INTRODUCTION
Optimization of the physicochemical properties of a drug molecule is important in the development of solid oral dosage forms. The solid state properties of a drug compound such as the crystalline phase, amorphous, pseudopolymorph and salt will significantly affect the dissolution rate and bioavailability of drug compounds in the systemic circulation. For poorly soluble drugs, in particular, the dissolution process is a rate limiting step for absorption in the gastrointestinal tracts [1]. Some of current approaches have been proposed to improve the dissolution rate and bioavailability of drug compounds including the formation of inclusion complexes with β-cyclodextrin [2], the formation of eutectic mixture and co-crystalline phase [3,4], nanoparticle formulation [5], and amorphous solid dispersion system [6].

Valsartan is one of poorly soluble drugs, an orally active angiotensin II receptor antagonist. It has been used to lower the blood pressure in hypertensive patients. Valsartan is classified as Class II compound according to the biopharmaceutical classification system with high permeability but low aqueous solubility with a dissolution rate dependent absorption [7]. The gastrointestinal absorption of valsartan can be enhanced by increasing its dissolution rate. Several methods have been proven effective to improve dissolution rate of valsartan including formation of self-microemulsifying system [7], nanosuspension [8], formation of mucoadhesive pellets [9], and solid dispersion system [6].

The aim of this study was to prepare and characterize solid dispersion system of valsartan and D(−) mannitol using co-grinding technique, and to investigate the mechanisms responsible for the improved dissolution rate of valsartan from solid dispersion system. MATERIALS AND METHODS
Materials
Valsartan was purchased from Baoji Guokang Bio Technology CO., Ltd (China). D(−)-Mannitol was obtained from Merck (Germany). All other chemicals and solvents were of analytical grade.

Methods
Preparation of solid dispersion
Solid dispersion system of valsartan – D(−) mannitol at various weight ratios (1:1, 1:3, and 1: 5) were prepared by co-grinding technique. The binary mixtures were ground in planetary ball milling apparatus (FRITSCH, pulverisette 7, Germany) for 120 minutes at 500 rpm. Co-ground products were kept in a desiccator until further characterization.

X-ray powder diffraction analysis (XRPD)
XRP diffractograms were recorded using X-ray diffractometer (PAN Analytical The Netherlands). Samples were exposed to Cu-Kα radiation source at 40 kV and 12 mA. The diffraction patterns were obtained in 2θ range of 10-40°.

Differential scanning calorimetry (DSC) analysis
The thermal analysis was performed using TA Mettler Toledo FP90 DSC (Switzerland). Samples of solid dispersion and intact valsartan were weighed approximately 1-2 mg in aluminum pan. The heating was set from 50 to 250°C at a heating rate of 10°C/minute.
Results and Discussion

XRPD method is most commonly used to investigate the solid state properties of any solid active pharmaceutical ingredients materials [3]. In this study, XRPD measurement was performed for each raw materials and solid dispersion samples. XRP diffractograms of intact valsartan and solid dispersions with D-mannitol are shown in Fig. 1. The presence of numerous characteristic peaks in the XRP diffractogram of valsartan in low intensity indicates that valsartan is in semicrystalline state with characteristic peaks appearing at a diffraction angle of 2θ at 10.20, 11.47, 13.69, 20.49, 21.76, 23.17, 26.06 (Fig. 1a). Meanwhile, D(−) mannitol is present as a high crystalline in nature with characteristic peaks appearing at a diffraction angle of 2θ at 10.41, 14.58, 18.66, 20.28, 20.91, 23.34, 28.10, 29.37, 31.67, 33.54, 38.56 (Fig. 1b). After preparation of solid dispersion by co-grinding with D(−) mannitol, characteristic peaks of valsartan were disappeared, only characteristic peaks of D-mannitol were exist (Fig. 1c-e). This indicated that the semicrystalline phase of valsartan was transformed to amorphous state.

Thermal analysis of DSC was performed on intact valsartan, D(−) mannitol, and solid dispersion system to investigate the interaction between valsartan and D(−) mannitol in the solid state [3]. The DSC thermogram of intact valsartan shows a single endothermic peak at 91.07°C, due to the melting of the drug. The DSC thermogram of D(−) mannitol exhibited a single sharp melting endothermic peak at 166.35°C (Fig. 2a and b). The characteristic endothermic peak of valsartan disappeared in all thermograms of solid dispersion system (Fig. 2c-e). Thus, the semicrystalline drug was embedded in the hydrophilic carrier and its solid state properties changed to amorphous one [10]. Previous studies have reported that disappearance of the characteristic endothermic peaks of the valsartan dispersed in Gelucire 50/13 is due to melting of the drug in the matrix [13].

SEM analysis was performed to observe the surface and crystal habit of different samples (intact valsartan, D(−) mannitol and solid dispersions system). SEM of the raw materials revealed that valsartan was characterized by irregular shaped crystals, whereas D(−) mannitol formed big polyhedral shape particles (Fig. 3a and b). Solid dispersions prepared by co-grinding technique represented a reduction of particles size of these binary mixtures (Fig. 3c-e).
This indicated that cogrinding process may decrease particle size of valsartan in this system.

Dissolution rate profile of intact valsartan and solid dispersions are shown in Fig. 4. It is obvious from the figure that all solid dispersions of valsartan showed superior dissolution rate compared with intact valsartan. Solid dispersions of valsartan with D(-)mannitol in different ratios (1:1, 1:3, and 1:5) showed a marked enhancement in the drug dissolution rate, in which about 88.45%, 89.52, and 83.47% of the incorporated valsartan was dissolved within the first 45 minutes from solid dispersions, respectively. Valsartan as a poorly water soluble drug was embedded in the crystal lattice of D(-)mannitol during co-grinding process in the planetary ball mill apparatus. This strategy is a simple way to enhance the drug dissolution. The similar results have been reported for ketoprofen solid dispersion powders prepared with D(-)mannitol and PVP K-30 [14].

CONCLUSION
This study clearly shows that solid dispersion of valsartan with D(-)mannitol prepared by co-grinding technique has successfully improved the dissolution rate compared with intact valsartan. Co-grinding process may cause a phase transformation of the semicrystalline form to the amorphous state.

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