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Oral absorption of a valsartan-loaded spray-dried emulsion based on hydroxypropylmethyl cellulose

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ABSTRACT

The aim of this study was to develop a novel valsartan-loaded spray-dried emulsion based on hydroxypropylmethyl cellulose (HPMC) with enhanced oral absorption. The valsartan-loaded redispersible dry emulsion was prepared by using a high-pressure homogenization and spray-drying process with water, Capryol 90, HPMC, and different surfactants, based on the results of the solubility study. The spray-dried emulsions formed small and homogeneous emulsions with a mean droplet emulsion size ranging from 133.5 to 152.5 nm at the dispersion state in water. The valsartan-loaded redispersible dry emulsion with HPMC/poloxamer 407 showed enhanced pH-independent valsartan release, resulting in a dramatically enhanced oral bioavailability of valsartan compared to the raw material and commercial product. Therefore, a formulation strategy using the redispersible dry emulsion with HPMC/poloxamer 407 is very effective for the development of a new dosage form containing valsartan.

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1. Introduction

The poor water solubility of active pharmaceutical ingredients is a serious problem for drug development. Various formulation strategies such as cocrystals, complexation with a hydrotropic agent or cyclodextrin, solid dispersions, lipid-based formulations, and particle size reduction (nanonization) can be used to overcome this problem [1–5]. Especially, lipid-based drug delivery systems have been increasingly utilized for improving dissolution and solubility, leading to the enhanced bioavailability of poorly water-soluble compounds [6]. Among the lipid-based drug delivery systems, emulsion and self-microemulsifying formulations have been widely used for poorly water-soluble drugs [7,8]. Compared to emulsion, a self-microemulsifying formulation is generally comprised of a relatively high surfactant level for self-emulsifying, which might lead to irritation of the gastrointestinal tract [9]. In addition, emulsion and self-microemulsifying drug delivery system (SMEDDS) formulations exist as liquid forms. Therefore, the conversion from a liquid formulation to a solid form have provided a great advantage for manufacturing solid dosage forms such as tablets and capsules. The dried emulsion is a solid form, and it can be prepared by spray drying the homogeneous oil-in-water (O/W) emulsions containing soluble solid carriers [10,11]. Several commercially available solid carriers have been explored in this context, including dextran, lactose, polyvinyl alcohol (PVA), and hydroxypropylmethyl cellulose (HPMC) [12,13]. Recently, it was reported that a dramatic enhancement in the bioavailability of poorly water-soluble drugs could be achieved when a small amount of surfactant is used in the dry emulsion formulation [14–16].

In this study, a spray-dried emulsion based on HPMC and surfactants was applied to the development of a novel dosage form containing valsartan with enhanced oral absorption. Valsartan, which is (*S*)-3-methyl-2-(*N*-{[2′-(2*H*-1,2,3,4-tetrazol-5-yl)biphenyl-4-yl]methyl}pentanamido)butanoic acid, is clinically used for hypertensive patients as an angiotensin II receptor antagonist [17]. Valsartan is a Biopharmaceutical Classification System (BCS) class II drug that is insoluble in water (3.08 μg/mL) [18]. In this study, a valsartan-loaded redispersible dry emulsion was prepared by using a high-pressure homogenization and spray-drying process with water, oil, surfactant, and HPMC. The physicochemical properties and dissolution profiles of the spray-dried emulsion were

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characterized. In addition, the oral absorption of valsartan from the spray-dried emulsion was evaluated in rats. The relationship between the *in vitro* dissolution data and the *in vivo* pharmacokinetic parameters was also investigated.

2. Materials and methods

2.1. Materials

Valsartan was obtained from Aurobindo Pharma (India). Capryol 90, Capmul MCM, Labrafil M 2125 CS, Maisine, and Gelucire 44/14 were kindly provided by Masung Co. (Korea). Span 20, Tween 20, and Tween 80 were purchased from Duksan Chemical Co. (Korea). HPMC 2910 and irbesartan were purchased from Shin-Etsu Chemical Co. (Japan) and Sigma Chemical Co. (USA), respectively. Poloxamer 407 was obtained from BASF Co. (Germany). For comparison, Diovan® tablets containing 40 mg of valsartan were purchased from the market.

2.2. Solubility studies of valsartan in various excipients

The solubility of valsartan in various excipients and excipient aqueous solutions was measured at 37 ± 0.1 °C. First, an excess amount (1000 mg) was added into a capped glass vial containing 1 mL of the liquid excipient or 5 mL of the excipient aqueous solution. The samples were sonicated for 1 h, followed by incubation in a shaking water bath at 100 rpm for 5 days. After incubation, the samples were centrifuged at 13,000 rpm for 10 min. Then, an aliquot of the sample was immediately filtered through a 0.45-μm syringe filter (Whatman Inc., USA). The filtrate was diluted with acetonitrile and methanol, and the concentration of valsartan was determined by using high-performance liquid chromatography (HPLC) analysis with the Waters™ HPLC system (USA). Twenty microliters of the sample was injected into a C18 analytical column (CAPCELL PAK C18 UG120, 5 μm, 4.6 mm × 150 mm, Shiseido Fine Chemicals, Japan) by using an autosampler. Separation and elution were achieved by using a 60:40 mixture of acetonitrile and water that was adjusted to pH 3.0 with diluted phosphoric acid at an eluent flow rate of 1.0 mL/min. Valsartan was detected by UV absorbance at a wavelength of 247 nm.

2.3. Preparation of the valsartan-loaded spray-dried redispersible emulsion

Based on the solubility study, Capryol 90 and HPMC were selected. First, 2 g or 4 g of valsartan was dissolved in 20 g of Capryol 90. Subsequently, the mixture was added to 150 g of an aqueous solution containing 30 g of HPMC with/without surfactants. The emulsion was pre-homogenized by using an Ultra-Turrax® T25 (IKA, Germany) at 20,000 rpm for 5 min. The obtained emulsion was subsequently homogenized by using a microfluidizer (Nano DeBEE, USA). Initially, 3 cycles at 50 MPa were conducted as a pre-step, and then 10 cycles at 100 MPa were performed. A continuous water cooling system was used during the homogenization process to maintain the temperature of the suspension at around room temperature. The resulting emulsion was dried by spray drying with a Buchi Mini Spray Dryer (B-191, Buchi, Switzerland) under the following conditions: 120–135 °C inlet temperature, 75–80 °C outlet temperature, 2–5 mL/min feed rate, and 5 kPa atomization air pressure.

2.4. Characterization of the valsartan-loaded spray-dried redispersible emulsion

The morphology of the valsartan-loaded spray-dried redispersible emulsion was observed by using scanning electron microscopy (SEM; JSM-7000f, Jeol Ltd., Japan). To measure the droplet size in water, the valsartan-loaded spray-dried redispersible emulsion (equivalent to 1 mg of valsartan) was dispersed by gently mixing it with distilled water (25 mL) for 30 s. The resulting emulsion was incubated for 3 min at room temperature before the samples were withdrawn for droplet size measurement. The particle size distribution and mean diameters of the emulsion were determined by using dynamic light scattering (DLS) techniques (BI-9000; Brookhaven, USA). The particle size of the valsartan-loaded spray-dried redispersible emulsion particles was also determined by using a HELOS laser diffraction analyzer (Sympatec GmbH, Germany) equipped with a RODOS vibrating trough disperser. The dissolution profile of the valsartan-loaded spray-dried redispersible emulsion was obtained by using a USP rotating paddle apparatus (Electrolab, India) at 37 °C and 50 rpm in 900 mL of pH 1.2 (HCl and NaCl) or pH 6.8 (phosphate buffer) medium. Samples corresponding to the equivalent of 40 mg of valsartan were dispersed in the dissolution medium. The samples (3 mL) were collected at pre-determined intervals for analysis and were replaced with 3 mL of fresh dissolution medium after each sample collection. HPLC was used to determine the amount of drug dissolved in each medium after filtration by using a 0.05-μm syringe filter followed by dilution with methanol. Dissolution tests were also performed for the raw material, commercial product, and valsartan-loaded spray-dried redispersible emulsion in 900 mL of each dissolution medium: pH 1.2 (HCl and NaCl), pH 4.0 (acetate buffer), pH 6.8 (phosphate buffer), and water.

2.5. Pharmacokinetics in rats

The study protocol was conducted in compliance with institutional guidelines for the care and use of laboratory animals and was approved by the ethics committee of Kyungsung University. Twenty male Sprague-Dawley rats weighing approximately 250 g (Orient Bio, Inc., Korea) were fasted for 16 h prior to the experiment and were subsequently divided into 4 groups. Each rat received small gelatin capsules (Size 9; Torpac, USA) filled with the raw material, commercial product (cut to a small size), or the valsartan-loaded spray-dried redispersible emulsion (F3 or F7) with 1 mL of water at 5 mg/kg of valsartan by using a dosing apparatus. Blood samples (0.35 mL) were drawn through the retro-orbital plexus at specified time intervals and were placed in heparinized tubes. Plasma samples were obtained by centrifugation at 10,000 rpm at 4 °C for 5 min and were stored at −70 °C until the valsartan concentration was measured. The plasma concentrations of valsartan and irbesartan (internal standard; IS) were analyzed by using a Sciex API 4000 triple quadrupole LC–MS/MS system equipped with a TurboIonSpray™ ionization source operated in the positive ion mode [19]. The ion spray voltage was set at 5000 V. The collision energy (CE), declustering potential (DP), collision exit potential (CXP), and entrance potential (EP) were 25, 81, 8, and 10 V for valsartan and were 30, 60, 16, and 10 V for IS, respectively. Quadrupoles Q1 and Q3 were set to unit resolution and the dwell time was 200 ms. Multiple reaction monitoring (MRM) analysis was conducted by monitoring the precursor ion to product ion transitions from 436.0 → 291.0 *m/z* for valsartan and 429.1 → 207.2 *m/z* for the IS. Data integration was performed with Analyst 1.4.1 software (Applied Biosystems). The HPLC Agilent 1100 Series (Agilent Technologies, Santa Clara, CA, USA) is equipped with a solvent degasser, binary pumps, an autosampler, and a column heater. The chromatography was run on a Phenomenex Kinetex C_{18} column (50 × 2.1 mm, 2.6 μm) with a guard cartridge (C_{18}, 3.0 × 4.0 mm, Phenomenex) at 30 °C. The mobile phase composition was a mixture of MeOH and ammonium acetate (pH 4.0, 5 mM) (70:30, v/v), which was delivered at a flow rate of 0.2 mL/min. Valsartan and the IS were extracted by protein precipitation. Plasma sample aliquots

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