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고체 분산체를 이용한 발사르탄의 용출 특성 개선

Improving dissolution characteristics of valsartan using solid dispersion technique

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고체분산체를 이용한 발사르탄의 용출 특성 개선

임 영 빈

지 도 교 수: 한 효 경

조선대학교 대학원 약학과

심혈관계 질환에 주로 쓰이는 발사르탄은 낮은 생체이용률을 보여주며 이는 low pH 에서의 낮은 용해도가 하나의 원인이 된다. 그러므로 본 연구에서는 발사르탄의 용해도를 향상시키는 계면활성제를 검색하고, 고체분산체 기술을 이용하여 발사르탄의 low pH 에서의 용출률을 개선하고자 하였다. 발사르탄의 용해도 향상을 위해 계면활성제로 폴록사머 407, 크레모포어, 솔루톨, SLS, 트윈 80 등을 사용하였는데, 이 중에서 폴록사머 407 이 낮은 pH 에서 가장 좋은 효과를 나타내었다. 따라서 폴록사머 407 을 이용하여 발사르탄의 고체분산체를 제조하였다. 용매법을 이용하여 제조된 고체분산체중에서 약물과 폴록사머 407 의 비율이 1:3 또는 1:5 일 경우에, 용출률의 pH 의존성이 현저하게 감소되고

낮은 pH 에서도 좋은 용출양상을 보여주었다. Powder X-ray diffraction (PXRD)와 differential scanning calorimetry (DSC) 분석 결과는 고체분산체중의 약물이 무정형 상태임을 나타내었다. 결론적으로, 본 연구결과는 폴록사머 407 을 이용한 고체분산체가 낮은 pH 에서 발사르탄의 용해도와 용출특성을 효과적으로 개선할 수 있음을 보여주었다.

Abstract

Improving dissolution characteristics of valsartan using solid dispersion technique

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Valsartan, a drug for the treatment of cardiovascular disease, exhibited low bioavailability which should be caused by, at least in part, limited solubility at low pH. Therefore, the aim of this study was to investigate the effect of surfactant on the solubility of valsartan and improve the dissolution profiles of valsartan via the preparation of solid dispersion (SD). Among tested surfactants including micronized poloxamer 407, creomophor, solutol, SLS and tween 80, micronized

poloxamer 407 appeared to be most effective to enhance the solubility of valsartan at low pH. Thus, SD of valsartan was prepared by using poloxamer 407. The dissolution profiles of SDs (Drug:poloxamer = 1:3 or 1:5) were not pH-dependent and they showed desirable dissolution profiles over the pH range of 1.2 to 7.0. The results of powder X-ray diffraction (PXRD) and differential scanning calorimetry (DSC) indicated that the drug in SDs was in the amorphous form. In conclusion, SDs containing micronized Poloxamer 407 appeared to be useful for improving the dissolution rate as well as solubility of valsartan at low pH.

1. Introduction

Valsartan, (S)-N-valeryl-N-([2'-(1H-tetrazol-5-yl)biphenyl-4-yl]-methyl)-valine, is a specific competitive antagonist of the angiotension II receptor and widely used for the treatment of hypertension [1]. Valsartan has low bioavailability of about 23~39% in humans, which might be related to its poor aqueous solubility [2]. The solubility of valsartan appears to be pH-dependent and exhibits very low solubility at acidic condition [3]. Therefore, improving the solubility of valsartan at low pH may lead to enhanced bioavailability of valsartan.

In order to improve the solubility and dissolution rate of a poorly water soluble drug, solid dispersion (SD) with hydrophilic polymers such as hydroxypropyl-cellulose and polyvinyl-pyrrolidone was widely used as a common method [4, 5]. A drug dispersed in carriers has peculiar properties such as amorphous form of drug crystallinity and reduced particle size which leads to better wettability due to surface

area enhancement. Therefore, in many cases, SD enhances the dissolution profiles of poorly soluble drugs [6]. In addition, there is evidence that surfactant enhances the solubility and dissolution rate of poorly soluble drugs [7-9]. Therefore, the present study aimed to (i) investigate the effect of surfactant on the solubility of valsartan and (ii) improve the dissolution profiles of valsartan at low pH via the preparation of solid dispersion. Effect of surfactants such as micronized poloxamer 407, creomophor, solutol, SLS and tween 80 on the solubility of valsartan was examined and based on the solubility data, SD of valsartan with poloxamer 407 was prepared by using the solvent method. There are two major preparation methods for solid dispersion including the melting method and the solvent method [9-10]. However, our preliminary data indicated the probability of incomplete miscibility of the drug and the carrier in the molten form, so that SD of valsartan

was prepared by using solvent method and subsequently, their dissolution profiles were evaluated at various pH.

2. Materials and Methods

Materials: Valsartan was kindly provided by Samil Pharm. Co., Ltd. Micronized poloxamer 407, creomophor and solutol were obtained from BASF Korea, Ltd. Sodium lauryl sulfate and tween 80 were purchased from Sigma Co. (St. Louis, MO).

Preparation of physical mixture: Physical mixture was obtained by simply mixing valsartan and Micronized Poloxamer 407 using a spatula in a mortar. The weight ratio of drug and polymer was kept at 1:0.5, 1:1, 1:3 and 1:5.

Preparation of solid dispersion by solvent method: Valsartan and micronized Poloxamer 407 were first dissolved in a 95% ethanol. The amount of 95% ethanol used varied depending on the weight of drug

and polymer. After the complete dissolution, the solvent was removed under vacuum at room temperature. The weight ratios of drug to each carrier include 1:0.5, 1:1, 1:3 and 1:5.

Solubility studies: Solubility of valsartan was determined by placing an excess of valsartan (100mg) in 15mL of water under shaking at room temperature for 24h. In addition, pH dependency of valsartan solubility was determined at pH 1.2, pH 6.8 and pH 10. After equilibration, the supernatant was filtered and the drug concentration in the filtrate was measured by using HPLC assay. Valsartan solubility was also determined in the presence of 0.5%, 1%, 2% and 4% of various surfactants (micronized poloxamer 407, creomophor, solutol, SLS and tween 80)

Valsartan release from physical mixture (PM) and solid dispersion (SD) with micronized Poloxamer 407: The released amounts of valsartan from PM and SD were determined in 1mL of

water and pH1.2 buffer, respectively. The PM and SD equivalent to 2mg of valsartan were used. After shaking at room temperature for 12hr, 24hr, 48hr and 72hr, the concentration of valsartan was determined as described above.

In vitro dissolution study: Dissolution studies were conducted using USP paddle method at 50rpm or 100rpm using 300mL of dissolution medium at 37℃ in a DST 600A dissolution tester (Fine Science Institute, South Korea). For all the prepared SDs (drug-polymer=1:0.5, 1:1, 1;3 and 1;5), the sample equivalent to 6mg of valsartan was exposed to two different media (pH1.2 buffer and water) for 6 hr. The samples were withdrawn at predetermined time intervals (5, 10, 15, 30, 45, 60, 120, 180, 240, 300 and 360 min) and then analyzed by using HPLC assay. After each sample collection, an equivalent amount of fresh medium was added to maintain a constant dissolution volume. Dissolution studies were also conducted at pH 4.0 and pH 6.8 with the

SD having the drug-polymer ratio of 1:5.

HPLC analysis: Valsartan was analyzed by the HPLC assay. Naproxen was used as the internal standard for the assay. The chromatographic system was consisted of a pump (LC-10AD), an automatic injector (SIL-10A) and a UV detector (SPD-10A) (Shimadzu Scientific Instruments, Tokyo, Japan). An octadecylsilane column (Gemini C18, 4.6 × 250 mm, 5 μM; Phenomenex, Torrance, CA, USA) was eluted with a mobile phase consisting of 10mM phosphate buffer:acetonitrile (55:45, v/v%, pH 2.7). The flow rate was 1.0 mL/min with the detection wavelength set at 265 nm. The calibration curve from the standard samples was linear over the concentration range of 0.025–5 μg/mL.

Thermal analysis (DSC): Thermal analyses were carried out using a DSC (DSC 50, Shimadzu Scientific Instrument, MD). The amount of sample used ranged from 0.83 to 5 mg. Samples were placed in

aluminum pans and heated at a scanning rate of 10℃/min from 25 to 120℃, using nitrogen as a purge gas. An empty pan was used as a reference.

Powder X-ray diffraction (PXRD): The measurements were performed at 2Θrange of 3~50° with a step size of 0.03 and a measuring time of 1s per step (X-rat diffractometer D/MAX-3C, Riguku Co., Japan).

3. Results & Discussion

As summarized in Fig. 1, the solubility of valsartan was pH dependent and significantly decreased by lowering pH. Those results are consistent with the findings by Mbah et al. [3]. Since surfactants can enhance the solubility and dissolution rate of poorly soluble drugs, we investigated the effect of surfactants on the solubility of valsartan to improve its solubility, particularly at low pH. Five commonly used

surfactants including micronized Poloxamer 407, creomophor, solutol, SLS and tween 80 were selected and their effect on the solubility of valsartan was examined by varying the surfactant concentration. As illustrated in Fig. 2 and Fig. 3, the effect of surfactant on the enhancement of drug solubility was more obvious at low pH compared to the results in water. Among tested surfactants, micronized poloxamer 407 appeared to be most effective to enhance the solubility of valsartan at pH 1.2, particularly in low surfactant concentration. Therefore, micronized Poloxamer 407 was selected for the preparation of solid dispersion of valsartan.

SD was prepared by using solvent method at drug-polymer ratios of 1:0.5, 1:1, 1:3 and 1:5, respectively. To examine the advantage of SD preparation compared to the conventional powder formulation, the released amount of valsartan from SDs was compared to that from PM. As shown in Fig. 4 and Fig. 5, released amounts of valsartan were

increased as pH and amount of poloxamer 407 was increased. And the released amount of valsartan from SD was greater than that from PM, implying that SD preparation may be effective to enhance the solubility of valsartan.

The DSC thermograms of valsartan, poloxamer 407, their PMs and SDs were shown in Fig. 6. The DSC curves of pure valsartan and poloxamer 407 exhibited single endothermic peaks at 100.84℃ and 56.3℃, respectively. However no valsartan peak was observed from PM and SD, suggesting that valsartan was molecularly dispersed in carrier and was present in an amorphous state [11]. Interestingly, the DSC thermograms of valsartan in PMs were similar to those from SD. This result might be explained by that due to the low melting point (about 55℃) of poloxamer 407, valsartan in PM should be dissolved in the melted poloxamer solution when thermal analysis was carried out and thus, the melting peak of valsartan did not appear. Therefore,

PXRD was used to identify the crystallinity of valsartan PMs and SDs. The PXRD patterns of valsartan, poloxamer 407, their SDs are shown in Fig. 7. The PXRD patterns of pure valsartan had three noticeable peaks at 5.8°, 14.4° and 22.1° and valsartan was low crystalline in nature as compared to the diffraction pattern of telmisartan that is a specific competitive antagonist of the angiotension II receptor like valsartan [6]. The PXRD patterns of poloxamer 407 had two characteristic peaks at 19.1° and 23.3°. Although almost all peaks from valsartan were overlapped with peaks of poloxamer 407, the peak at 5.8° was distinctive. Therefore, if this peak disappears (or a large reduction), it will reflect an amorphous form of valsartan [12]. As shown in Fig. 7, there was no peak at 5.8° in SDs.

The dissolution characteristics of SDs were examined and shown in Fig. 8. Initial release rates of valsartan were faster with SDs having the drug-polymer ratio of 1:3 and 1:5 than those from SDs having the

drug-polymer ratio of 1:0.5 and 1:1. In addition, all the SDs completely released the drug after 4hr in water. Similar appearance of initial release rate was observed at pH 1.2, but maximum dissolution rates were relatively lower than in water (about 50% at 1:1 and 1:3, about 25% at 1:0.5). However, as shown in Fig. 9, the dissolution profile of SD (Drug:poloxamer=1:5) was not pH-dependent and showed desirable dissolution profiles at low pH. Interestingly, initial release rates of valsartan from SDs having a drug-carrier ratio of 1:0.5 or 1:1 showed the delayed drug release in both water and pH 1.2 buffer, which can be explained by, at least in part, that low initial dissolution rate may be resulted from the hydrophobic interaction of valsartan and sticky property of poloxamer. Therefore, we also evaluated the dissolution profile at 100 rpm and the enhanced initial dissolution rate of valsartan was observed (Fig. 10).

Collectively, the results indicated that the preparation of SDs

significantly improved the solubility and dissolution profiles of valsartan at low pH.

4. Conclusion

SDs containing micronized poloxamer 407 appeared to be useful for improving the dissolution rate as well as the solubility of valsartan at low pH. Therefore, the preparation of SDs may provide the possibility to develop oral dosage forms of valsartan having higher bioavailability.

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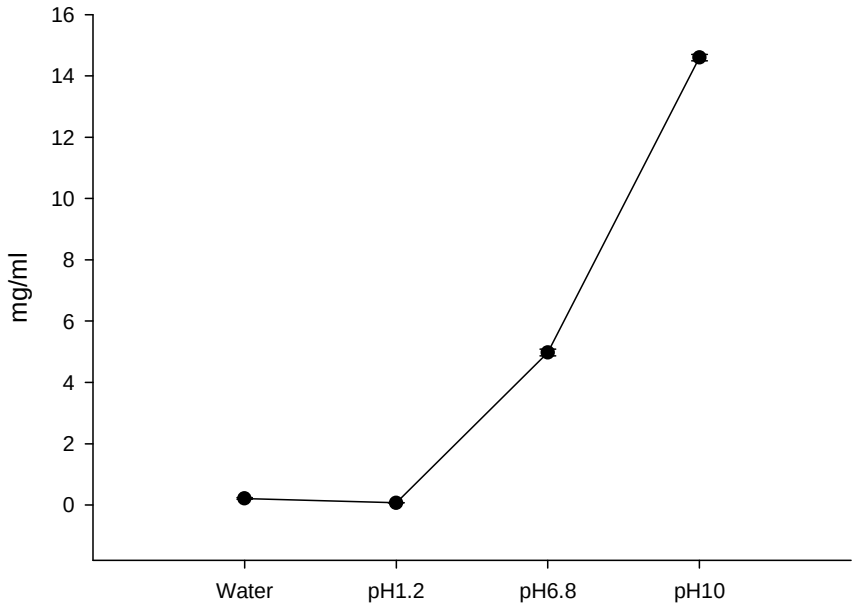

Figure 1. pH dependency of valsartan solubility (Mean±SD, n=3)

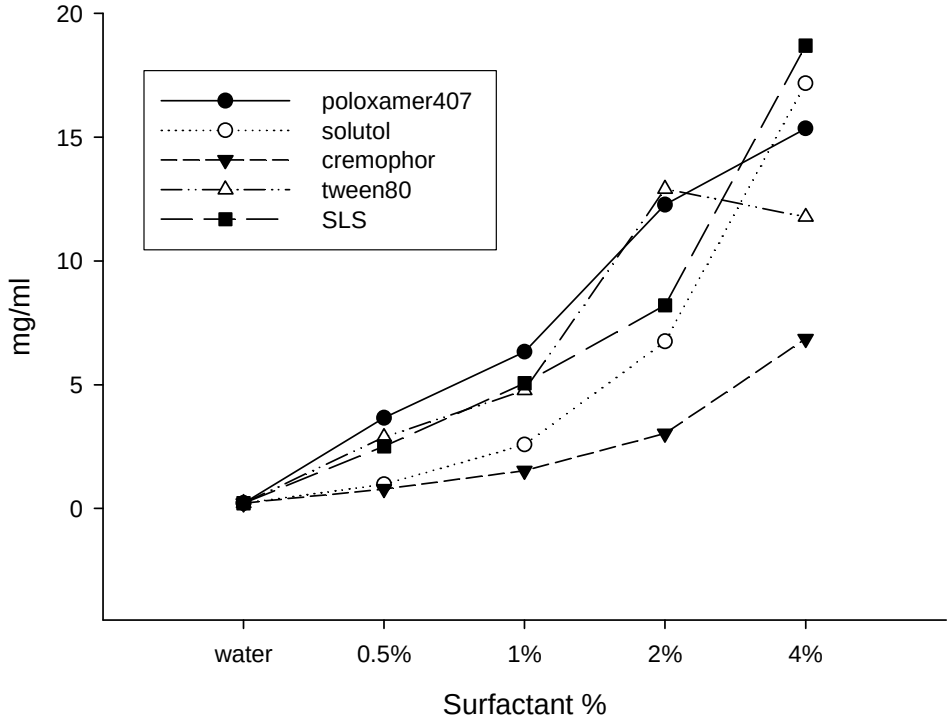

Figure 2. The effect of surfactants on the solubility of valsartan in water (Mean±SD, n=3)

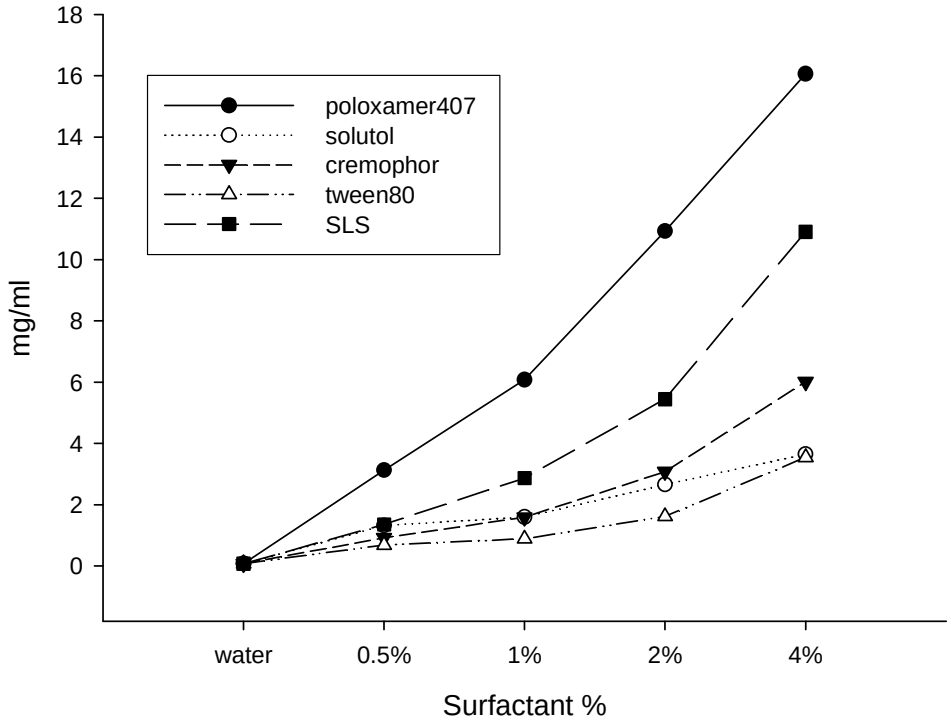

Figure 3. The effect of surfactants on the solubility of valsartan at pH 1.2 (Mean±SD, n=3)

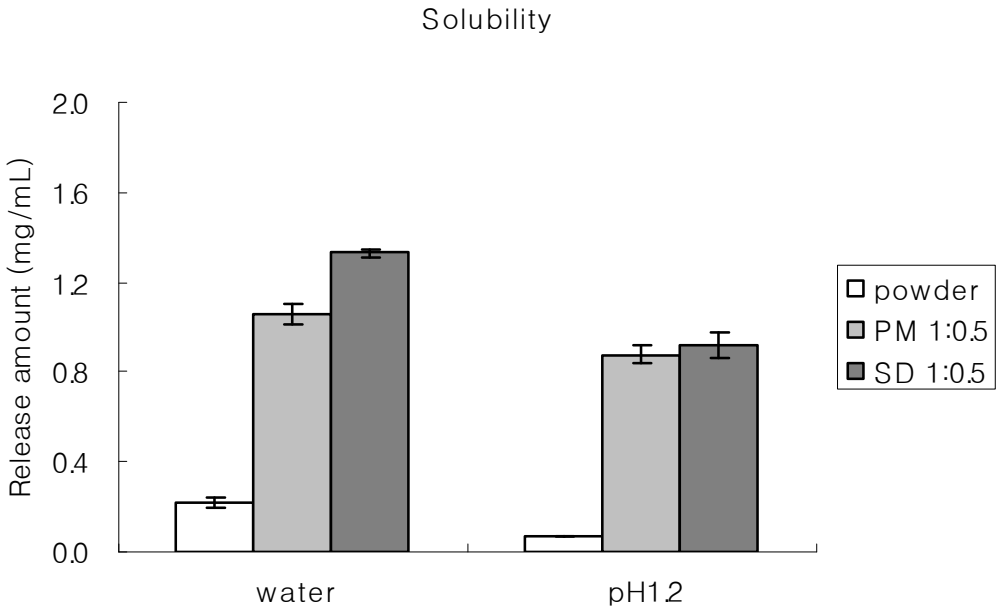

Figure 4. Released amount of valsartan from PM and SD. The ratio of valsartan to micronized poloxamer 407 was 1:0.5 (Mean±SD, n=3)

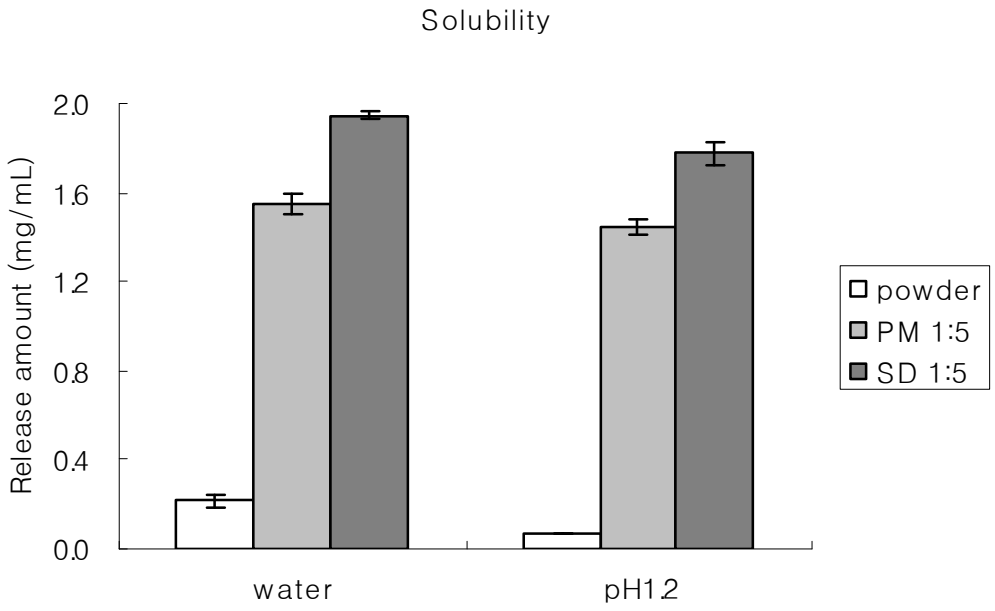

Figure 5. Released amount of valsartan from PM and SD. The ratio of valsartan to micronized poloxamer 407 was 1:5 (Mean±SD, n=3)

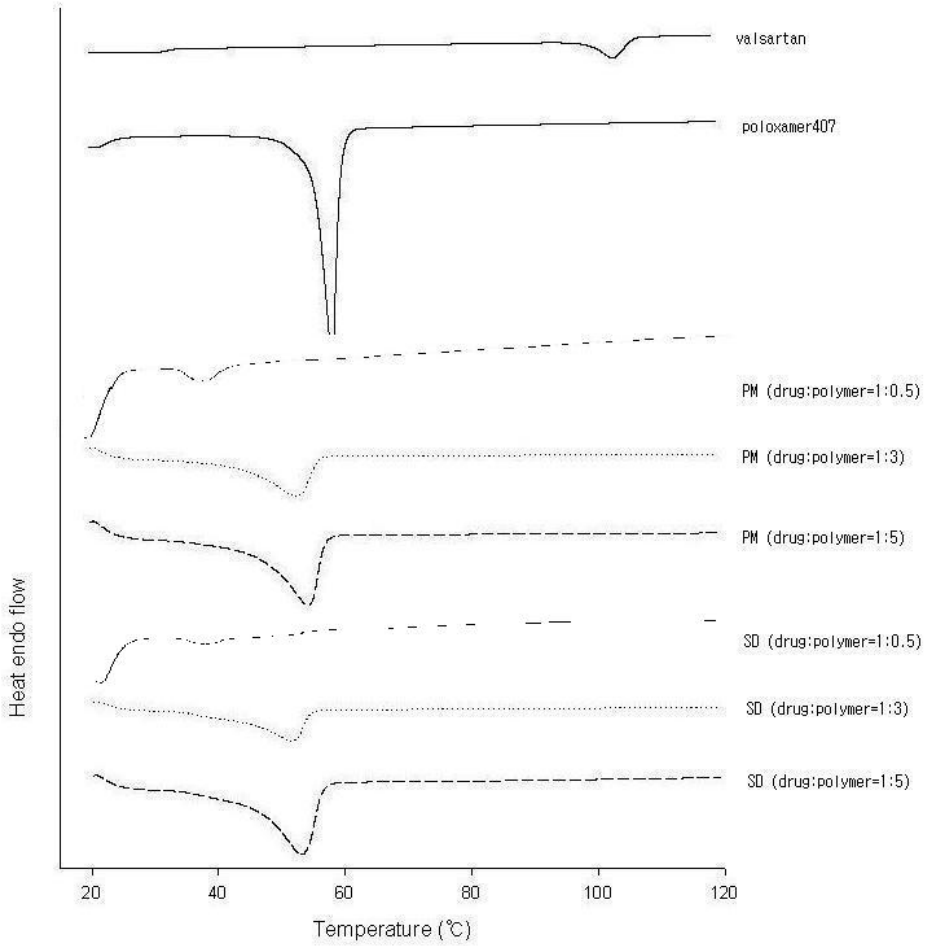

Figure 6. DSC thermograms of valsartan, poloxamer and their PMs and SDs prepared by solvent method. The ratio of valsartan to carrier was 1:0.5, 1:3 and 1:5.

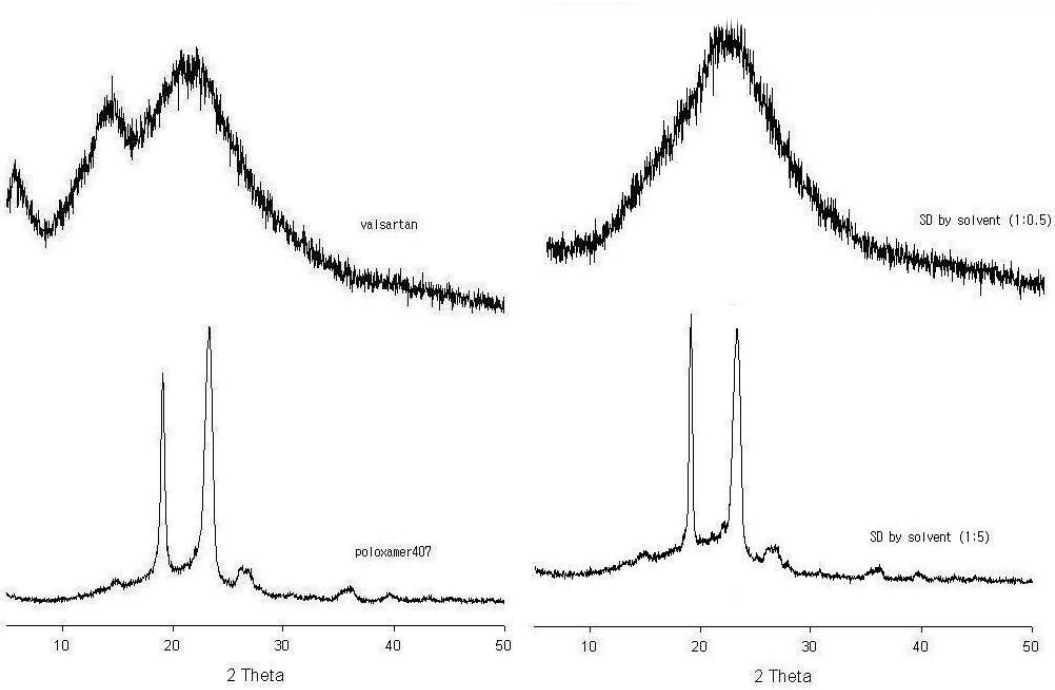

Figure 7. PXRD patterns of valsartan, poloxamer and their SDs prepared by solvent method. The ratio of valsartan to carrier was 1:0.5 and 1:5.

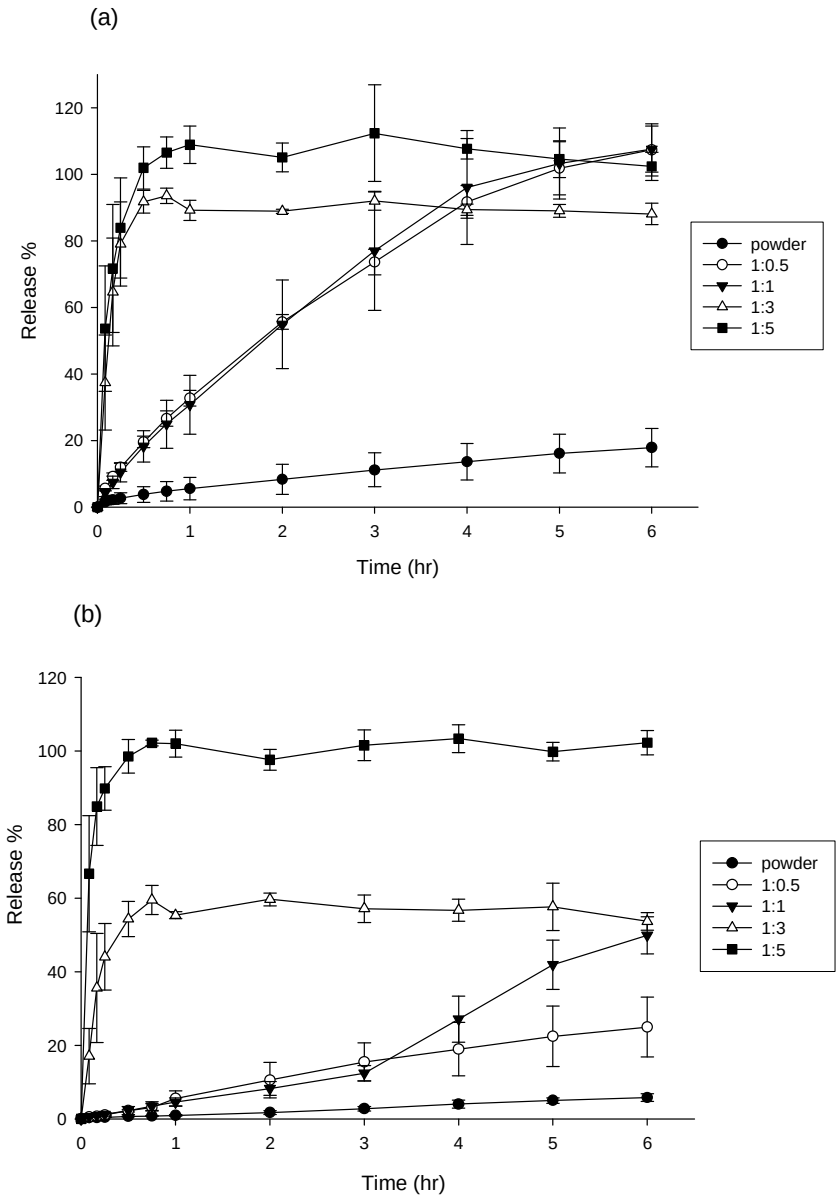

Figure 8. Dissolution profiles of valsartan SD prepared by varying the ratios of valsartan/poloxamer using solvent method (50rpm, Mean±SD, n=3) (a) water (b) pH1.2

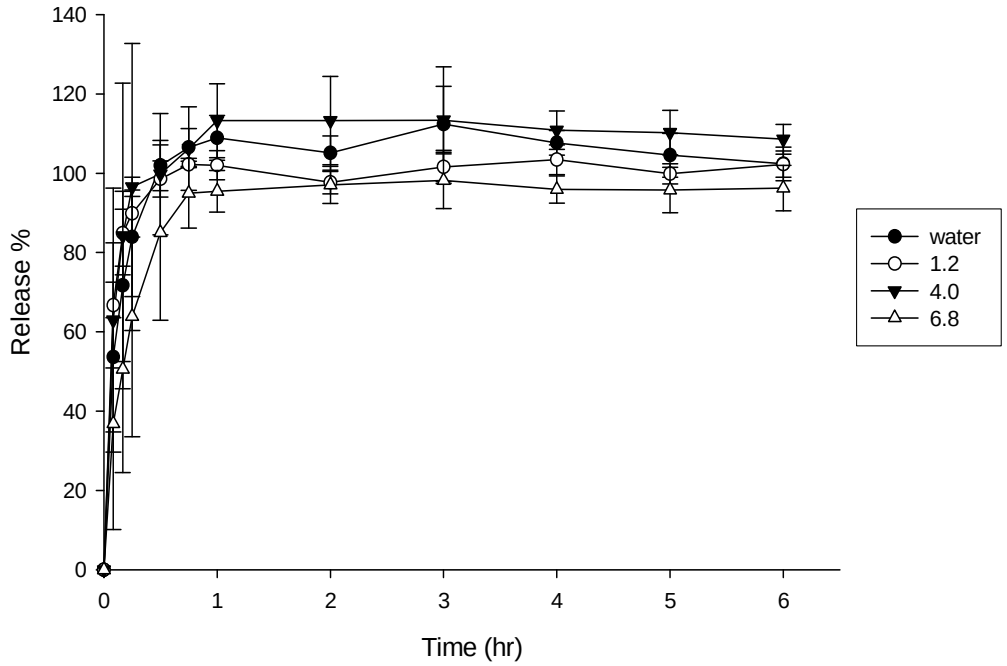

Figure 9. Dissolution profiles of valsartan SDs prepared by solvent method at various pH conditions (50rpm, Mean±SD, n=3)

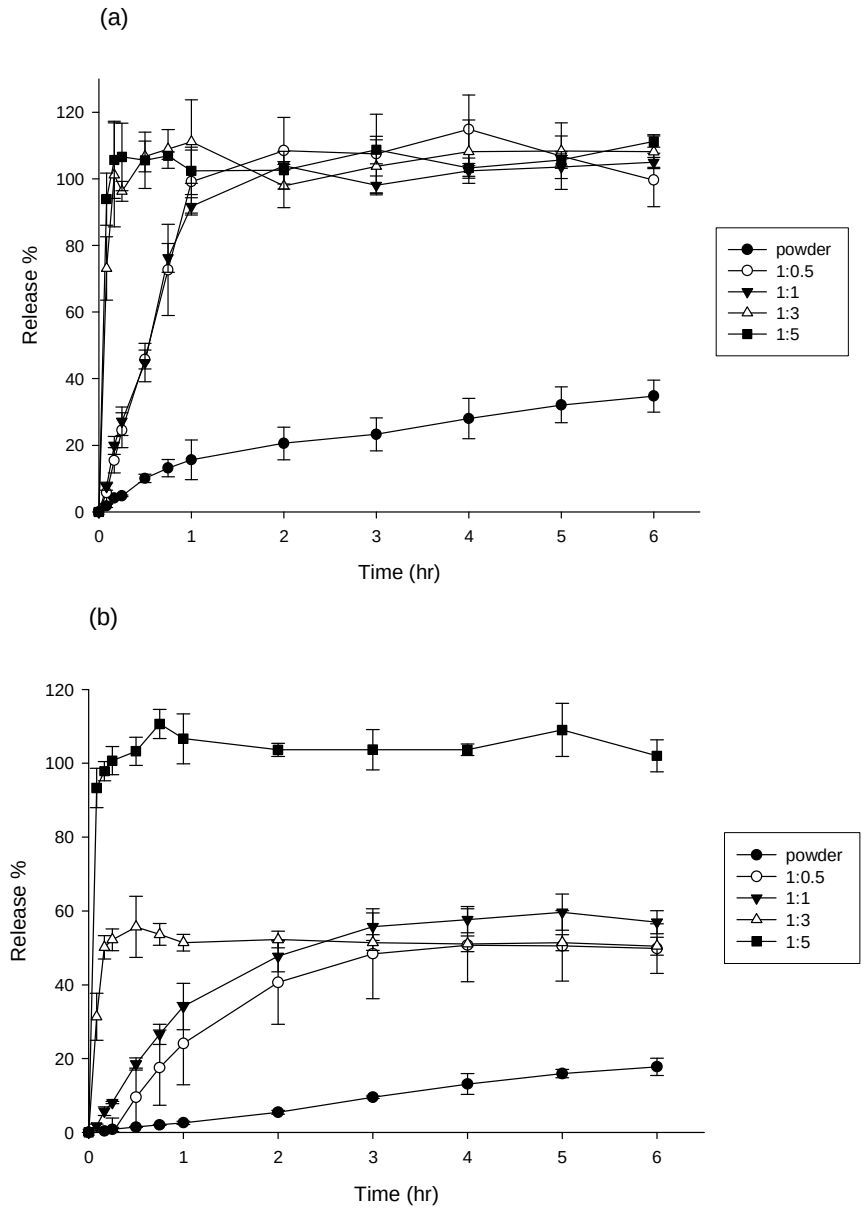

Figure 10. Dissolution profiles of valsartan SD prepared by varying the ratios of valsartan/poloxamer using solvent method (100rpm, Mean±SD, n=3) (a) water (b) pH1.2