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Formulation and *in vitro* characterization of novel sildenafil citrate-loaded polyvinyl alcohol-polyethylene glycol graft copolymer-based orally dissolving films

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ABSTRACT

This work was aimed to develop novel sildenafil citrate (SC)-loaded polyvinyl alcohol (PVA)-polyethylene glycol (PEG) graft copolymer (Kollicoat® IR)-based orally dissolving films (ODFs) using a solvent casting method. Formulation factors such as plasticizers and disintegrants were optimized on the basis of characteristics of blank ODFs. The SC-loaded ODF with a loading capacity up to 6.25 mg in an area of 6 cm^2 was prepared and evaluated in terms of mechanical properties, disintegration time and dissolution rate. The physicochemical properties of drug-loaded ODF were also investigated using the scanning electron microscope (SEM), X-ray diffraction (XRD), differential scanning calorimetry (DSC) and Fourier transform infrared spectroscopy (FT-IR). The blank ODF composed of Kollicoat® IR, sodium alginate (ALG-Na) and glycerol (10:2:1.5, w/w) had a remarkably short disintegration time of about 20 s. The SC-loaded ODF showed a delayed disintegration time (about 25 s), but exhibited improved mechanical properties when compared to the blank ODF. SC was homogenously dispersed throughout the ODF and the crystalline form of drug had been partly changed, existing strong hydrogen bonding between the drug and carriers. The Kollicoat® IR/ALG-Na based ODFs containing SC might be an alternative to conventional tablet for the treatment of male erectile dysfunction.

1. Introduction

Orally dissolving films (ODFs) are strip type preparations with active molecules dissolved or dispersed in film forming materials (Choudhary et al., 2012; Cilurzo et al., 2008; Kunte and Tandale, 2010). An ODF is simply placed on a patient's tongue without drinking any water, and subsequently disintegrates and dissolves to release the drug for mucosal or gastrointestinal absorption. In addition, compared with traditional orally disintegrating tablets (ODTs), it can be prepared using simple preparation process and are easy to carry, store and handle (Shimoda et al., 2009; Yellanki et al., 2011).

Generally, ODFs are prepared by using water soluble polymers with good film forming properties. Numerous types of hydrophilic polymers, such as polyvinyl alcohol (Arya et al., 2013; Scott et al., 2013), hydroxypropyl methylcellulose (Yellanki et al., 2011; Figueroa et al., 2012), pullulan (Avani and Renuka, 2011; Mishra and Amin, 2011; Sakata and Otsuka, 2009) and maltodextrin (Kunte and Tandale, 2010; Patel et al., 2009) have been widely studied or used in marketed products. Due to their good chemical stability, biocompatibility, and low toxicity, these polymers have been attracting a great deal of attention for the formulation of new products in the last few years (Cilurzo et al., 2010; Koland et al., 2010; Mahesh et al., 2010). However, the longer disintegration time and poor mechanical property still limit the clinical application of ODFs.

Kollicoat® IR, a polyvinyl alcohol (PVA)-polyethylene glycol (PEG) graft copolymer is a pharmaceutical excipient has been widely used as a coating polymer for instant release formulations (Fouad et al., 2011). It is hydrophilic and easily dispersible in water, highly flexible through integrated plasticizer, and easy to formulate and process (Muschert et al., 2011). Although Kollicoat® IR-based oral films had been raised great interests in recent years (Mahesh et al., 2010; Reddy et al., 2013; Sultana et al., 2013), few detailed studies for the formulation and *in vitro* characterization could be found from the literature search.

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On the other hand, sodium alginate (ALG-Na), an indigestible biomaterial produced by brown seaweeds has been usually 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 and Breitkreutz, 2010), resulting in rapid water absorption and swelling properties. Therefore, the disintegrating roll of ALG-Na could be expected when it was incorporated into Kollicoat® IR-based ODFs.

Sildenafil citrate (SC) is an active ingredient for treatment of male erectile dysfunction (ED) (Boolell et al., 1996; Liu et al., 2010). The dosage forms of SC for clinical application are tablets. But like any other general tablets, it is not convenient to take when there is no water nearby. In order to avoid this shortcoming, we designed novel SC-loaded Kollicoat® IR/ALG-Na based ODFs with a short disintegration time by a solvent-casting method. Blank ODFs were optimized with different type and amount of plasticizers and disintegrants 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. Materials and methods

2.1. Materials

Sildenafil citrate (SC) was received as a gift sample from EuraPharm Co. (Suwon, Korea). Polyvinyl alcohol-polyethylene glycol graft copolymer (Kollicoat® IR) was kindly provided by BASF Pharma (Shanghai, China). Polyethylene glycol (PEG) with different viscosity grades (400 and 4000), glycerol, carboxymethyl starch sodium (CMS-Na), and sodium alginate (ALG-Na) were purchased from Simopharm Chemical Reagent Co. (Shanghai, China). All other chemicals used were of analytical grade.

2.2. Preparation of orally dissolving films (ODFs)

2.2.1. Preparation of blank ODFs

The blank ODFs were prepared by a solvent-casting method (Cilurzo et al., 2010). Briefly, accurately weighed Kollicoat® IR was dispersed in water and the dissolution was facilitated by heating the solution at 80 °C with magnetic stirring until it became clear. Subsequently, desired amounts of the other ingredient were added in the Kollicoat® IR solution and blended continuously 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 was carefully poured on a stainless steel plate ($15 \times 15\ cm^2$) to form a uniform liquid layer and then dried into film in a hot air oven at 60 °C for 12 h. The films were removed from the stainless steel plate carefully and cut into strips of dimensions $2 \times 3\ cm^2$ and stored in an air tight glass bottle. The detailed formulation compositions of blank ODFs are given in Table 1.

2.2.2. Preparation of SC-loaded ODFs

The preparation process of SC-loaded ODF was similar with that of blank ODFs. For the drug-loaded ODF, the amount of each SC was accurately weighted and uniformly suspended in the blank ODF solution, followed by casting on a stainless steel plate ($15 \times 4\ cm^2$). The rest procedure was same as that for preparation of blank ODFs as described above. The formulation composition of SC-loaded ODF is also given in Table 1.

2.3. Disintegration test

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 $1 \times 1\ cm^2$ samples. The results were expressed as the average of three determinations.

2.4. Film thickness

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

2.5. Mechanical properties of ODFs

The mechanical properties of the ODFs were measured by using universal testing machine (Instron 3365, USA). The ODFs were cut into small strips with the dimension of $20 \times 5\ mm^2$. 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 liner proportion of elastic deformation on the load displacement profile, there will be a corresponding strain when putting a stress on an object (Mishra and Amin, 2011). 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).

$$\text{Elastic modulus} = \frac{\text{Force at corresponding strain}}{\text{Cross-sectional area of the flim} \times \text{Corresponding strain}} \quad (1)$$

Table 1
Formulation compositions of blank and SC-loaded ODFs.

Ingredients	Formulation											
(g)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
SC	–	–	–	–	–	–	–	–	–	–	–	0.0625
Kollicoat® IR	1	1	1	1	1	1	1	1	1	1	1	0.27
PEG 4000	0.25	–	–	–	–	–	–	–	–	–	–	–
PEG 400	–	0.25	–	–	–	–	–	–	–	–	–	–
Glycerol	–	–	0.25	0.20	0.15	0.15	0.15	0.15	0.15	0.15	0.15	0.0405
ALG-Na	–	–	–	–	–	–	0.10	0.15	0.20	–	–	0.054
CMS-Na	–	–	–	–	–	0.10	–	–	–	0.15	0.20	–
Water (mL)	20	20	20	20	20	20	20	20	20	20	20	20