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Preparation and characterization of pH-independent sustained release tablet containing solid dispersion granules of a poorly water-soluble drug

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ABSTRACT

Sustained release (SR) tablets containing solid dispersions (SD) granules of a poorly water-soluble drug were prepared to investigate the controlled pH-independent release of the drug. Losartan potassium (LST), an anti-hypertensive agent was chosen as a model drug because of its pH-dependent solubility and short elimination half-life. Poloxamer 188 was used as an SD carrier. A free-flowing SD granule was prepared by adsorbing the melt of the drug and poloxamer 188 onto the surface of an adsorbent, Aerosil 300 (fumed silicon dioxide), followed by direct compression with polyethylene oxide (PEO, 5×10^6) to obtain an SD-loaded SR (SD-SR) matrix tablet. Differential scanning calorimetry (DSC) and powder X-ray diffraction (PXRD) revealed partially amorphous structures of the drug in the SD granules. Scanning electron microscopy (SEM) and energy dispersive X-ray spectroscopy (EDS) images indicated adsorption of SD granules onto the surface of the adsorbent. The SD granules dissolved completely within 10 min, a dissolution rate much higher than that of pure LST. Moreover, pH-independent sustained release of LST from the SD-SR tablet was achieved for 2 h in gastric fluid (pH 1.2) and for 10 h in intestinal fluid (pH 6.8). A combination of SD techniques using surface adsorption and SR concepts is a promising approach to control the release rate of poorly water-soluble drugs in a pH-independent manner.

1. Introduction

One of the most promising methods for promoting the dissolution of poorly water-soluble drugs is the delivery of an SD via an efficient carrier (Horisawa et al., 2000; Tran et al., 2008, 2009, 2010a). Polyethylene glycol, poloxamer, Gelucire and polyvinylpyrrolidone are the most widely used SD carriers because of their strong hydrophilic properties and ability to form molecular adducts with many compounds (Karavas et al., 2007). However, the difficulty of pulverization, poor compressibility and poor flow of SDs prepared with water-soluble polymers are challenging factors (Gupta et al., 2001; Fujii et al., 2005). These properties have led to a decrease in the usefulness of SDs and handling difficulties in the manufacturing process (Takeuchi et al., 2004).

Recently, adsorbents such as fumed silicon dioxides have been used in the preparation of SDs to improve the manufacturing process. An inert core of an adsorbent can be used to adsorb the melted SD on its surface for better flowability and compressibility (Gupta et al., 2001; Chauhan et al., 2005). For instance, Neusilin was used to improve the bulk properties and dissolution rate of a Gelucire-based SD (Gupta et al., 2001).

On the other hand, sustained release (SR) systems are known to maintain therapeutically effective concentrations of drugs with short elimination half-lives in circulation over an extended period (Cao et al., 2004). The SR dosage forms that release drugs pH-independently in the gastrointestinal tract are preferred to avoid numerous biopharmaceutical variables and reduce intra- and inter-individual variations in bioavailability (Rao et al., 2003). Moreover, SR dosage forms containing poorly water-soluble drugs require both solubilization and release-modulation for therapeutic efficacy (Yi et al., 2008a; Tran et al., 2010b).

Against this background, a combination of SD via surface adsorption and SR are proposed. SR dosages containing SD (SD-SR) are an attractive pharmaceutical approach to improve the dissolution rate of poorly water-soluble drugs and patient compliance in the case of model drugs with poor solubility and short elimination half-life (Tanaka et al., 2005; Yi et al., 2008b; Sahoo et al., 2009; Tran et al., 2010b). However, there are few reports on the design of pH-independent controlled release of poorly water-soluble drugs using free-flowing SDs.

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The objective of this study was to prepare free-flowing SD granules using an adsorbent and then obtain a SD-SR tablet for pH-independent release of a poorly water-soluble drug. The SD-SR tablet was prepared via direct compression of SD granules and PEO, which was used as a hydrophilic carrier. PEO is one of the most common hydrophilic carriers in designing oral controlled-release hydrophilic matrix tablets that swell to form a gelatinous surface layer when exposed to an aqueous medium (Maggi et al., 2002). Losartan potassium (LST) was chosen as a weakly acidic model drug. LST is a potent, highly specific angiotensin II type 1 receptor antagonist with anti-hypertensive activity (Chopra et al., 2007). It is readily absorbed from the gastrointestinal tract with approximately 33% oral bioavailability and a plasma elimination half-life ranging from 1.5 to 2.5 h (Seburg et al., 2006; Chopra et al., 2007). LST demonstrates a pH-dependent solubility and is poorly soluble in gastric fluid.

2. Materials and methods

2.1. Materials

Losartan potassium (LST) was purchased from Du-Hope International Group (Batch No. 20070101, Nanjing, China). Fumed silicon dioxide (Aerosil 300) was obtained from Degussa (Frank am Main, Germany). Poloxamer 188 was a gift from BASF Korea (Seoul, Korea). PEO (Polyox WSR Coagulant, molecular weight: 5×10^6) and carbomer 934 (polycarbophil) was donated by Myungmoon Pharm. Co., Ltd. (Seoul, Korea). Microcrystalline cellulose (MCC, Avicel PH-102) was obtained from Colorcon Korea (Suwon, Korea). Magnesium stearate was purchased from Katayama Chemical Co. (Osaka, Japan). HPLC-grade acetonitrile was purchased from Fisher Scientific Korea Ltd. (Seoul, Korea). All other chemicals and solvents were analytical grade and used without further purification.

2.2. Preparation of SD granules

The SD granules were prepared using a hot melt method. The poloxamer 188 carrier was melted in a beaker at 60 °C in an oil bath and the drug was added while stirring to obtain a homogenous mixture. Various adsorbents (Aerosil 300, polycarbophil, MCC, betonite) were added gradually to the molten mixture with continuous stirring. The dispersion was cooled at −70 °C followed by passing through a sieve 400 μm in diameter. The weight ratio of LST, poloxamer 188 and adsorbent was 1:1:1. A physical mixture (PM) was obtained by mixing LST, poloxamer 188 and adsorbent using a spatula.

2.3. Physical characterization of SD granules

Differential scanning calorimetry (DSC) of SD granules was carried out with a heating rate of 10 °C/min using a DSC 2910 (Japan). Powder X-ray diffraction was performed at room temperature with an X-ray diffractometer (Panalytical Co., Netherlands) using Ni-filtered Cu Kα radiation (voltage 40 kV, current 20 mA). The scanning rate was 2°/min over a 2θ range of 5–60° and with an interval of 0.02°.

The surface morphology of the prepared SD granules was determined by scanning electron microscopy (SEM) (JEOL JSM-5410) equipped with an energy-dispersive X-ray spectroscopy (EDS) Oxford ISIS micro-analytical system. The samples were sputter-coated with a gold layer in advance to make them conductive. Samples used for energy dispersive X-ray microanalysis were coated with a 100 Å thickness carbon film under reduced pressure.

Table 1
Formulation compositions (mg) in the preparation of SR tablets containing SD granules.

Code	LST	PM	SD	PEO	MCC	Magnesium stearate
F1	–	–	150	147	–	3
F2	–	–	150	50	97	3
F3	–	–	150	30	117	3
F4	–	–	150	15	132	3
F5	–	150	–	30	117	3
F6	50	–	–	30	217	3

The PM and SD granules contain drug, poloxamer and Aerosil 300 (1:1:1, w/w).

2.4. Flowability of SD granules

The flowability of SD granules was characterized by measuring angle of repose and Carr's compressibility index. Angle of repose was determined by pouring the dispersion granules through a funnel (10 mm diameter orifice) onto a flat surface and measuring the angle between the horizontal and the slope of the heap of granules. Bulk density was calculated by measuring the volume of 4 g granules in a 10 ml cylinder. The cylinder was tapped 100 times until no further reduction in the volume of the SD granules was observed. Tapped density was calculated using the volume of the SD granules after tapping. Carr's compressibility index (CI) were determined according to the following formula:

$$\mathrm{CI} = \left(\frac{\text{Tapped density} - \text{Bulk density}}{\text{Tapped density}} \right) \times 100$$

2.5. Tablet preparation containing SD granules

The SD-SR tablets equivalent to 50 mg of LST was prepared via direct compression after mixing PM or SD granules with different amounts of PEO, MCC as filler and 1% magnesium stearate as a lubricant (Table 1). A homogenous blend was passed through a 250 μm sieve and then directly compressed into tablets using a rotary tablet machine with a 9 mm single punch diameter (Korea Machine, Anyang, Korea). Tablet hardness for all formulations was measured with an Erweka hardness tablet tester (Erweka, Germany) and was in the range of 90 ± 5 N. The weight of each tablet was 300 ± 3 mg.

2.6. Dissolution test

The dissolution of SD granules and SD-SR tablets containing 50 mg LST was performed using a DST-810 dissolution tester (Labfine, Seoul, Korea) according to the USP 26/NF 21 (2003) dissolution II paddle method at a rotation speed of 50 rpm in 900 ml medium kept at 37 ± 0.5 °C. Gastric fluid (pH 1.2) was used for SD granules. For SD-SR tablets, the medium was gastric fluid (pH 1.2) for 2 h followed by 10 h in intestinal fluid (pH 6.8). After each interval, 1 ml of dissolution medium was withdrawn and filtered immediately, and then 1 ml of refresh medium was compensated. LST dissolution was subjected to HPLC (Jasco, Japan) equipped with an autosampler and UV detector. A 20 μl volume was applied to a C18 column (Phenomenex Gemini, 5 μm, 150 × 4.6 mm) using a mixture of distilled water, acetonitrile, phosphoric acid and triethylamine (55:45:1:1) as a mobile phase. The flow rate was 1 ml/min. The drug concentration was determined at 220 nm.

3. Results and discussion

3.1. Effect of adsorbent types on dissolution rates of SD granules

LST revealed pH-dependent solubility, in which LST was poorly soluble in simulated gastric fluid and soluble in simulated intestinal fluid. LST had a solubility of 400 μg/ml at pH 1.2 (gastric fluid) and

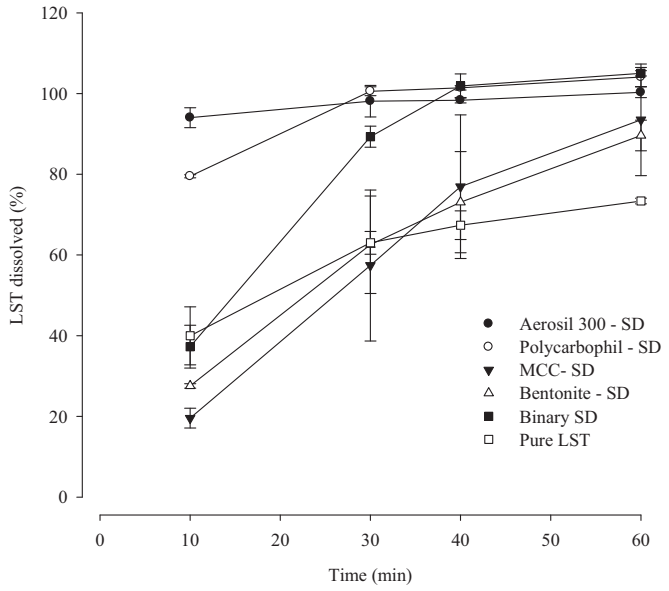

Fig. 1. Effect of adsorbent types on dissolution rate of ternary SD in gastric fluid (pH 1.2).

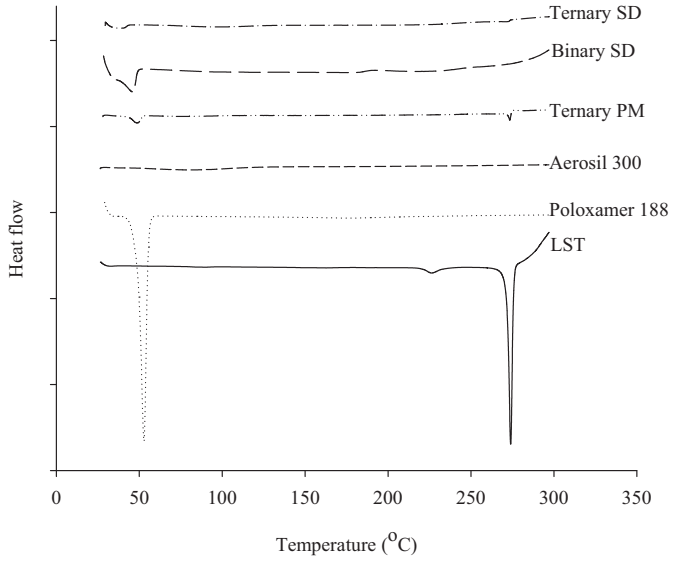

Fig. 2. DSC thermograms of the ternary PM, and SD granules consisting of LST, poloxamer and Aerosil 300.

253 mg/ml at pH 6.8 (intestinal fluid). The commercial LST product, Cozaar shows pH-dependent release because of this pH-dependent solubility of LST (data not shown). The dissolution rate of SD was highly affected by adsorbent type (Fig. 1). The binary SD composed of LST with poloxamer 188 improved the drug dissolution up to 30% and completely dissolved within 1 h (100% versus 70%). The hydrophilic properties of poloxamer 188 as a carrier probably led to improved dissolution by increased wetting and reduced interfacial tension between the drug and the dissolution medium (Leonardi et al., 2007). However, the binary SD was extremely sticky, leading to difficulty in subsequent manufacturing processes. Thus, the surface adsorption technique was combined with the preparation of SD granules to overcome this limitation. Among adsorbents, Aerosil 300 and polycarbophil showed complete dissolution of LST within 10 min and 30 min, indicating that these adsorbents enhanced initial dissolution of the drug through formation of less sticky SD granules. Therefore, dissolution enhancement is a function of both SD and surface adsorption (Gupta et al., 2001). The addition of MCC and bentonite did not produce SD in a powder form. Dissolution of SDs prepared with MCC and bentonite was much slower than that of ternary SDs prepared with Aerosil 300 and polycarbophil, had broad variations, and was not completed within 1 h. The differences in dissolution rates of ternary SDs were due to the difference in surface areas and powder properties among adsorbents, of which Aerosil 300 possesses the greatest surface area at approximately 300 g/cm^2. The hydrophilic and free-flowing property of the silica particles also contributed to improved drug dissolution from the SD (Takeuchi et al., 2004). Thus, Aerosil 300 was invariably used to prepare the free-flowing SD granules with complete enhancement of drug dissolution.

3.2. Characterization of SD granules using Aerosil 300

Fig. 2 showed DSC thermograms of the PM and the SD granules consisting of drug, poloxamer and Aerosil 300. The endothermic peak for LST was 275 °C, which corresponds to the melting point of the drug. Poloxamer and Aerosil 300 appear as amorphous materials without characteristic peaks in the thermogram. The characteristic peak of LST was maintained partially at this temperature in the PM thermogram and almost disappeared in the thermograms of binary and ternary SDs. The DSC result indicated that LST existed in the partially crystalline state in the PM but changed to an amorphous form in the SD.

The PXRD diffraction patterns of pure LST, binary SD, ternary PM and ternary SD granules are shown in Fig. 3. Pure crystalline LST is characterized by prominent diffraction peaks in the range of 7–35° 2θ in PXRD. The crystallinity of LST decreased in the binary SD, ternary PM, and ternary SD and changed into partially amorphous form in the SD granules. The lower intensity of LST in PM and SD resulted from the dilution effect by increasing the ratio of the SD carriers compared to pure LST. The difference in crystallinity of LST based on the PXRD pattern and DSC was associated with the heating process during DSC measurement. The DSC and PXRD results indicate the absence of significant interactions between drug and excipients in the preparation of SD granules.

The surface morphologies of pure materials (LST, poloxamer 188, and Aerosil 300), ternary PM and SD granules were observed

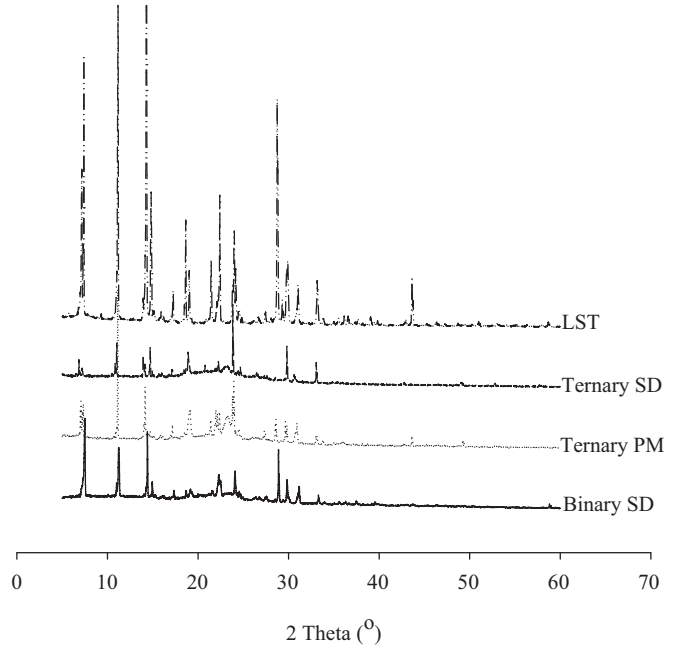

Fig. 3. PXRD of LST, binary SD of LST and Pluronic F68, ternary PM, and SD granules.

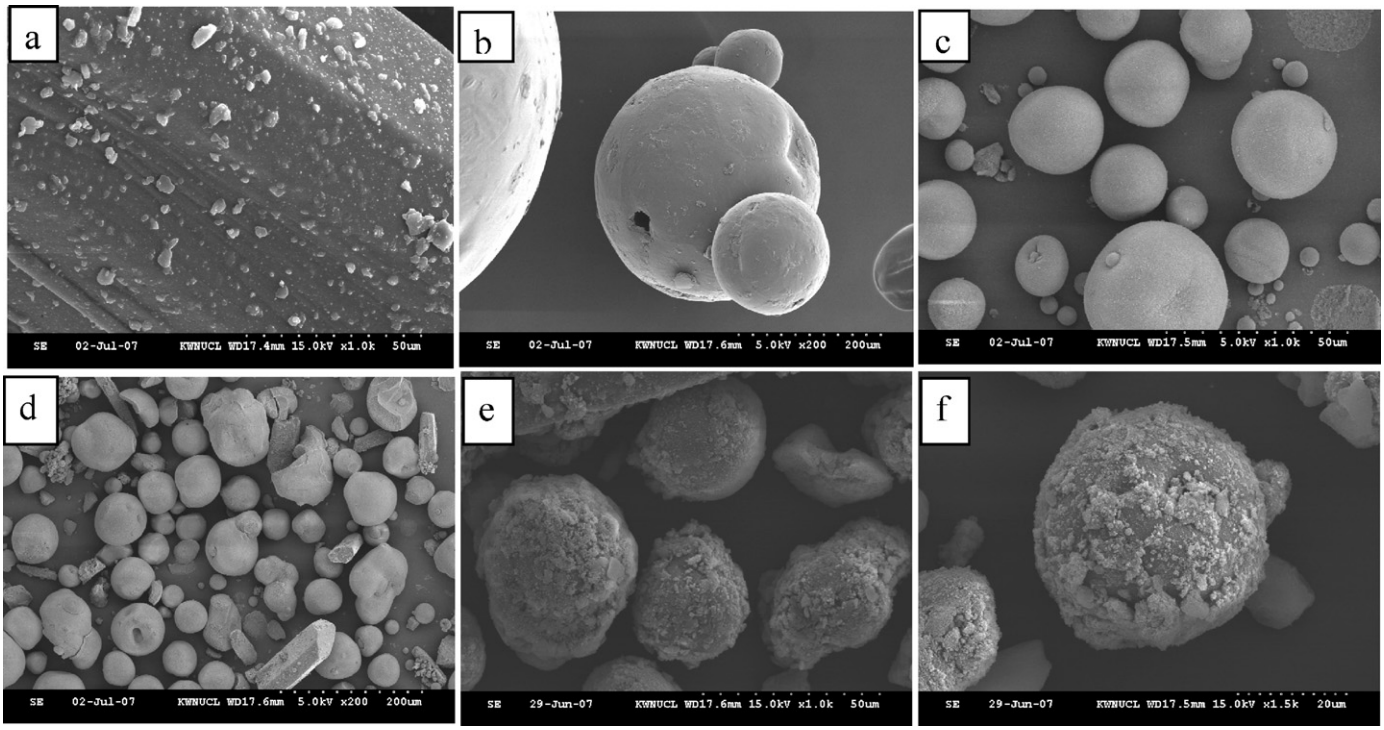

Fig. 4. SEM images of (a) LST, (b) poloxamer 188, (c) Aerosil 300, (d) ternary PM, (e and f) SD granules.

by SEM (Fig. 4). Pure LST showed an aggregate of large and small crystals, while poloxamer 188 and Aerosil 300 consist of spherical particles with smooth surfaces. The ternary PM had irregularly shaped particles of separated drug, carrier and Aerosil 300 (Fig. 4d). Surface adsorption of the SD solution onto the surface of Aerosil 300 particle was confirmed, resulting in free-flowing SD granules (Fig. 4e). The SD granules were spherical and had a rough outer layer over the surface of the silica particles.

The surface adsorption phenomenon was confirmed by examining the distribution of Cl and Si atoms in the free-flowing SD granules using EDS mapping. This method allows estimation of the compositions and distribution of atomic components in the samples (Barra et al., 2000). Since chloride is a unique element in the chemical structure of LST, chloride was selected for elemental maps. Si, from Aerosil 300, was also mapped. As with pure LST, the result indicated that the chloride content was homogenously distributed throughout the samples (Fig. 5a). Si (Aerosil 300) appeared with high intensity (Fig. 5b), while Cl was observed with lower density around the SD granules (Fig. 5c). The SEM images and the EDS maps indicated adsorption of drug particles and the poloxamer 188 particles onto the surface of the silica nanoparticles, producing free-flowing SD granules. To our knowledge, this is the first attempt to characterize the morphology of SD granules formed by adsorption and SD using EDS and SEM.

The powder properties of SD granules were further characterized by measuring bulk properties of pure drug, the PM and the SD (Table 2). The angle of repose for the SD granules was found to be $27.02 \pm 3.04^{\circ}$. A value close to 25° indicates good flowability of the SD granules (Gupta et al., 2001). A compressibility index of 10.2% indicated good compressibility of the SD granules into tablet. In contrast, the angle of repose and compressibility index values for the pure drug ($47.60 \pm 4.21^{\circ}$ and $27.04 \pm 3.14\%$, respectively) and the corresponding PM powder ($32.55 \pm 2.68^{\circ}$ and $18.60 \pm 0.84\%$, respectively) indicate poorer flowability and compressibility compared to SD granules. Although the PM exhibited crystals of irregular shape and poor flow characteristics compared to SD granules, the angles of repose between 30° and 34° demonstrated passable flow due to the presence of over 30% free-flowing Aerosil 300. It is well known that poorly flowing powders cause manufacturing difficulties in the tablet compression process. Bulk properties of the SD granules were significantly improved by adding an adsorbent like Aerosil 300. Thus, the co-melt of poloxamer 188 and drug adsorbed onto the larger surface of Aerosil 300 can facilitate the formation of freely-flowing SD granules which could be further processed into a sustained release matrix tablet.

Table 2
Powder properties of pure drug, PM and SD granules.

Properties	Material		
	Pure LST	PM	SD granules
Angle of repose (°)	47.60 ± 4.21	32.55 ± 2.68	27.02 ± 3.04
Bulk density (g/ml)	0.48 ± 0.03	0.40 ± 0.01	0.42 ± 0.02
Tapped density (g/ml)	0.65 ± 0.004	0.49 ± 0.01	0.47 ± 0.03
Compressibility index (%)	27.04 ± 3.14	18.60 ± 0.84	10.20 ± 1.75

3.3. *pH-independent release of LST from SD-SR tablets*

To achieve pH-independent release of drug, free flowing SD granules were compressed with different amounts of PEO as a SR carrier. Fig. 6 shows the effect of PEO amount on LST release from SD-SR tablet in gastric fluid (pH 1.2) for 2 h and subsequently in intestinal fluid (pH 6.8) for 10 h. Higher PEO content used was correlated with lower drug release due to the formation of a strong gel layer (Maggi et al., 2000, 2002). As a result, different release patterns of LST from SD-SR matrix tablets were obtained by modifying the PEO content of the tablets. When the amount of PEO in the tablets decreased from 49% (F1) to 10% (F3), LST release increased from 8.4% to 16% in gastric fluid after 2 h and from 55% to 90% in intestinal fluid after 12 h. Further decrease of PEO to 5% (F4) resulted in a drastic increase in LST release and was unable to sustain drug release over an extended period. The formulation with a low level of PEO polymer exhibited higher burst release as the hydrophilic matrix tablet absorbs water and starts to swell (Chopra et al., 2007).

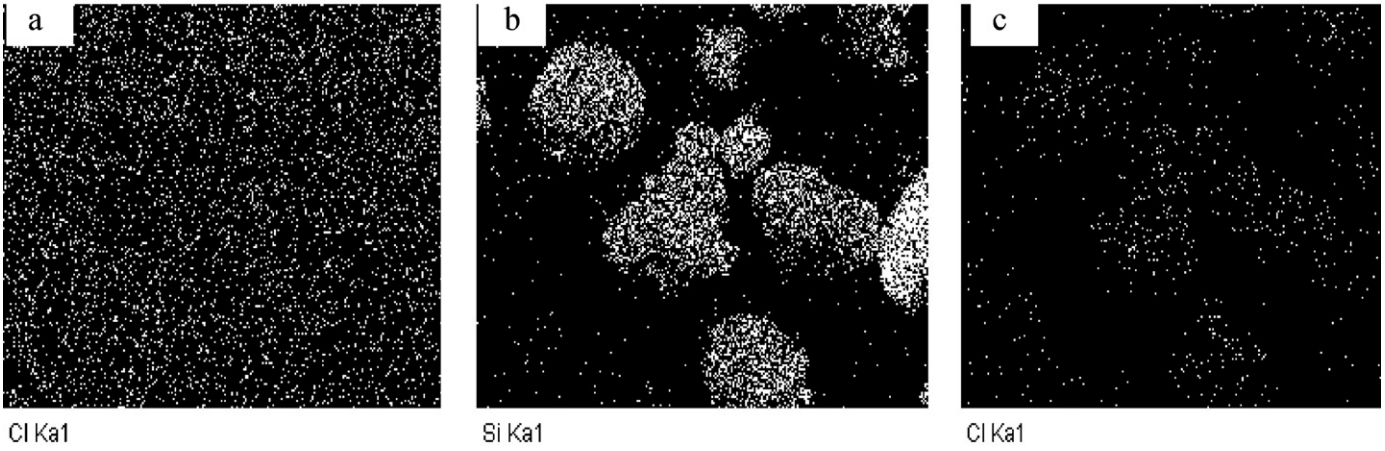

Fig. 5. EDS images of (a) Cl distribution in pure LST, (b) Si distribution in the SD granules, and (c) Cl distribution in the SD granules.

At 10% PEO (F3), the drug release exhibited near zero-order and linear release in both dissolution media. At other PEO concentrations, there was a transition point in dissolution rate when changing from gastric medium to intestinal fluid due to pH-dependent drug solubility and the higher sustaining effect of PEO. The amount of PEO was found to play a key role in modifying the pH dependency of drug release from SD-SR tablets. It has been reported that the dissolution profiles of extended release and dual release tablets containing SD depend on the amount of PEO 5,000,000 as a release modulator (Yi et al., 2008a).

A combination of polymer swelling, drug dissolution from the SD granules and matrix erosion determines drug release kinetics from swellable PEO matrices. The pH-independent zero-order release of LST from the SD-SR tablets using hydrophilic PEO resulted from the net effect of solubilization and release modulation of PEO. The synchronization between swelling and erosion of high molecular weight PEO leading to zero-order kinetic of drug release has been recognized (Maggi et al., 2000, 2002).

To clarify the important role of SD-SR tablets in pH-independent release of LST in both gastric and intestinal fluid, dissolution profiles of SR tablets containing LST alone, ternary PM and SD granules are compared in Fig. 7. Although LST release from SD-SR tablets in gastric fluid was 7% higher than that from LST and PM-loaded tablets, the increased drug release from the SD-SR tablets in intestinal fluid was significantly higher at 10 h. LST release from LST tablets, PM tablets, and the SD-SR tablets was 43.7%, 68.6%, and 100% after 12 h, respectively. This might be ascribed to enhanced drug solubility and faster water penetration from the dissolution media into the SD-SR tablets as compared to LST and PM-loaded SR tablets. This indicates that the SD granules improved the solubility and dissolution of LST at pH 1.2 and could facilitate drug release, leading to pH-independent release from SD-SR tablets, unlike the LST and PM-loaded tablets. The result suggests that compressing free-flowing SD granules would be more effective than drug alone or PM powders in achieving the desired pH-independent release of LST. In the previous report, compressed tablets containing SD had smooth surfaces with small pores were more efficient than PM in retarding verapamil release (Sahoo et al., 2009). However, SR dosage forms containing SD are not always successful due to the recrystallization of amorphous and supersaturated drugs when contacting water for a long period of time (Tanaka et al., 2005; Tran et al., 2009). The solubility and dissolution rate of nilvadipine SD with crospovidone was

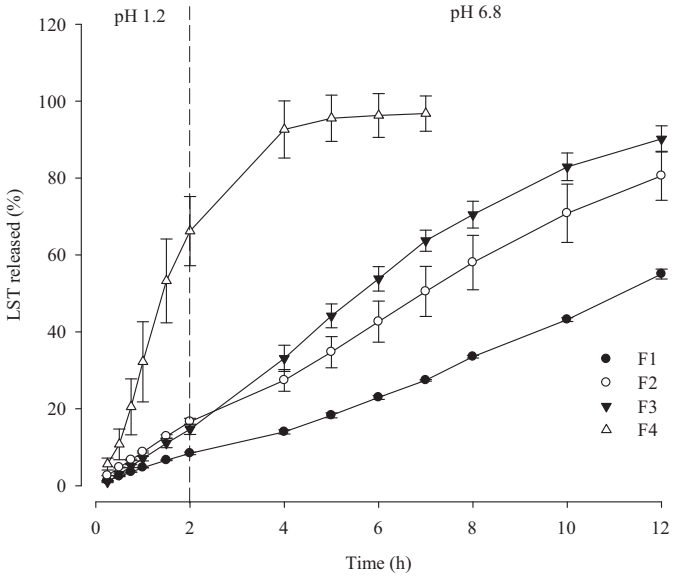

Fig. 6. Effect of PEO amount on LST release from SD-SR tablet in gastric fluid (pH 1.2) for 2 h and subsequently in intestinal fluid (pH 6.8) for 10 h.

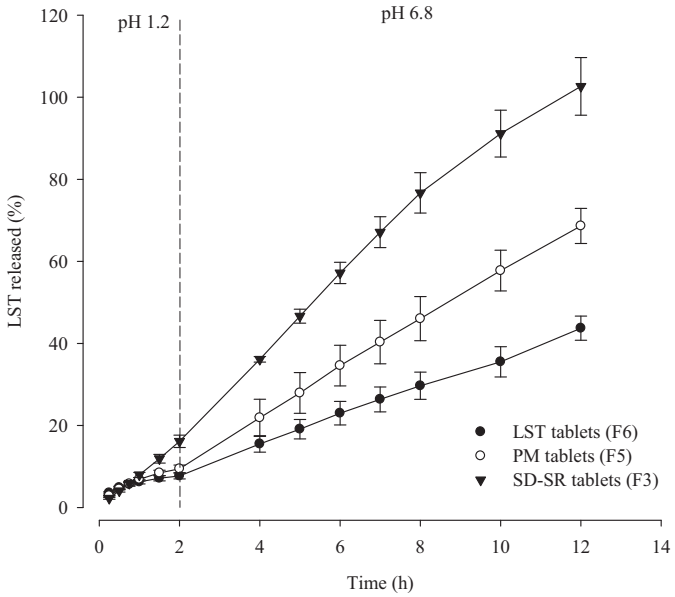

Fig. 7. Dissolution profiles of SR tablets containing LST alone (F6); ternary PM powder (F5), and SD granule (F3) in gastric fluid (pH 1.2) for 2 h and subsequently in intestinal fluid (pH 6.8) for 10 h.

significantly increased through formation of amorphous structures and then decreased at around 180 min due to recrystallization of the nilvadipine at supersaturated concentrations (Hirasawa et al., 2003). Nevertheless, our free-flowing SD granules improved the LST dissolution rate in pH 1.2 medium by enhancing wetting and surface area without recrystallization using poloxamer and Aerosil. Thus, pH-independent and zero-order release of LST from SD-SR tablets was achieved over a prolonged period with the aid of the surface-adsorbed SD and the synchronization of swelling and erosion of hydrophilic PEO at an appropriate concentration.

4. Conclusions

A free-flowing SD granule was obtained by surface adsorption of poloxamer-based SD on Aerosil nanoparticles. SD granules showed enhanced dissolution of LST without recrystallization. These results show that a combination of surface adsorption of SD and hydrophilic SR carriers is a promising approach to control the release rate of poorly water-soluble and pH-dependent drug like LST in a pH-independent manner. The ternary SD granules were directly compressed into tablets using hydrophilic PEO without any processing problems. The resulting SD-SR tablet revealed pH-independent and linear release of LST for 2 h in gastric fluid and continuously in intestinal fluid for 12 h.

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