ASIAN JOURNAL OF PHARMACEUTICAL SCIENCES 11 (2016) 744–750

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Preparation and characterization of spray-dried valsartan-loaded Eudragit® E PO solid dispersion microparticles

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ARTICLE INFO

Article history:
Received 8 April 2016
Received in revised form 20 May 2016
Accepted 27 May 2016
Available online 2 June 2016

Keywords:
Valsartan
Eudragit E PO
Solubility
Solid dispersion
Spray-drying

ABSTRACT

The purpose of this study was to develop the immediate release stomach-specific spray-dried formulation of valsartan (VAL) using Eudragit® E PO (EPO) as the carrier for enhancing dissolution rate in a gastric environment. Enhanced solubility and dissolution in gastric pH was achieved by formulating the solid dispersion using a spray drying technique. Different combinations of drug–polymer–surfactant were dissolved in 10% ethanol solution and spray-dried in order to obtain solid dispersion microparticles. Use of the VAL–EPO solid dispersion microparticles resulted in significant improvement of the dissolution rate of the drug at pH 1.2 and pH 4.0, compared to the free drug powder and the commercial product. A hard gelatin capsule was filled with the VAL–EPO solid dispersion powder prior to the dissolution test. The increased dissolution of VAL from solid dispersion microparticles in gastric pH was attributed to the effect of EPO and most importantly the transformation of crystalline drugs to amorphous solid dispersion powder, which was clearly shown by scanning electron microscopy (SEM), differential scanning calorimetry (DSC), and powder X-ray diffraction (P-XRD) studies. Thus, VAL, a potential antihypertensive drug in the form of a solid dispersion microparticulate powder, can be effectively delivered in the immediate release dosage form for stomach-specific drug delivery.

1. Introduction

Approximately 970 million people worldwide have hypertension and thus are at an increased risk for cardiac events [1]. Notably, hypertension is the most common risk factor for cardiovascular disease, exceeding diabetes mellitus, obesity, dyslipidemia, and smoking. Uncontrolled hypertension specifically leads to increased fatal and nonfatal stroke and myocardial infarction, along with heart failure and chronic kidney disease [2]. Antihypertensive therapy with appropriate reduction in blood pressure has been shown to reduce this increased risk [3,4].

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Peer review under responsibility of Shenyang Pharmaceutical University.
http://dx.doi.org/10.1016/j.ajps.2016.05.002

Valsartan (N-pentanoyl-N-{[2'-(1H-tetrazol-5-yl) biphenyl-4-yl] methyl}-L-valine) is a nonpeptide, orally active, specific angiotensin II antagonist acting on the AT1 receptor subtype. It is indicated for hypertension, heart failure and post-myocardial infarction, and is categorized as angiotensin-II receptor blocker [5,6]. According to the Biopharmaceutical Classification System (BCS), valsartan is considered a BCS class II compound with low solubility and high permeability [7–9]. Valsartan is not entirely lipophilic and exhibits pH-dependent solubility, with solubility of 16.8 g/l and 0.18 g/l in phosphate buffer solution (PBS) pH 8.0 and water, respectively. Being a weakly acidic drug (pKa = 4.37), valsartan is generally in the ionized form at higher pH, and thus has greater solubility [10]. At the lower pH in the stomach, valsartan exists mainly in the unionized form, which can facilitate permeation, but drug solubility is the limiting factor. Therefore, a well-designed formulation that improves the solubility and drug release of valsartan at low pH is desirable for promoting more favorable pharmacokinetics of valsartan.

For several decades, methacrylate copolymers with the brand name Eudragit have been used in oral drug delivery systems [11,12]. Eudragit® E PO (EPO) dissolves in the gastric pH because of its basic site containing tertiary amine groups, which are ionized in gastric fluid [4].

Eudragit® E PO is a cationic copolymer based on dimethylaminoethyl methacrylate, butyl methacrylate, and methyl methacrylate, and is basically used in coating and film forming. In recent years, its use has not been limited to only coating, but also for the preparation of new formulations including microcapsules and nanoparticles to improve the solubility of poorly water soluble drugs [13,14].

In the current study, the EPO was used as the polymer for preparation of valsartan-loaded EPO solid dispersion microparticles, basically meant for an immediate drug release in the gastric pH condition. The formulations with different drug/polymer ratio of 1:2, 1:3 and 1:4 were prepared and the corresponding solid dispersion was obtained by spray-drying technique. Poloxamer 407, a nonionic polyoxyethylene-polyoxypropylene copolymer, was used as the surface active agent in the formulations. Scanning electron microscopy (SEM), differential scanning calorimetry (DSC), and powder X-ray diffraction (P-XRD) were performed for physical characterization of the solid dispersion microparticles. The effect of drug/polymer ratio on the drug dissolution was compared with that of the free drug powder and the commercial product.

2. Materials and methods

2.1. Materials

Valsartan was supplied by Hanmi Pharm. Co. (Suwon, Korea). Eudragit® E PO was purchased from Evonik Industries (Darmstadt, Germany). Lutrol® F127 (Poloxamer 407) and Pluronic® F68 (Poloxamer 188) were purchased from BASF Corporation (Ludwigshafen, Germany). Acetic acid was purchased from DC Chemical Co., Ltd. (Namyangju, Korea). Sorbitan monolaurate 20 (Span 20), sorbitan monooleate 80 (Span 80), polysorbate 20 (Tween 20), and polysorbate 80 (Tween 80) were purchased from Duksan Chemical Co. (Ansan, Korea). The commercial product (Diovan®; in a tablet form) was purchased from the market. All other chemicals were of reagent grade and were used without further purification.

Table 1 – Solubility of valsartan in various surfactants.

Surfactants	Aqueous solubility of valsartan (μg/ml)
Poloxamer 188	504.1 ± 105.7
Poloxamer 407	839.3 ± 71.1
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 indicates the solubility of valsartan in distilled water containing 10% surfactant (mean ± S.E., $n = 3$).

2.2. Solubility study in various surfactants

An excess of valsartan powder (about 1 g) was added to 10 ml of 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, followed by shaking in a water bath at 25 °C for 3 days, and then centrifuged at 3000 × g for 10 min (Eppendorf, USA) and filtered through a membrane filter (0.45 μm). HPLC was performed for analysis of the concentration of valsartan in the resulting solution, as described below.

2.3. Preparation of valsartan-loaded EPO solid dispersion microparticles

Valsartan-loaded EPO solid dispersion microparticles were prepared using a lab-scale Buchi 191 nozzle-type mini spray dryer (Flawil, Switzerland). Then, 0.5 g of pre-sieved valsartan and various amounts of Eudragit EPO in the drug–polymer ratio of 1:2, 1:3, and 1:4 was dissolved in 20 ml of ethanol, while various amounts of poloxamer 407 at the constant ratio of 1:2 (poloxamer 407:Eudragit E PO) were dissolved in 180 ml water. Subsequently, valsartan–EPO solution was dispersed in the poloxamer 407 solution under magnetic stirring with the addition of 0.2 ml of acetic acid, which gave a fine homogenous clear solution. Details on the compositions of the valsartan–EPO solid dispersion are shown in Table 2. The resulting clear solutions were immediately spray-dried. The inlet and outlet temperatures were 120 °C and 65–70 °C, respectively. The flow rate was maintained at the speed of 3 ml/min using a peristaltic pump. The spray-pressure was 4 kg/cm^2. Atomization of the drying air was maintained at an aspirator setting of 10, indicating that the pressure in the aspirator vessels was –25 mbar. The direction of air flow was the same as that of the sprayed products [15,16].

Table 2 – Formulations of valsartan-loaded Eudragit-EPO solid dispersion microparticles.

Formulations	F-1	F-2	F-3
Valsartan	0.5	0.5	0.5
Eudragit-E PO	1.0	1.5	2.0
Poloxamer 407	0.5	0.75	1.0

2.4. Determination of drug content

Appropriate weight of valsartan–EPO solid dispersion microparticles equivalent to 50 mg valsartan was dissolved in 50 ml methanol and diluted appropriately to obtain a final concentration of 100 μg/ml. The samples were analyzed by HPLC method. The drug content of the solid dispersions was determined in triplicate.

2.5. HPLC conditions

As reported previously, the HPLC system was composed of a Hitachi HPLC system consisting of a pump (Model L2100), an auto sampler (Model L2200), and an ultraviolet detector (Model L2420). A C_{18} analytical column (Inertsil® ODS-3, 5 μm, 0.46 cm ×15 cm, GL Sciences Inc., Japan) was used. The mobile phase consisted of a mixture of HPLC grade acetonitrile (ACN) and purified water (60:40 v/v), and the pH was adjusted to pH 3.0 with 10% phosphoric acid, and it was filtered under vacuum and degassed before use. The standard and test samples were monitored at a UV absorption wavelength of 247 nm and a flow rate of 1.0 ml/min [17–19]. All experiments were performed in triplicates.

2.6. Solid state characterization

2.6.1. Scanning electron microscopy (SEM)

Morphological analysis was performed using an S-4100 scanning electron microscope (SEM) (Hitachi, Tokyo, Japan). The SEM photomicrographs were taken for comparison of the morphology of pure valsartan powder, Eudragit E PO powder, poloxamer 407, and the valsartan–EPO solid dispersion microparticles. The samples were fixed on a brass-stub using double-sided adhesive tape and made electrically conductive by coating in a vacuum (6 Pa) with platinum (6 nm/min) using a Hitachi Ion Sputter (E-1030) for 120 s at 15 mA. The SEM images were analyzed using an image analysis system (ImageInside Ver 2.32).

2.6.2. Differential scanning calorimetry (DSC)

The thermal analyses of pure valsartan powder, Eudragit EPO powder, poloxamer 407, and the valsartan–EPO solid dispersion microparticles were performed using differential scanning calorimetry (DSC Q200 v24.2 build 107, TA Instruments, New Castle, DE, USA). The samples (about 1.50 mg) were placed in standard aluminum pans, and dry nitrogen was used as effluent gas. All samples were scanned at a temperature ramp speed of 10 °C/min and the heat flow from 40 to 350 °C.

2.6.3. Powder X-ray diffraction (P-XRD)

The P-XRD patterns of pure valsartan powder, Eudragit EPO powder, poloxamer 407, and the valsartan–EPO solid dispersion microparticles were measured using the X'Pert PRO diffractometer (PAN analytical, Netherlands) at room temperature using monochromatic Cu Kα-radiation ($\gamma = 1.5406$Å) at 30 mA and 40 kV over a range of 2θ angles from 10° to 50° with an angular increment of 0.02°/s.

2.7. In vitro dissolution study

Hard gelatin capsules, '0' size (Suheung capsule Co. Ltd., Seoul, South Korea), were filled with the accurately weighed valsartan–EPO solid dispersion microparticles equivalent to 40 mg of valsartan. The dissolution test was performed at 36.5 °C using the US Pharmacopoeia dissolution apparatus 1 (basket method) at 50 rpm with 900 ml of hydrochloric acid buffer pH 1.2, acetate buffer pH 4.0, and phosphate buffer pH 6.8 as the dissolution media; 1 ml of dissolution samples was withdrawn at 0, 5, 15, and 30 min, followed by addition of an equal volume of fresh dissolution media maintained at the same temperature in order to keep the volume of dissolution media constant and to maintain the sink condition [20,21]. The withdrawn samples were filtered through a syringe filter (0.45 μm) and analyzed using HPLC.

2.8. Data analysis and statistical evaluation

All experiments were performed at least three times and the data were expressed as the mean ± standard deviation (S.D.). Levels of statistical significance ($P < 0.05$) were assessed using the Student *t*-test between two means for unpaired data using Microsoft Office Excel 2007.

3. Results and discussion

3.1. Solubility study in various surfactants

For selection of a suitable surfactant for preparation of valsartan–EPO solid dispersion microparticles, the solubility of valsartan in distilled water containing 10% of various surfactants was assessed (Table 1). Among the surfactants tested, poloxamer 407 showed the highest solubility of valsartan, which was approximately 800 μg/ml. Poloxamer 407, known as Lutrol or Pluronic F127, is a hydrophilic non-ionic surfactant used widely in pharmaceutical formulations due to its low toxicity and solubilizing ability. Thus, poloxamer 407 was selected as the surfactant for the development of the valsartan–EPO solid dispersion microparticles.

3.2. Preparation of valsartan–EPO solid dispersion microparticles

Valsartan–EPO solid dispersion microparticles were prepared using a spray drying technique. The schematic diagram of the preparation of valsartan–EPO solid dispersion microparticles is shown in Fig. 1. Briefly, EPO and valsartan at various ratios of 1:2, 1:3, and 1:4 corresponding to formulations F-1, F-2, and F-3, respectively, were dissolved in 20 ml ethanol, while poloxamer 407 was dissolved in 180 ml of water. The ethanolic solution was slowly poured into water containing poloxamer 407 with continuous stirring. To obtain a clear solution, 0.2 ml of acetic acid was added dropwise to the hydro-alcoholic solution, which provided an acidic environment, so that EPO dissolved along with valsartan. Due to the presence of poloxamer 407, the solubility of valsartan in the resultant hydro-alcoholic solution was increased so that the clear solution was obtained. The solution was immediately spray-dried to obtain the white valsartan–EPO solid dispersion microparticulate powder. The results of analysis for the drug content (%) considering the quantity of powders equivalent to 50 mg valsartan

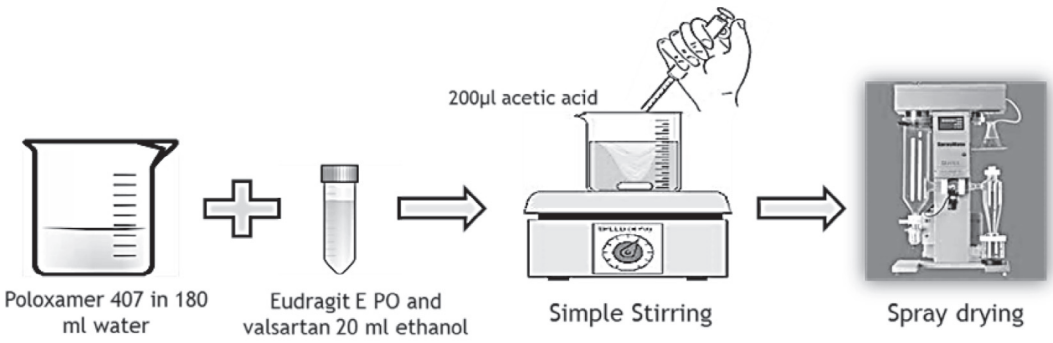

Fig. 1 – Schematic diagram of preparation of valsartan-loaded Eudragit E PO microparticles.

were 100.7%, 99.5%, and 99.2 % for formulations F1, F2, and F3, respectively.

3.3. *Solid state characterization of valsartan–EPO solid dispersion microparticles*

Various tests including SEM analysis, DSC measurements, and P-XRD calorimetry were performed for the solid state characterization of valsartan–EPO solid dispersion microparticles. The morphology of the representative SEM images of the valsartan powder, Eudragit E PO, poloxamer 407, and valsartan–EPO solid dispersion microparticles (formulation F-1, F-2 and F-3) is shown in Fig. 2. The SEM micrographs of the valsartan powders (Fig. 2A) showed irregular-shaped crystalline particles, whereas Eudragit EPO and poloxamer 407 (Fig. 2B and 2C) were observed as amorphous smooth particles. On the other hand, formulations F-1, F-2 and F-3 were spherical in shape with smooth morphology and particle size than 5 µm, as shown in Fig. 2D, 2E, and 2F. However, among the three formulations, F-2 showed good particle size distribution with relatively more uniform size and spherical morphology, which may be attributed to the optimum weight ratio of the valsartan/Eudragit EPO/poloxamer 407 of 0.5/1.5/0.75.

The DSC thermographs of valsartan powder, Eudragit EPO, poloxamer 407, and valsartan–EPO solid dispersion microparticles are shown in Fig. 3. Valsartan powder showed the characteristic single sharp endothermic peak at approximately 110 °C, corresponding to its melting point and crystalline nature. No distinct peaks were observed for Eudragit EPO in the range of 40–150 °C. The broad endothermic peak of poloxamer 407 was observed at approximately 50 °C, while no peak was observed in the case of valsartan–EPO solid dispersion microparticles corresponding to the strong molecular dispersion between the valsartan and the Eudragit EPO.

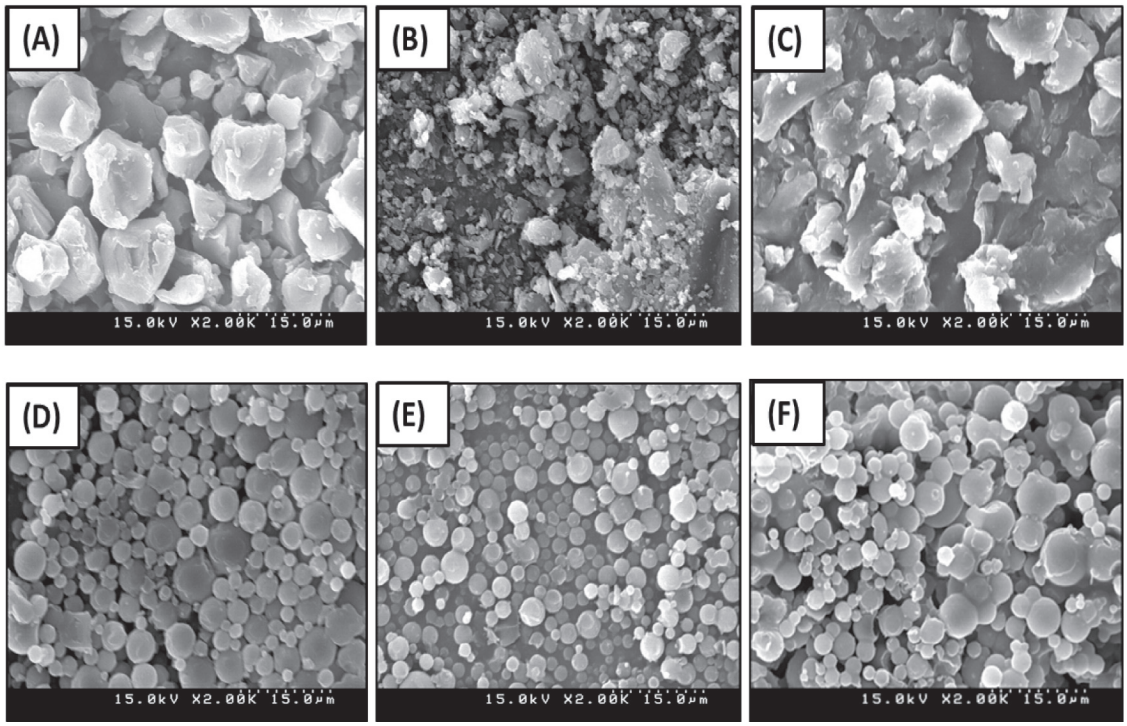

Fig. 2 – Scanning electron micrographs of (A) Eudragit E PO, (B) valsartan powder, (C) Poloxamer 407, (D) F-1, (E) F-2, and (F) F-3.

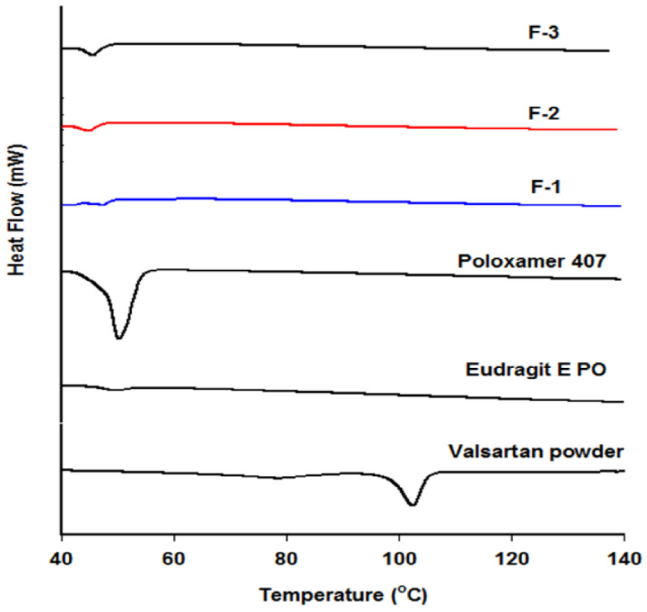

Fig. 3 – Differential scanning calorimetric thermograms of valsartan powder, Eudragit E PO, poloxamer 407, F-1, F-2, and F-3.

However, a small peak corresponding to that of poloxamer 407 was observed in all formulations with the intensity proportional to the increase in the poloxamer 407 content.

The powder X-ray diffractometry pattern of VAL showed intrinsic peaks at the diffraction angles, showing a typical crystalline pattern (Fig. 4). No intrinsic peaks were observed in the case of Eudragit EPO, but poloxamer exhibited two sharp peaks at the angles between 15° and 25°. Formulations F-1~F-3 showed the characteristic peaks of poloxamer 407, but of

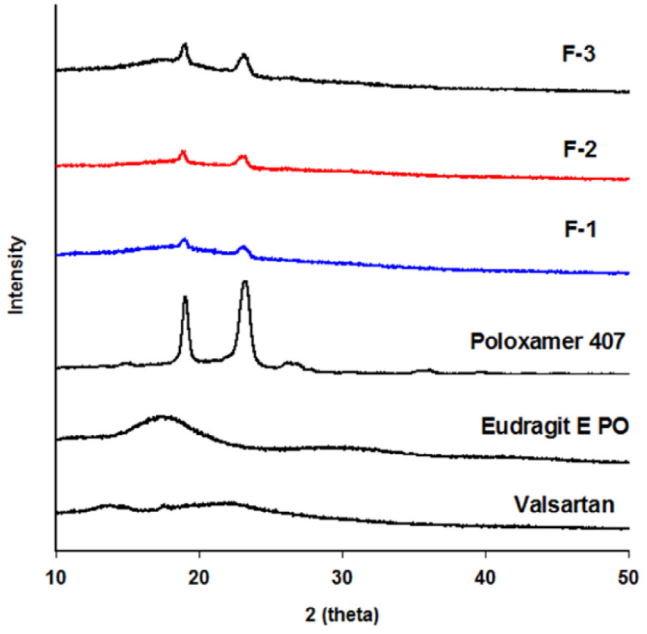

Fig. 4 – Powder X-ray diffractometry patterns of valsartan powder, Eudragit E PO, poloxamer 407, F-1, F-2, and F-3.

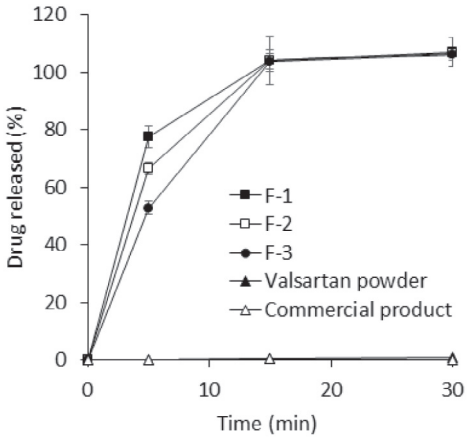

Fig. 5 – *In vitro* dissolution profiles of valsartan powder, formulations F-1, F-2, F-3, and commercial product at hydrochloric acid buffer pH 1.2. Each value represents the mean ± standard deviation ($n = 3$).

reduced intensity proportional to the amount of the poloxamer 407 present in the formulations. Thus, both the DSC and the XRD results demonstrated that valsartan strongly interacted with both Eudragit EPO and poloxamer 407 and was transformed itself into the molecularly dispersed form, which was obtained as the valsartan–EPO solid dispersion microparticles.

3.4. In vitro *dissolution study*

The *in vitro* dissolution study of valsartan–EPO solid dispersion microparticles, free drug powder and the commercial product was performed in hydrochloric acid buffer pH 1.2, acetate buffer pH 4.0, and phosphate buffer pH 6.8. As shown in Fig. 5, the % release of valsartan from the valsartan–EPO solid dispersion microparticles in hydrochloric acid buffer pH 1.2 was almost 100% in 15 min, while that of free valsartan powder and the commercial product were less than 1.0% in 15 min. The % release of valsartan from the valsartan–EPO solid dispersion microparticles in acetate buffer pH 4.0 was almost 100% in 30 min, while that of free valsartan powder and the commercial product were less than 1.0% in 30 min (Fig. 6). The % release of valsartan from the valsartan–EPO solid dispersion microparticles in phosphate buffer pH 6.8 was almost 20%, while that of free valsartan powder and the commercial product were more than 28% and 90%, respectively, in 30 min. The absorption window of valsartan is basically in the region of the stomach, because it is largely present in a unionized form in the acidic pH and better absorbed from the acidic pH of the stomach than the basic pH condition of the intestine which can facilitate permeation; however, drug solubility is the limiting factor [9,22]. Our results clearly demonstrated that the release of valsartan was specifically completed in the gastric region (pH ranging from 1.2 to 4.0) corresponding to the enhanced solubility of valsartan using Eudragit E PO as the solid dispersion carrier. Therefore, use of valsartan–EPO solid dispersion microparticles as the delivery system for the immediate release of valsartan in the gastric environment was advantageous, leading to rapid absorption and immediate pharmacological action (Fig. 7).

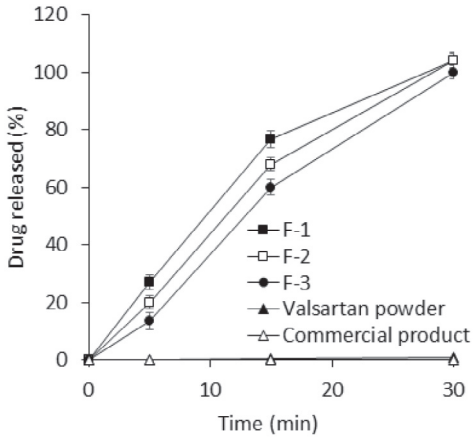

Fig. 6 – *In vitro* dissolution profiles of valsartan powder, formulations F-1, F-2, F-3, and commercial product at acetate buffer pH 4.0. Each value represents the mean ± standard deviation ($n = 3$).

4. Conclusion

In this study, the immediate release valsartan–EPO solid dispersion microparticles was developed by spray drying technique. The solid-state characterization such as SEM, DSC, and P-XRD studies clearly demonstrated smooth spherical morphology and strong molecular dispersion between valsartan, Eudragit EPO and poloxamer 407. In addition, valsartan–EPO solid dispersion microparticles exhibited an immediate release dissolution profile in pH 1.2 and pH 4.0, compared with the free valsartan powder. Therefore, the developed formulation with immediate drug release profile could be an effective drug delivery system in the treatment of hypertension.

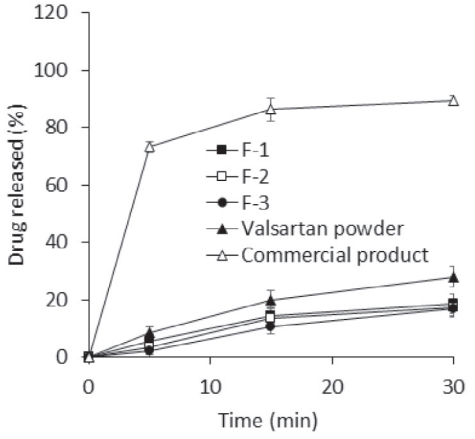

Fig. 7 – *In vitro* dissolution profiles of valsartan powder, formulations F-1, F-2, F-3, and commercial product at phosphate buffer pH 6.8. Each value represents the mean ± standard deviation ($n = 3$).

Acknowledgment

This research was supported by the National Research Foundation of Korea (NRF) grant funded by the Korea government (MSIP) (No. 2015R1A2A2A01004118 and No. 2015R1A2A2A04004806).

REFERENCES

[1] Taylor JY, Sun YV, Hunt SC, et al. Gene-environment interaction for hypertension among African American women across generations. Biol Res Nurs 2010;12:149–155.
[2] Messerli FH, Williams B, Ritz E. Essential hypertension. Lancet 2007;370:591–603.
[3] McVeigh GE, Flack J, Grimm R. Goals of antihypertensive therapy. Drugs 1995;49:161–175.
[4] Wang SL, Lin SY, Chen TF, et al. Eudragit E accelerated the diketopiperazine formation of enalapril maleate determined by thermal FTIR microspectroscopic technique. Pharm Res 2004;11:2127–2132.
[5] Criscione L, de Gasparo M, Buhlmayer P, et al. Pharmacological profile of valsartan: a potent, orally active, nonpeptide antagonist of the angiotensin II AT1-receptor subtype. Br J Pharmacol 1993;110:761–771.
[6] Markham A, Goa KL. A review of its pharmacology and therapeutic use in essential hypertension. Drugs 1997;54:299–311.
[7] Dressman JB, Reppas C. In vitro–in vivo correlations for lipophilic, poorly water-soluble drugs. Eur J Pharm Sci 2000;11:S73–S80.
[8] Brunella C, Cleelia DM, Maria I, et al. Improvement of solubility and stability of valsartan by hydroxypropyl-β-cyclodextrin. J Incl Phenom Macro 2006;54:289–294.
[9] Saydam M, Takka S. Bioavailability file: valsartan. FABAD J Pharm Sci 2007;32:185–196.
[10] Flesch G, Muller P, Lloyd P. Absolute bioavailability and pharmacokinetics of valsartan, an angiotensin II receptor antagonist, in man. Eur J Clin Pharmacol 1997;52:115–120.
[11] Dittgen M, Durrani M, Lehmann K. Acrylic polymers. A review of pharmaceutical applications. STP Pharm Sci 1997;7:403–437.
[12] Skalsky B, Petereit HU. Chemistry and application properties of polymethacrylate systems. In: Mc Ginity JW, Felton LA, editors. Aqueous polymeric coatings for pharmaceutical Dosage Forms. 3rd ed. New York, NY: Informa Healthcare USA, Inc.; 2008. p. 237–278.
[13] Tang J, Xu N, Ji H, et al. Eudragit nanoparticles containing genistein: formulation, development, and bioavailability assessment. Int J Nanomedicine 2011;6:2429–2435.
[14] Moustafine RI, Bukhovets AV, Sitenkov AY, et al. Eudragit E PO as a complementary material for designing oral drug delivery systems with controlled release properties: comparative evaluation of new interpolyelectrolyte complexes with counter charged Eudragit L100 copolymers. Mol Pharm 2013;10:2630–2641.
[15] Newa M, Bhandari KH, Li DX, et al. Preparation, characterization and in vivo evaluation of ibuprofen binary solid dispersions with poloxamer 188. Int J Pharm 2007;343:228–237.
[16] Marasini N, Tran TH, Poudel BK, et al. Fabrication and evaluation of pH-modulated solid dispersion for telmisartan by spray-drying technique. Int J Pharm 2013;441:424–432.
[17] Yan YD, Sung JH, Kim KK, et al. Novel valsartan-loaded solid dispersion with enhanced bioavailability and no crystalline changes. Int J Pharm 2012;422:202–210.

[18] Poudel BK, Marasini N, Tran TH, et al. Formulation, characterization and optimization of valsartan self-microemulsifying drug delivery system using statistical design of experiment. Chem Pharm Bull 2012;60:1409–1418.
[19] Li H, Wang Y, Jiang Y, et al. A liquid chromatography/tandem mass spectrometry method for the simultaneous quantification of valsartan and hydrochlorothiazide in human plasma. J Chromatogr B 2007;852:436–442.
[20] Choi H, Oh Y, Kim C. In situ gelling and mucoadhesive liquid suppository containing acetaminophen: enhanced bioavailability. Int J Pharm 1998;165:23–32.
[21] Yong CS, Li DX, Oh DH, et al. Retarded dissolution of ibuprofen in gelatin microcapsule by cross-linking with glutaraldehyde. Arch Pharm Res 2006;29:520–524.
[22] Siddiqui N, Husain A, Chaudhry L, et al. Pharmacological and pharmaceutical profile of valsartan: a review. J Appl Pharm Sci 2011;1:12–19.