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Preparation, characterization and *in vitro* evaluation of a polyvinyl alcohol/sodium alginate based orodispersible film containing sildenafil citrate

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In this work, we developed a sildenafil citrate (SC)-loaded polyvinyl alcohol (PVA)/sodium alginate (ALG-Na) based orodispersible film (ODF) using a solvent casting method. Formulation factors such as the type and amount of plasticizers and disintegrants were optimized on the basis of characteristics of blank ODF, including the disintegration time, elastic modulus (EM) and percentage of elongation (E%). SC-loaded ODF with a loading capacity up to 25 mg in an area of 6 cm^2 was prepared and evaluated in terms of mechanical properties, disintegration time and dissolution rate. The surface morphology of ODF was visualized under a scanning electron microscope (SEM). The physicochemical properties of ODF were investigated using X-ray diffraction (XRD), differential scanning calorimetry (DSC) and fourier transform infrared spectroscopy (FT-IR). The blank ODF composed of PVA, polyethylene glycol 400 (PEG 400) and ALG-Na (20:5:2, w/w) had a remarkably short disintegration time of about 20 s. However, the loading of drug extended the disintegration time (100 s) of ODF, while it still maintained satisfactory mechanical properties. SC was homogenously dispersed throughout the films and the crystalline form of drug changed, with strong hydrogen bonding between the drug and carriers. The PVA/ALG-Na based ODF containing SC prepared by the simple solvent casting method might be an alternative to conventional SC tablets for the treatment of male erectile dysfunction.

1. Introduction

Male erectile dysfunction (ED) is a frequent disease for men and can have a profound effect on the quality of life with subjects often reporting increased anxiety, lack of self-confidence, tension and difficulty in the relationship with their partner. With the fast pace of life and increasing pressure on people, it should be paid great attention to the patient who suffers from this disease (Liu et al. 2010).

Sildenafil citrate (SC) is an active ingredient for treatment of ED with a dose of 50 to 100 mg (Boolell et al. 1996). In addition, it also indicated for treatment of pulmonary arterial hypertension with a dose of 20 mg given three times daily (Galiè et al. 2005). The dosage forms of SC for clinical application are tablets. Administration is not convenient when there is no water nearby. In this case, fast disintegration dosage forms such as orally disintegrating tablets (ODT) would be preferred (Kumar et al. 2010). However, ODTs are easy to shatter because of relatively low hardness, and their preparation procedures are more complex. Furthermore, the disintegrated materials contained in ODT are insoluble and remain in the mouth until swallowing, leading to poor patient compliance (Shimoda et al. 2009).

Orodispersible films (ODFs) are strip type preparations with active ingredients dissolved or dispersed in film forming materials. An ODF is simply placed on a patient's tongue, and can rapidly hydrate and adhere onto the site of application. It subsequently disintegrates and dissolves to release the drug for mucosal or gastrointestinal absorption. Compared with ODTs, ODFs can be prepared using simple preparation processes and are easy to carry, store and handle (Yellanki et al. 2011).

Generally, ODFs are prepared by using water soluble and fast disintegrating polymers which also possess good film forming properties. Numerous types of hydrophilic polymers, such as hydroxypropyl methylcellulose (HPMC) (Kunte et al. 2010; Yellanki et al. 2011; Figueroa et al. 2012), maltodextrin (MDX) (Kunte et al. 2010; Cilurzo et al. 2008; Cilurzo et al. 2010; Patel et al. 2009), polyvinyl alcohol (PVA) (Arya et al. 2012; Scott et al. 2013) and pullulan (Avani et al. 2011; Choudhary et al. 2012; Mahesh et al. 2010; Mishra et al. 2011) have been widely studied or used in marketed products. Among them, PVA, a biodegradable and water soluble polymer has received increased attention because of its good film forming capability, remarkable chemical and mechanical stability (Koland et al. 2010; Barona et al. 2012). Ideally, an ODF should immediately disintegrate and release its components into the oral cavity. However, the application of PVA as the unique film forming material appeared non-porous, which makes the films hard to dissolve in water rapidly (Zhou et al. 2009). Therefore, it is essential to incorporate appropriate disintegrants into the formulation to promote the disintegration of the film.

Sodium alginate (ALG-Na) is a natural polymer extracted from brown seaweed having high biological safety. In most cases, it

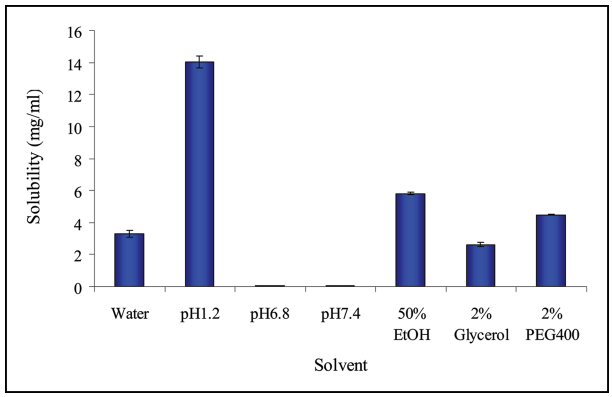

Fig. 1: Solubility of SC in different solvents (n = 3).

has been used as a film forming material in combination with other polymers such as sodium carboxymethyl cellulose, Carbopol 974P and chitosan (Yehia et al. 2009; Boateng et al. 2009; Garsuch et al. 2010), resulting in increased drug loading or mucoadhesive properties of the films. Although ALG-Na shows rapid water absorption and swelling properties, no information about the disintegrating roll of ALG-Na has been reported when it was incorporated into polymer-based ODF.

In this study, we designed novel SC-loaded PVA/ALG-Na based ODFs with a short disintegration time by a solvent-casting method. Blank ODFs were formulated with different types and amounts of plasticizers and disintegrants, and evaluated in terms of disintegration time, film thickness and mechanical properties. In addition, the surface morphology, dissolution rate and physicochemical properties of SC-loaded ODFs were also evaluated.

2. Investigations, results and discussion

2.1. Solubility study

Initially, screening of appropriate solvents and plasticizers is essential for ODF development prepared by a solvent-casting method. Solubility studies were aimed at identifying suitable solvents having maximal solubilizing potential for the drug. The results of the solubility of SC in various vehicles are shown in Fig. 1. Among the aqueous vehicles, SC showed the highest solubility of 14 mg/ml at pH 1.2 and relatively higher solubility of 3.3 mg/ml in water. However, it is hardly dissolved at pH 6.8 and pH 7.4, because SC is a weak base with a pKa of 8.7 (Farghali et al. 2012). On the other hand, the solubilities of SC in 50 % EtOH, 2 % glycerol and 2 % PEG400 were 5.8 mg/ml, 2.6 mg/ml and 4.5 mg/ml, respectively. In our pre-formulation study, it was found that a uniform film was hard to prepare with higher drug loading than 25 mg in an area of 6 cm^2 using pH 1.2 vehicle or EtOH-water (50:50, v/v) solvent mixture (data not shown). In particular, precipitation of SC usually occurred in the process of drying when an EtOH-water solvent mixture was used to dissolve the drug. The possible reason is that SC dissolved in EtOH-water solvent mixture was more likely to precipitate by the rapid evaporation of solvent. Therefore, distilled water was routinely used as a solvent for the preparation of drug-loaded ODFs, and SC powder was just suspended and not dissolved in film forming solution in this study.

2.2. Preparation and evaluation of blank ODFs

In this study, particular attention was given to the selection of a proper plasticizer and disintegrant to prepare a blank film which could disintegrate fast and had a suitable ductility and flexibility.

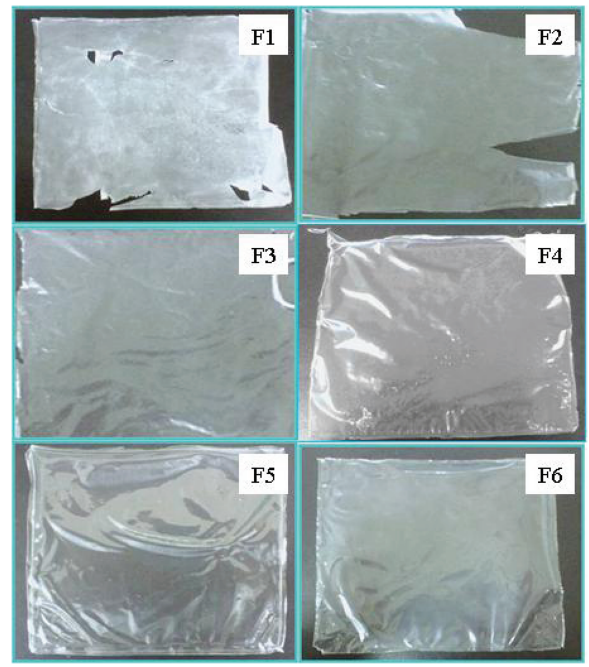

Fig. 2: Appearance of the blank ODFs prepared with different plasticizers (F1) PEG 4000, (F2) PEG 1000, (F3) PEG400, (F4) glycerol, (F5) PEG4000:PEG400 = 3:2, (6) PEG4000: glycerol = 3:2.

The detailed formulation compositions used to prepare blank ODFs are given in Table 1.

2.2.1. Effect of plasticizer

Because blank ODF made of PVA without any additives was crisp and lack of flexibility, PEG 400, PEG 1000, PEG 4000 and glycerol were added as the plasticizers to improve the ductility and flexibility of the film. Figure 2 shows the appearance of blank ODFs prepared with different plasticizers. Among the PEGs with different molecular weight, PEG 400 could render the suitable appearance of films (F3). However, the films plasticized with PEG 4000 (F1) and PEG 1000 (F2) were very fragile and difficult to strip from the stainless steel plate. In contrast, the film prepared with glycerol as a plasticizer was extremely stick (F4), which may be caused by the hygroscopicity of glycerol (Hoque et al. 2011). Thus, to overcome these problems, various combinations of plasticizers such as PEG 4000: PEG 400 (3:2) or PEG 4000: glycerol (3:2) were used and the corresponding ODFs (F5 and F6) also showed acceptable appearance.

The disintegration time of the film is one of the most important quality attributes for evaluating the ODFs. As shown in Fig. 3,

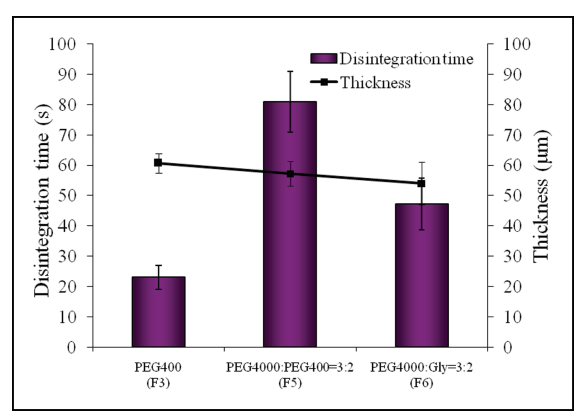

Fig. 3: Effect of plasticizer type on the disintegration time and thickness of blank ODFs (n = 6).

Table 1: Formulation compositions of various blank and SC-loaded ODFs

Ingredients (g)	Formulation														
	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12	F13	F14	F15
SC	-	-	-	-	-	-	-	-	-	-	-	-	-	-	0.25
PVA1788	1	1	1	1	1	1	1	1	1	1	1	1	1	1	0.27
PEG4000	0.25	-	-	-	0.15	0.15	-	-	-	-	-	-	-	-	-
PEG1000	-	0.25	-	-	-	-	-	-	-	-	-	-	-	-	-
PEG400	-	-	0.25	-	0.1	-	0.15	0.20	0.30	0.25	0.25	0.25	0.25	0.25	0.067
Glycerol	-	-	-	0.25	-	0.1	-	-	-	-	-	-	-	-	-
ALG-Na	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	-	-	0.05	0.15	0.2	0.027
CMS-Na	-	-	-	-	-	-	-	-	-	0.1	-	-	-	-	-
Water (mL)	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20

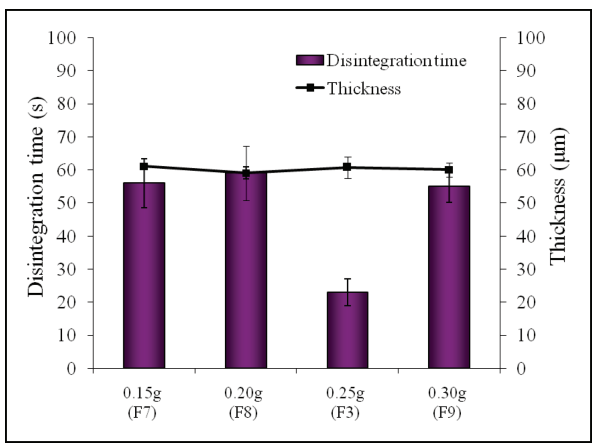

Fig. 4: Effect of PEG400 amount on the disintegration time and thickness of blank ODFs (n = 6).

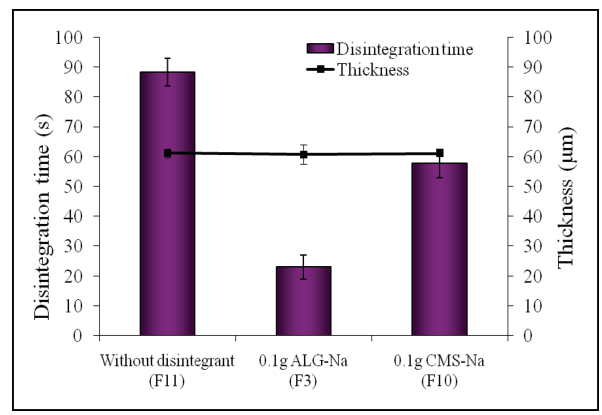

Fig. 5: Effect of disintegrant type on the disintegration time and thickness of blank ODFs (n = 6).

the disintegration time of F3 (PEG 400) was much shorter than those of F5 (PEG 4000/PEG 400 = 3:2) and F6 (PEG 4000/Glycerol = 3:2) when used the same amount of plasticizer. The change in the amount of PEG 400 (F3, F7, F8, F9) also leads to the change in the disintegration time of the films as shown in Fig. 4. Interestingly, the films incorporated with 0.25 g of PEG 400 (F3) disintegrated much faster than other films. This could be attributed to the fact that water absorbency of films was predominantly influenced by PEG content when the PEG molecular weight was low. Alternatively, it was observed that the water absorbency increased with the content of plasticizer to a certain percentage and then decreased (Kwon et al. 2007). That is why the film containing 0.25 g of PEG showed relatively shorter disintegration time in this study.

2.2.2. Effect of disintegrant

The effects of disintegrants on disintegration time of the films were also evaluated. In this study, polyvinylpolypyrrolidone (PVPP), carboxymethyl starch sodium (CMS-Na) and sodium alginate (ALG-Na) and microcrystalline cellulose (MCC) were used to decrease the disintegration time of the films, respectively. It was found that the surface of the films containing PVPP or MCC were rough because of the relatively large particle size of PVPP and MCC. As shown in Fig. 5, the disintegration time of ODFs prepared without any disintegrants (F13) was about 90 s. As expected, both ALG-Na (F3) and CMS-Na (F10) could remarkably decrease the disintegration time of the films. Further, the disintegration time of F3 was much shorter than F10 when used the same amount of disintegrant. As shown in Fig. 6, the change in the amount of ALG-Na (F3, F14, F15 and F16) also leads to the change in the disintegration time of films. In particular, films disintegrated much faster when the amount of ALG-Na was 0.1 g (F3). This indicates that ALG-Na can be used as a disintegrant only in certain proportions. ALG-Na is a water-soluble polymer with rapid water absorption and swelling properties. The film (F12) showed a relatively long disintegration time of 60 s when 0.05 g of ALG-Na was added. In this case, ALG-Na could not exhibit rapid water uptake due to its low amount. As the amount of ALG-Na increased to 0.1 g, the disintegration time of film (F3) decreased significantly due to its rapid water absorption. In contrast, it was found that the disintegration time of films increased when ALG-Na amount further increased up to 0.2 g (F13, F14). This could be attributed to the strong gelling property of ALG-Na, which further resulting in delayed disintegration time of films. For the thickness of blank ODFs, there was no significant difference among each formulation. The thickness of each film varied from 60 to 70 micrometers.

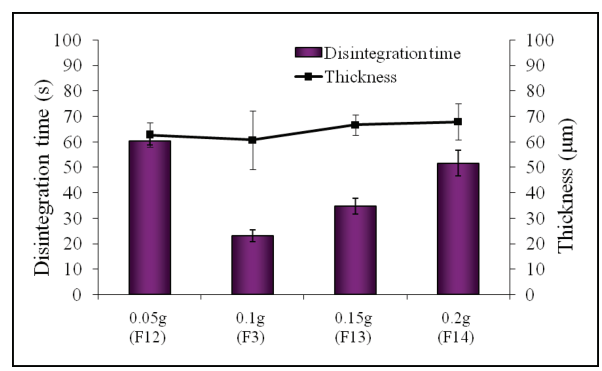

Fig. 6: Effect of ALG-Na amount on the disintegration time and thickness of blank ODFs (n = 6).

Table 2: Mechanical properties of various blank ODFs (n = 6)

Formulation	EM (MPa)	E (%)
F3	9.2 ± 2.7	313.3 ± 87.3
F5	9.3 ± 3.2	453.6 ± 218.6
F6	5.3 ± 2.7	722.7 ± 182.0
F7	8.5 ± 2.0	517.4 ± 70.0
F8	11.4 ± 3.3	490.4 ± 106.6
F9	6.9 ± 1.0	674.8 ± 50.7
F10	8.5 ± 1.3	474 ± 35.7
F11	6.9 ± 1.5	450.3 ± 82.1
F12	3.2 ± 0.5	744.6 ± 108.7
F13	3.4 ± 0.5	705.6 ± 145.5
F14	12.7 ± 2.3	483.0 ± 195.2

2.2.3. Mechanical properties

On the other hand, a suitable ODF requires acceptable percentage elongation and low elastic modulus. Table 2 shows the comparative mechanical properties of various blank ODFs prepared in the study. The films plasticized with PEG 4000 (F1) and PEG 1000 (F2) were very fragile and difficult to strip from the stainless steel plate. So the mechanical properties of F1 and F2 have not been measured. In contrast, the film plasticized with glycerol (F4) was extremely sticky and its mechanical properties has also not been checked in this study. All other ODFs showed relatively low elastic modulus with less than 15 MPa and high elongation % with more than 300 %.

2.3. Preparation and evaluation of SC-loaded ODF

The SC-loaded ODF (F15) was prepared on the basis of blank ODF (F3). The films were characterized in terms of physicochemical properties, mechanical properties, in vitro disintegration time and dissolution rate. The detailed formulation composition used to prepare SC-loaded ODF is given in Table 1.

2.3.1. SEM of films

The surface morphologies of SC (pure drug), blank (F3) and SC-loaded (F15) ODFs were assessed using the SEM. As shown in Fig. 7A, SC presented regular acicular crystal at 300 × magnification. The blank ODF (Fig. 7B) showed an uniform film with small pores, which may promote the water absorption and shorten the disintegration time of the film. On the contrary, some drug crystals could still be observed in SC-loaded ODF and fewer pores were formed throughout the whole film (Fig. 7C).

2.3.2. X-ray diffraction (XRD)

XRD was used to verify the solid state transformation of SC in ODF. Fig. 8 shows the XRD results of SC (pure drug), SC-loaded ODF (F15) and its physical mixture (PM). The X-ray diffractogram of pure drug displayed intense and sharp crystalline peaks, and the crystalline drug signal was still detectable in the PM of drug and carriers. However, some crystalline peaks disappeared or were significantly decreased in SC-loaded ODF (F15). This indicated that the original crystalline form of SC had been changed when a drug was loaded in the films.

2.3.3. DSC thermograms

The DSC thermograms of SC (pure drug), SC-loaded ODF (F15) and its physical mixture (PM) are shown in Fig. 9. A sharp endothermic peak of SC appeared at about 198 °C, which was

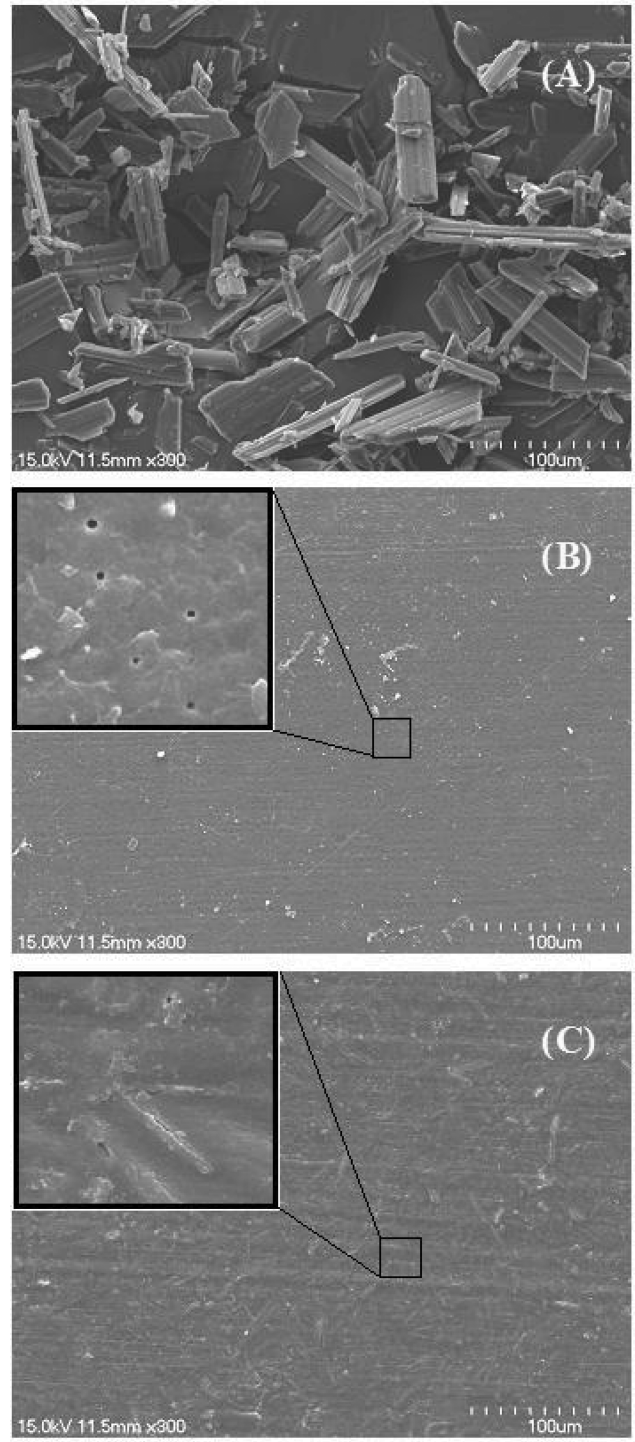

Fig. 7: Scanning electron microscopy of (A) SC, (B) blank (F3) and (C) SC-loaded (F15) ODFs.

corresponding to the melting point of the drug. A weak endothermic peak of SC still appeared at its melting point in the PM. But no obvious melting drug peak was observed in the thermogram of SC-loaded ODF (F15) except the weak endothermic peak at 180.91 °C. This indicated that the crystalline form of SC had been partially converted into its amporphous form (Lee et al. 2012). Moreover, it implied that some interactions between SC and excipients could be occurred in drug-loaded ODF during the preparing process.

2.3.4. FT-IR spectroscopy

FT-IR was carried out to further characterize possible interactions between the drug and carriers in SC-loaded ODFs. Fig. 10

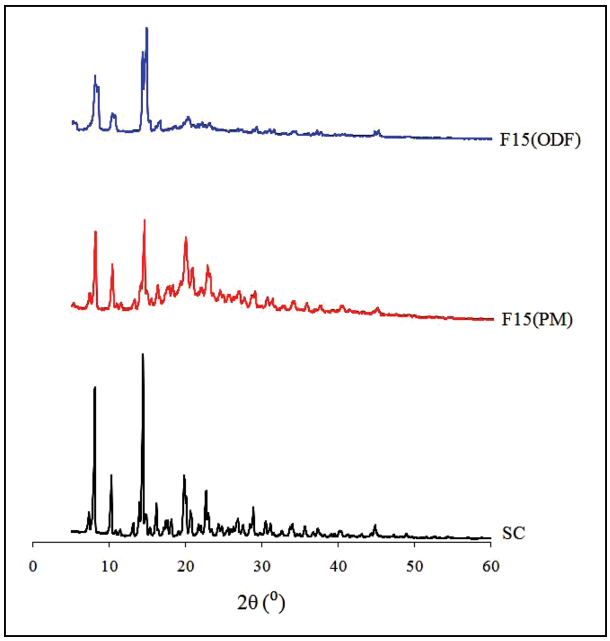

Fig. 8: X ray diffractograms of pure drug (SC), SC-loaded ODF (F15) and its physical mixture (PM).

shows the FT-IR spectra of SC (pure drug), blank (F3) and SC-loaded (F15) ODFs. There was a distinct absorption band of the drug at 1702 cm^{-1} that belongs to the carbonyl group for SC, while the corresponding peak was absolutely disappeared and could not be further found in SC-loaded ODF (F15). This might be due to the existence of hydrogen bonding between carbonyl group of SC and hydroxyl group of PVA and /or PEG 400.

2.3.5. *Disintegration time and mechanical properties*

In order to investigate the effect of drug on disintegration time and mechanical properties, the amount of carriers and the ratio of polymer to plasticizer in drug-loaded film (F15) were maintained equivalent with the optimized blank film (F3). After preparation of SC-loaded ODF (F15), the disintegration time and mechanical properties of the film were evaluated. As shown in Fig. 11, the disintegration time, thickness, EM and E % for the drug-loaded ODF (F15) were 100.7 µm, 105.7 s, 13.7 MPa, 133.2 %, respectively. Compared with the blank ODF (F3), the

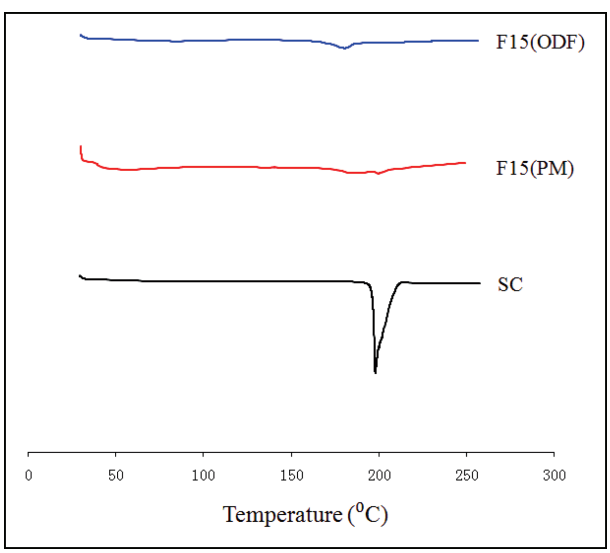

Fig. 9: DSC thermograms of pure drug (SC), SC-loaded ODF (F15) and its physical mixture (PM).

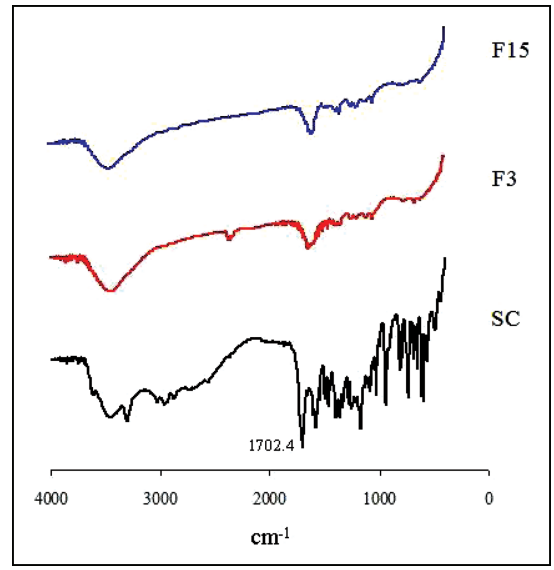

Fig. 10: FT-IR spectra of SC, blank (F3) and SC-loaded (F15) ODFs.

disintegration time and thickness of SC-loaded ODF (F15) were remarkably increased. The longer disintegration time of drug-loaded film might be due to the poor solubility of SC in water as well as the increased thickness of film after adding a drug. On the other hand, The EM of drug-loaded ODF was increased and the E % was decreased oppositely compared with the blank ODF. The changes of mechanical properties could also be attributed to the drug loading. Drug loading could decrease the portion of polymer and plasticizer in drug-loaded films, and further weaken the molecular interactions between polymer and plasticizer. Appar-

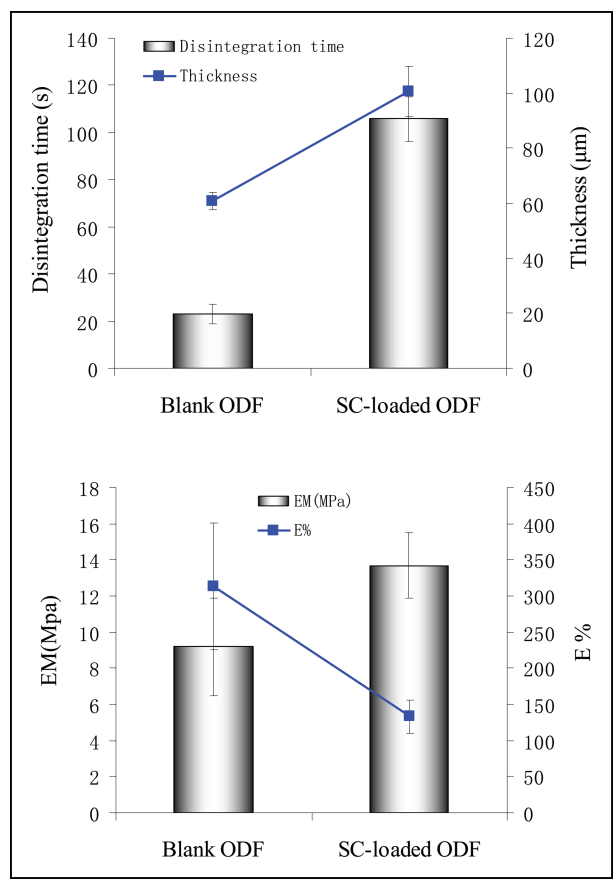

Fig. 11: Thickness, disintegration time and mechanical properties of blank (F3) and SC-loaded (F15) ODFs. (n = 6).

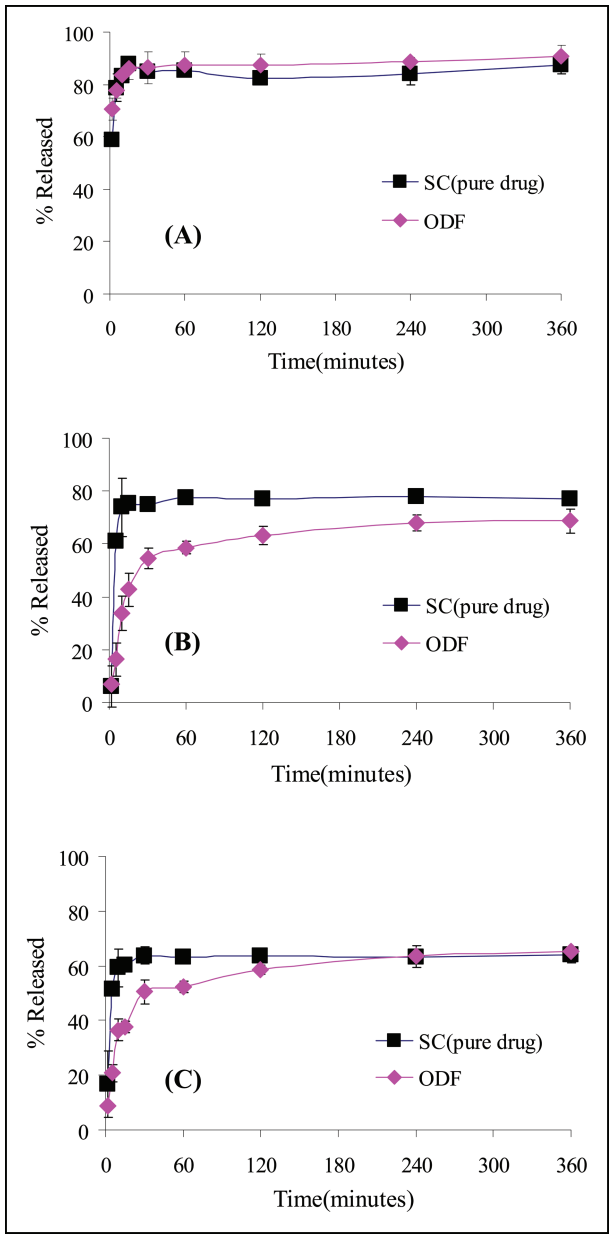

Fig. 12: Dissolution profiles of SC from the pure drug and SC-loaded ODF (F15) with 25 mg drug loading in different pH media (n = 3). (A) pH1.2, (B) pH6.8, (C) pH7.4.

ently SC-loaded ODF was less flexible than blank ODF in this study.

2.3.6. *In vitro dissolution study*

The drug content in a single ODF was determined by a HPLC method, and was about 98.76 ± 1.46 %. In order to investigate the dissolution rate of drug from SC-loaded ODF (F15), a dissolution study was carried out in three different pH media (pH 1.2, pH 6.8 and pH 7.4) (Fig. 12). Both SC (pure drug) and F15 exhibited different dissolution profiles under various pH conditions. Higher dissolution rate of SC was found at pH 1.2 (Fig. 12A) compared to that at pH 6.8 (Fig. 12B) or pH 7.4 (Fig. 12C). At pH 1.2, SC was under sink condition due to its high water solubility, and the dissolution rate of drug reached more than 90 % within 1 h. In contrast, the maximum dissolution rates were relatively low at pH 6.8 and pH 7.4 with less than 80 % and 66 % at 6 h respectively. This could be attributed to the fact that SC was poorly soluble at higher pH (Fig. 1), which resulting in non-sink conditions for drug dissolution. As shown in Fig. 12A, there was no difference for the dissolution rates between the pure drug and SC-loaded ODF (F15) at pH 1.2. This may be due to the fact that dissolution rate of SC is dominating for release of SC from F15 in pH 1.2 dissolution medium. However, in Fig. 12B and Fig. 12C, it is shown that the initial dissolution rate of SC from the film was much lower than that of pure drug at pH 6.8 or pH 7.4, indicating dissolution rate of polymers is a dominating factor controlling the release rate of SC from ODF. These results might be due to the pH-dependent solubility of SC as well as the surface morphology of drug-loaded film, which affects the gelling and disintegration properties of ALG-Na (Wu et al. 2002).

2.4. *Conclusions*

In this study, novel SC-loaded ODF composed of PVA and ALG-Na were prepared by a simple solvent casting method. Different types and amounts of plasticizers and disintegrants were optimized on the basis of characteristics of blank ODF, including the disintegration time, elastic modulus (EM) and percentage of elongation (E%). The blank ODF composed of PVA, polyethylene glycol 400 (PEG 400) and ALG-Na (20:5:2, w/w) had a remarkably short disintegration time of about 20 s. The loading capacity of SC in the ODF can be up to 25 mg in an area of 6 cm^2. However, the drug-loaded ODF exhibited a relatively longer disintegration time of 100 s. SC was homogenously dispersed throughout the film and the crystalline form of the drug had been changed. It could be found that strong hydrogen-bonding interactions between the drug and carriers exist. The PVA/ALG-Na based ODF containing SC might be promising to be an alternative to SC tablets for the treatment of male erectile dysfunction.

3. Experimental

3.1. *Materials*

Sildenafil citrate (SC) was received as a gift sample from EuraPharm Co. (Suwon, Korea). Polyvinyl alcohol (PVA 1788), polyethylene glycol (PEG) with different viscosity grades (400, 1000 and 4000), glycerol, polyvinylpolypyrrolidone (PVPP), carboxymethyl starch sodium (CMS-Na) and sodium alginate (ALG-Na) were obtained from Simopharm Chemical Reagent Co.(Shanghai, China). Microcrystalline cellulose (MCC) was purchased from Asahikasei Co. (Tokyo, Japan). All other chemicals used were of analytical grade.

3.2. *Solubility study*

The solubility study of SC was carried out in different solvents. Briefly, excess of SC was added to a vial containing 2 ml of water, pH 1.2 HCl solution, pH 6.8 or pH 7.4 phosphate buffer, 50 % EtOH (v/v), 2 % glycerol (w/v) and 2 % PEG 400 (w/v), respectively. The phosphate buffers were prepared according to Chinese Pharmacopoeia 2005. After sealing the vials, the mixtures were shaken in a thermostat oscillator for 72 h at 37 ± 0.5 °C. The mixtures were then centrifuged at 4000 × g for 10 min. The supernatant was suitably diluted with a mobile phase and the drug concentration was determined by a HPLC method described below. The results were expressed as mean of three determinations.

3.3. *Preparation of ODF*

3.3.1. *Preparation of blank ODF*

The blank films were prepared by a solvent-casting method (Yellanki et al. 2011; Cilurzo et al. 2010). Briefly, a PVA solution was prepared by dissolving preweighed PVA in water and the dissolution was facilitated by heating the solution at 80 °C with magnetic stirring until it became clear. The resulting solution was then cooled to room temperature before adding the other ingredient. The desired amounts of other ingredients were added and blended continuously with the PVA solution by stirring until it became transparent. The entrapped air in the polymer solution was thoroughly removed by placing on a table for 12 h. The solution (20 ml) was carefully poured on a stainless steel plate (15 × 15 cm^2) to form a uniform liquid layer and then

dried into film in a hot air oven at 60 °C for 4 h. The films were removed from the stainless steel plate carefully and cut into strips of dimensions 2 × 3 cm^2 and stored in an air tight glass bottle.

3.3.2. Preparation of SC-loaded ODF

The preparation process of SC-loaded ODF was similar with that of blank ODF. SC was accurately weighed and uniformly suspended in the blank ODF solution, followed by casting on a stainless steel plate (15 × 4 cm^2). The following procedure was the same as that for the preparation of blank ODFs as described above.

3.4. Film thickness

The thickness of the ODFs was measured using calibrated digital vernier calipers. The thickness of each film was tested at three different positions and every position was measured three times.

3.5. In vitro disintegration studies

In vitro disintegration of the ODFs was determined in a glass of 100 mL distilled water with magnetic stirring about 100 rpm. The temperature of distilled water was 37 ± 0.5 °C. The disintegration time was the time when the films disintegrate into small pieces. The disintegration time was measured by using 1 × 1 cm^2 samples. The results were expressed as the average of three determinations.

3.6. Mechanical properties of ODFs

The mechanical properties of ODFs were measured with a universal testing machine (Instron 3365, USA) with load cell 10 N. The ODFs were cut into small strips with the dimension of 20 × 5 mm^2. The strips were held between two clamps at a distance of 6 mm and pulled by the clamps at the rate of 5 mm/min. Measurements of the mechanical properties of the film were done in triplicate for each formulation. Elastic modulus (EM) and percentage elongation (E %) at break were computed to evaluate the mechanical properties of the ODFs.
In the region of approximately linear proportion of elastic deformation on the load displacement profile, there will be a corresponding strain when putting a stress on an object (Mishra et al. 2011; Cilurzo et al. 2008). Elastic modulus is the ratio of applied stress and corresponding strain and calculated using the following Eq. (1). Percentage elongation at break (E %) was calculated by the following Eq. (2).

$$\text{Elastic moduls} = \text{force at coresonding strain} / (\text{cross-sectional area of the film} \times \text{corresponding strain}) \quad (1)$$

$$\text{Percentage elongation} = \text{increase in length} / \text{original length} \times 100\% \quad (2)$$

3.7. Scanning electron microscopy (SEM)

The surface morphology of ODFs was examined by means of a scanning electron microscope (Model S-4700, Hitachi, Japan) operating at 15 kV. The samples were fixed on a glass stub with double-sided adhesive tape and coated under vacuum with gold in an argon atmosphere prior to observation. The micrographs were recorded to study the morphological and surface characteristics of SC, blank film and SC-loaded film.

3.8. X-ray diffraction (XRD)

The XRD patterns of SC (pure drug), SC-loaded ODF (F15) and its physical mixture (PM) were recorded by using an X-ray diffractometer (MERCURY CCD, Japan) with tube anode Cu over the interval 5–60 °/2θ. The scanning rate was adjusted to 4 °/min.

3.9. Differential scanning calorimetry (DSC)

DSC measurements of SC (pure drug), SC-loaded ODF (F15) and its physical mixture (PM) were performed using a differential scanning calorimeter (Model 2010, TA Instruments, USA). Accurately weighed samples (3 mg) were sealed in aluminum pans. An empty aluminum pan was used as reference. The samples were heated at a scanning rate of 10 °C/min from 10 to 250 °C under a dry nitrogen gas purge.

3.10. Fourier transform-infrared (FT-IR) spectroscopy

The spectra of the samples including the SC (pure drug), blank (F3) and SC-loaded (F15) ODFs were characterized using a FTIR spectrophotometer (Model Excaliber Series UMA-500, Bio-Rad, USA). KBr pellets were prepared by gently mixing 1 mg of the sample with 200 mg KBr. The wavelength ranged from 400 to 4,000 cm^{-1} with a resolution of 2 cm^{-1}.

3.11. In vitro dissolution studies

The *in vitro* dissolution test was carried out according to USP paddle method at a rotation speed of 100 rpm in 900 ml of three different dissolution media maintained at 37 ± 1 °C. The dissolution media used were as follows: simulated gastric fluid (pH 1.2 ± 0.1 HCl solution), simulated intestinal fluids (pH 6.8 ± 0.1 or pH 7.4 ± 0.1 phosphate buffer). Samples of SC-loaded ODFs, equivalently containing 25 mg (6 cm^2), were fixed with clips and sunk into the media. Samples of 2 ml were withdrawn at predetermined time intervals and replaced with fresh medium. SC concentrations were analyzed by a HPLC method as described below. The results were expressed as the average of three determinations. On the other hand, the dissolution of SC from the pure drug substance was also performed to evaluate the effect of formulation factors on the dissolution of drug.

3.12. High performance liquid chromatography (HPLC) analysis

The drug concentration was determined with high performance liquid chromatography (HPLC, Waters 1525, America) equipped with UV detection set at 292 nm. The separation was performed at 30 °C on a Phenomenex® C18 (4.6 × 150 mm, 5 μm) column. Acetonitrile/water/triethylamine (32:68:0.5; v/v/v) was used as mobile phase and adjusted to pH 3.1. The flow rate was set at 1.0 mL/min. The injection volume was 20 μL.

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