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Preparation and characterization of fast dissolving flurbiprofen and esomeprazole solid dispersion using spray drying technique

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ABSTRACT

We aimed to develop an immediate-release flurbiprofen (FLU) and esomeprazole (ESO) combination formulation with enhanced gastric aqueous solubility and dissolution rate. Aqueous solubility can be enhanced by formulating solid dispersions (SDs) with a polyvinylpyrrolidone (PVP)-K30 hydrophilic carrier, using spray-drying technique. Aqueous and gastric pH dissolution can be achieved by macro-environmental pH modulation using sodium bicarbonate ($NaHCO_3$) and magnesium hydroxide ($Mg(OH)_2$) as the alkaline buffer. FLU/ESO-loaded SDs (FLU/ESO-SDs) significantly improved aqueous solubility of both drugs, compared to each drug powder. Dissolution studies in gastric pH and water were compared with the microenvironmental pH modulated formulations. The optimized FLU/ESO-SD powder formulation consisted of FLU/ESO/PVP-K30/sodium carbonate (Na_2CO_3) in a weight ratio 1:0.22:1.5:0.3, filled in the inner capsule. The outer capsule consisted of $NaHCO_3$ and $Mg(OH)_2$, which created the macro-environmental pH modulation. Increased aqueous and gastric pH dissolution of FLU and ESO from the SD was attributed to the alkaline buffer effects and most importantly, to drug transformation from crystalline to amorphous SD powder, clearly revealed by scanning electron microscopy, differential scanning calorimetry, and powder X-ray diffraction studies. Thus, the combined FLU and ESO SD powder can be effectively delivered as an immediate-release formulation using the macro-environmental pH modulation concept.

1. Introduction

Non-steroidal anti-inflammatory drugs (NSAIDs) are the most frequently used medicines to treat osteoarthritis and the mild to moderate pain associated with numerous conditions including headaches and migraines, dysmenorrhea, and muscle soreness. However, NSAIDs commonly cause various side effects such as stomach ulcers or gastrointestinal (GI) bleeding. The best supportive treatment in such conditions would be a stomach acid reducer such as the over-the-counter proton pump inhibitors. Acid reducers can lower the incidence of ulcers and GI bleeding in people taking NSAIDs. Therefore, a single formulation incorporating this combination with the added advantage of enhanced solubility and dissolution might prove beneficial and more economical for dual treatment (Alleso et al., 2009).

Flurbiprofen (FLU) is a potent nonsteroidal anti-inflammatory drug used to treat the inflammation and pain associated with arthritis (Pirnau et al., 2012). Although FLU has potent anti-inflammatory activity following oral administration, it has unwanted adverse effects such as GI irritation and other systemic side effects (Brogden et al., 1979). On the other hand, esomeprazole (ESO), bis (5-methoxy-2-[(*S*)-[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1-H-benzimidazole-1-yl) magnesium salt is a compound that inhibits gastric acid secretion (Scott et al., 2002). Both drugs exhibit low aqueous solubility and high permeability and, therefore, are considered as Class II agents according to the US Food and Drug Administration (FDA) Biopharmaceutics Classification System (US FDA, 2009). Furthermore, FLU exhibits pH-dependent solubility, which indicates that it is poorly soluble under low-pH conditions such as the gastric pH 1.2 but highly soluble at higher pH such as the intestinal pH 6.8 (Muraoka et al., 2004). Similarly, ESO degrades rapidly at low pH values and is photo- and heat-sensitive (Kristl, 2009; Tetsuro et al., 1992). Therefore, it is necessary to protect it from gastric acid when administered orally (Alai and Lin, 2013). Thus, acid-labile drugs are

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frequently formulated as enteric-coated dosage forms to prevent acid degradation.

Considering the limiting physicochemical properties of FLU and ESO (low aqueous solubility and instability at low pH), they were co-formulated using the solid dispersion (SD) technique to prepare SDs with enhanced aqueous solubility and dissolution rate. SDs enhance drug solubility by converting the drug's crystal lattice to an amorphous form, reducing the particle size, and increasing wettability by the action of the hydrophilic polymer (Marasini et al., 2013; Newa et al., 2007; Tran et al., 2013). However, SDs have various limitations such as the lack of appropriate carriers to adequately solubilize the drug and enhance solubility of pH-dependent and readily ionizable drugs. One approach for increasing the solubility of pH-dependent drugs involves the incorporation of various pH modifiers (alkaline or acidic agents) in the SD (Marasini et al., 2013; Tung et al., 2011). These agents alter the drug release rate by manipulating the microenvironmental pH in the vicinity of the SD formulation, thereby reducing drug recrystallization to a certain extent and increasing drug diffusion to the bulk medium (Bassi and Kaur, 2010; Tran et al., 2010).

The objective of the present study was to enhance the aqueous solubility of a combination of FLU and ESO by formulating them as an SD, and creating a macro-environment (slightly alkaline pH 5–8) in the stomach using a high concentration of buffers for the immediate and simultaneous dissolution of ESO and FLU. To this end, we developed an FLU and ESO combination immediate release SD formulation (FLU/ESO-SD) using a spray drying technique with PVP K30 as the hydrophilic carrier. The SD powder optimization was based on the results of an aqueous solubility study. Furthermore, the SDs were physically characterized using scanning electron microscopy (SEM), differential scanning calorimetry (DSC), and powder X-ray diffraction (P-XRD). The effects of macro- and microenvironmental pH modulation of the optimized formulation were compared during the dissolution study.

2. Materials and methods

2.1. Materials

FLU and ESO magnesium dihydrate were supplied by Hanmi Pharm. Co., (Suwon, South Korea). Sodium carbonate (Na_2CO_3), $NaHCO_3$, disodium hydrogen phosphate (Na_2HPO_4), trisodium phosphate (N_3PO_4), calcium carbonate ($CaCO_3$), magnesium oxide (MgO), and magnesium hydroxide ($Mg(OH)_2$) were purchased from DC Chemical Co., Ltd. (Namyangju, South Korea). Polyvinylpyrrolidone (PVP) K30 was purchased from BASF Chemical Co., (Ludwigshafen, Germany). All other chemicals were reagent grade and used without further purification.

2.2. Effect of alkalizer

A total of 1 and 0.22 g of pre-sieved FLU and ESO, respectively, were dissolved in 100 mL of ethanol, while 0.5 g of PVP K30 and varying amounts of sodium carbonate (Na_2CO_3) were dissolved in 100 mL water. Then, the FLU/ESO solution was dispersed in the carrier solution with magnetic stirring. The amount of Na_2CO_3 added was varied until a homogenously clear solution was obtained. The detailed compositions of the FLU/ESO solutions prepared are provided in Table 1.

Table 1
Composition of various flurbiprofen (FLU) and esomeprazole (ESO)-loaded solid dispersions (FLU/ESO-SDs) prepared using various polymer-to-alkalizer ratios.

Ingredients (g)	F1	F2	F3	F4	F5	F6	F7	F8
Flurbiprofen (FLU)	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0
Esomeprazole Mg dehydrate (equivalent to 100 mg ESO)	0.22	0.22	0.22	0.22	0.22	0.22	0.22	0.22
PVP K30	0.5	0.5	0.5	0.5	0.5	0.5	1.0	1.5
Na_2CO_3	–	0.1	0.2	0.3	0.4	0.5	0.3	0.3

PVP K30: polyvinylpyrrolidone K30.

2.3. Preparation of FLU/ESO-SD

The FLU/ESO-SD was prepared using a lab-scale Buchi 191 nozzle-type mini spray dryer (Flawil, Switzerland). Briefly, the FLU/ESO solutions were prepared using the same method used in Section 2.2. PVP K30, a hydrophilic polymer was selected due to its good stabilizing effect on the production of amorphous solid dispersion. Then the resulting dispersed solutions were immediately spray-dried at a spray pressure of 4 kg/cm^2. Atomization of the drying air was maintained at an aspirator setting of 10, which indicated that the pressure in the aspirator vessels was −25 mbar. The direction of the airflow was the same as that of the sprayed products. The inlet and outlet temperatures were 100 and 65–70 °C, respectively, while the feeding rate was 3 mL/min.

2.4. Aqueous solubility of FLU/ESO-SD

The solubility of the FLU/ESO-SDs prepared using varying amounts of the carriers was determined by adding excess amounts of the SD into 1 mL water. All the samples were shaken in an isothermal water bath at 25 °C for 3 days (100 rpm), centrifuged at 10,000*g* for 10 min (Eppendorf, NY, USA), and the supernatants were filtered through a membrane filter (0.45-μm). The filtered samples were then diluted with the mobile phase to obtain a suitable concentration for the quantification of FLU and ESO using a high-performance liquid chromatography (HPLC) method. The HPLC system (Hitachi, Tokyo, Japan) consisted of a pump (Model L2100), an autosampler (Model L2200), and an ultraviolet (UV) detector (Model L2420). A C_{18} analytical column (Inertsil® ODS-3: 5 μm, 0.46 cm × 15 cm, GL Sciences Inc., Japan) was used. For the analysis of FLU, the mobile phase consisted of a mixture of HPLC grade acetonitrile (ACN), purified water, and phosphoric acid (60:40:0.5 v/v) while for ESO, a mixture of vacuum-filtered and degassed ACN and phosphate buffer (35:65 v/v, pH adjusted to 6.8) was used. The effluent was monitored at a UV absorption wavelength of 254 and 300 nm for FLU and ESO, respectively, at a flow rate of 1.0 mL/min. The HPLC methods for both drugs were validated over the concentration range of 0.5 μg/ml to 250 μg/ml. All standard curves showed excellent linearity with $R^2 = 0.9999$. The inter-day and intra-day precision RSD values for both FLU and ESO were less than 8.4%, while inter- and intra-day accuracy for both drugs were more than 96%, respectively.

2.5. Solid-state characterization

2.5.1. SEM

Morphological analysis of FLU/ESO-SD was carried out using an S-4100 scanning electron microscope (SEM, Hitachi, Tokyo, Japan). The SEM photomicrographs were acquired to compare the crystal morphology of FLU and ESO powders, PVP-K30, the physical FLU/ESO mixture, and FLU/ESO-SD. The samples were fixed on a brass stub using double-sided adhesive tape and rendered electrically conductive by coating them 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).

2.5.2. Differential scanning calorimetry (DSC)

The thermal analysis of the FLU and ESO powders, PVP-K30, physical FLU/ESO mixture, and FLU/ESO-SDs was carried out using