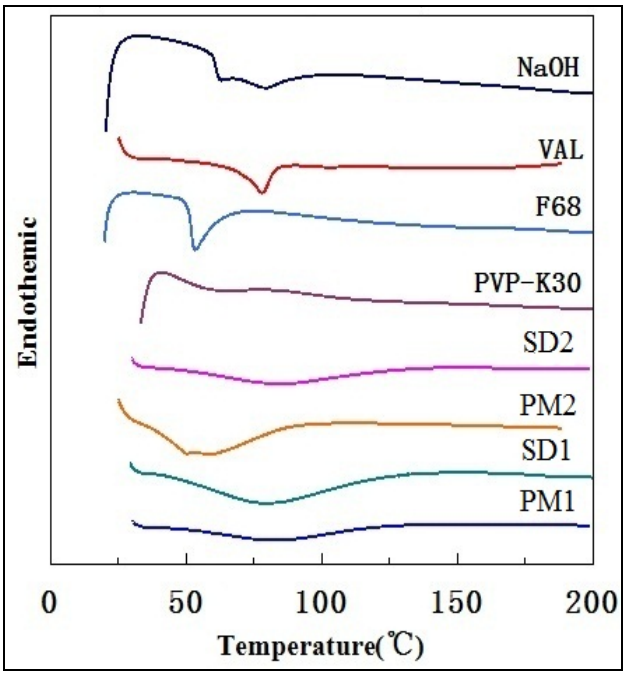

Fig. 3: DSC thermograms of VAL, excipients, SDs and their PMs.

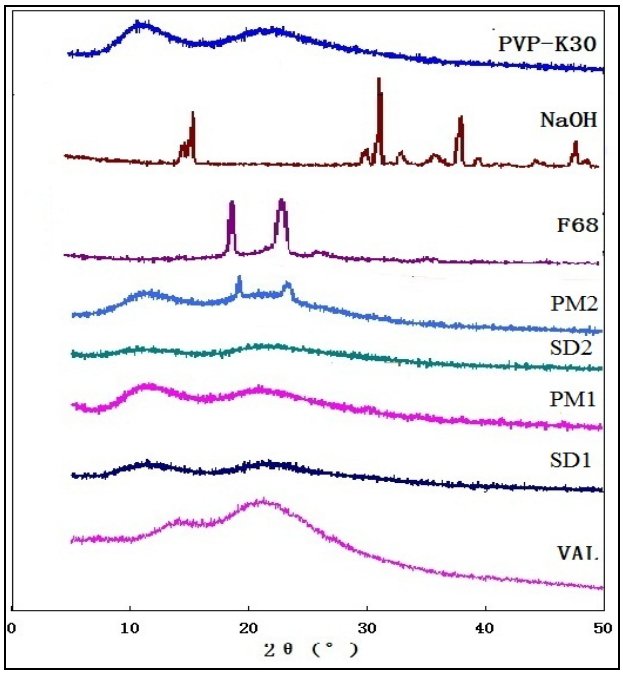

Fig. 4: XRD spectra of VAL, expients, SDs and their PMs

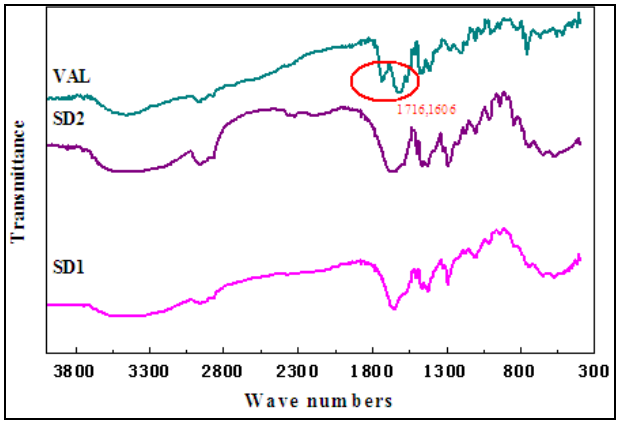

Fig. 5: FT-IR spectra of VAL and SDs

Table 1: Formulation compositions of SDs (unit: g).

Code	VAL	PVP K30	Poloxamer 188	NaOH
SD1	0.8	2.4	-	0.16
SD2	0.8	2.4	0.08	0.16

Table 2: Drug contents of SDs (n=3).

Code	Average drug content (%) (Mean ± SD)
SD1	100.45±0.78
SD2	100.30±1.85

DSC

The DSC thermograms of VAL, excipients, SDs and their PMs are shown in fig. 3. It showed that a sharp endothermic peak of VAL appeared at about 78°C, which was corresponding to the melting point of drug. However, there was no obvious melting drug peak in the thermograms of SDs. On the other hand, the endothermic peak of VAL also disappeared in the PMs.

XRD

The crystallinity of VAL in SDs was confirmed using XRD. The XRDs of VAL, excipients, SDs and their PMs are shown in fig. 4. VAL showed intrinsic crystalline properties with weak diffraction peaks. On the contrary, the VAL characteristic peaks were hardly observed in the SDs, while some peaks could still be observed in their PMs.

FT-IR characterization

FT-IR spectroscopy can detect the structural changes, which can lead to the transformation of chemical bonds between the drug and the carriers. fig. 5 illustrates the FT-IR spectra of SDs and VAL. The VAL spectrum showed two obvious absorption peaks at 1716 cm^{-1} for the carbonyl group C=O and at 1606 cm^{-1} for the C=N band. However, this two absorption bands was found to be changed in the SDs. The C=N band peak was disappeared and the C=O band peak broadened and diminished in PVP-based SDs. Some changes were also found in the vibration of C-H bond at 2962 cm^{-1}.

DISCUSSION

The hydrophilic polymer material PVP has been shown some significant inhibitory effects on the crystallization of drugs, giving amorphous SDs with increased solubilities and dissolution rates of drug (Karavas *et al*., 2007). In this study, novel PVP-based SDs were successfully prepared by a freeze-drying method. In addition, in order to avoid using organic solvents during the preparation of SDs, NaOH was used as an alkalizer to increase the solubility of VAL in polymeric solution.

In vitro dissolution rates of SDs were compared with the pure drug in pH1.2 and pH6.8 media. It could be found that SD1 and SD2 showed remarkably higher dissolution rates of VAL than the pure drug in both media. This could be attributed to the high hydrophilicity and dispersibility of PVP K30 in water (Li *et al*., 2010), and further the pH modulation effect by NaOH incorporated in SDs (Cao *et al*., 2012). In addition, the dissolution rates of VAL from all formula were higher at pH6.8 than at pH1.2 because of high solubility of drug at high pH conditions. On the other hand, the dissolution rate of SD2 containing a surfactant was faster than that of SD1 at pH1.2 (fig.2A), which might be caused by the solubilizing effect of poloxamer 188. Poloxamer 188 could decrease the surface tension between dissolution media and drug particle and hence bringing about additional wettability and solubilizing effect (Mura *et al*., 2005). Moreover, it always existed in an amphiphilic structure, which has the properties to self-assemble into micelles in aqueous solution (Dumortier *et al*., 2006). However, SD1 and SD2 presented no

difference of dissolution rates at pH6.8, showing almost identical values between each other (fig. 2B). This might also be due to the higher drug solubility at high pH. Overall, the drug release of SDs increased significantly which could be related to the decrease in interfacial tension between water insoluble drug and dissolution medium, improved wettability and micro-environmental solubility of drug in SDs (Bley *et al*., 2010). The molecular interactions between VAL and carriers and the changes of VAL crystallinity were evaluated in details as follows with the purpose of studying the mechanism of the increase of drug dissolution in molecular level.

In DSC analysis, there was no melting drug peak in the thermograms of SDs, which indicated that some interactions between VAL and excipients had occurred in the SDs. Moreover, the drug peak also disappeared in the PMs. This might be due to the phenomenon that VAL in PMs was dissolved in the melted polymer solution when thermal analysis was carried out (Yu *et al*., 2010). Because the DSC thermograms were not sufficient to explain the mechanisms of drug dissolution from the different formulations, it needs to be carried out clear investigation through other analyses.

In the XRD study, a large reduction of characteristic peaks or the disappearance of characteristic peaks indicated that most of drug was dissolved in the solid state or that the drug was in an amorphous state (Tran PHL *et al*., 2011). In addition, the crystalline state of drug could be further changed into a partially amorphous form in combination with an alkalizer, resulting in the better enhancement of drug dissolution (Tran TTD *et al*., 2009).

FT-IR spectroscopy can detect the structural changes, which can lead to the transformation of chemical bonds between the drug and the carriers. The changes of chemical band peaks in SDs were due to the interactions between VAL and carriers, which identified with the changes in the XRD patterns. Hence, it confirmed that the drug and carriers had some intermolecular interactions, leading to the changes of drug crystallinity and dissolution (Papadimitriou *et al*., 2012).

CONCLUSIONS

In this study, novel SDs containing VAL were prepared with water as a solvent by a freeze-drying method. It was found that the addition of an alkalizer and a surfactant to SDs was an alternative method to increase the VAL dissolution. The results of DSC, XRD and FT-IR suggest that some interactions such as intermolecular hydrogen bonding between drug and its carriers have occurred in the molecular level and the drug in SDs was amorphous, further resulting in improved dissolution rate of VAL. The current SD system has less potential toxicity and no environmental pollution compared to traditional SD systems, and it can provide a valid strategy for overcoming the problems of low bioavailability and solubility of poorly water-soluble drugs. Moreover, the freeze-drying technique might have wide application for the production of SD formulations in the future.

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