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Development of novel fast-dissolving tacrolimus solid dispersion-loaded prolonged release tablet

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ABSTRACT

The goal of this research was to develop a novel prolonged release tablet bioequivalent to the commercial sustained release capsule. A number of tacrolimus-loaded fast-dissolving solid dispersions containing various amounts of DOSS were prepared using the spray drying technique. Their solubility, dissolution and pharmacokinetics in rats were studied. DOSS increased drug solubility and dissolution in the solid dispersions. Compared with the drug powder, the solubility, dissolution and bioavailability of tacrolimus with the fast-dissolving solid dispersion containing tacrolimus/HP-β-CD/DOSS in the weight ratio of 5:40:4 were boosted by approximately 700-, 30- and 2-fold, respectively. Several tablet formulations were accomplished with this solid dispersion in combination with various ratios of HPMC/ethylcellulose. The release behaviour and pharmacokinetic studies in beagle dogs were assessed compared with the commercial prolonged release capsule. A decrease in HPMC/ethylcellulose ratios reduced the dissolution of tacrolimus from the tablets. Particularly, the tacrolimus-loaded prolonged release tablet consisting of fast-dissolving tacrolimus solid dispersion, HPMC, ethylcellulose and talc at the weight ratio of 20:66:112:2 exhibited a dissolution profile similar to that produced by the commercial prolonged release capsule. Furthermore, there were no significant differences in the AUC, C_{max}, T_{max} and MRT values between them in beagle dogs. Consequently, this tacrolimus-loaded prolonged release tablet might be bioequivalent to the tacrolimus-loaded commercial capsule.

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1. Introduction

Tacrolimus is an effective immunosuppressive agent. It is clinically used in the prophylaxis of organ rejection after hepatic and renal transplantation procedures (Arima et al., 2001). The oral route is considered the most suitable and safe way to administer the drug. However, the poor solubility of tacrolimus in an aqueous environment (about 1–2 μg/ml) limits its bioavailability after oral administration. Accordingly, the solid dispersion technique (Joe et al., 2010; Park et al., 2009; Watts et al., 2009, 2010; Yoshida et al., 2012), nanoparticle development (Sinswat et al., 2008), self-emulsifying drug delivery system (SEDDS) (Wang et al., 2011a,b) and inclusion complex formation (Arima et al., 2001; Gao et al., 2012) have been employed to boost the aqueous solubility and oral bioavailability of tacrolimus.

Furthermore, a commercial sustained release product (Advagraf®; Astellas Pharm. Co., Surrey, UK) enclosing 0.5, 1.3, or 5 mg tacrolimus in hard capsules for once-daily oral administration was made available in the market (First, 2008; Fischer et al., 2011). Controlled release oral drug delivery systems are useful in attaining and maintaining safe therapeutic plasma concentrations of drugs possessing a narrow therapeutic index (Zhao et al., 2013). However, controlled release delivery systems cannot be formulated with BCSII drugs demonstrating significantly limited solubility in aqueous media, (Fischer et al., 2011; Wang et al., 2011a). Thus, prior to developing controlled release delivery systems of such drugs, we need to employ certain techniques to resolve their solubility and dissolution problems in aqueous media, these drugs can be developed as sustained release oral products (Buckley et al., 2013; Butler and Dressman, 2010).

The spray-dried solid dispersion formulated with tacrolimus, hydroxypropyl-β-cyclodextrin (HP-β-CD) and dioctyl sulphosuccinate (DOSS) via the solvent evaporation technique was previously employed to increase the aqueous solubility of poorly water-solu-

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ble tacrolimus (Joe et al., 2010; Park et al., 2009). The solid dispersion system is one of the promising methods to ameliorate the aqueous solubility of poorly water-soluble drugs (Marasini et al., 2013; Yan et al., 2012). The crystalline drugs might go to the amorphous state after loading in the polymeric carriers. In this way, the solubility and dissolution of the loaded drug might be significantly improved. In this case, the drugs are molecularly dispersed in the polymeric carriers, to achieve maximum particle size reduction and surface area availability (Lee et al., 2013; Tran et al., 2013).

In this study, to optimise the solubility and dissolution of tacrolimus, fast-dissolving solid dispersions were prepared with different quantities of DOSS by the spray drying procedure. The influence of DOSS on the solubility and dissolution of the drug was assessed. Moreover, pharmacokinetic evaluation in rats was performed compared with the drug powder. Furthermore, to develop a novel prolonged release tablet bioequivalent to the commercial prolonged release capsule, the best selected tacrolimus-loaded fast-dissolving solid dispersion was punched together with various ratios of hydroxypropyl methylcellulose (HPMC)/ethylcellulose. The release profile and pharmacokinetics of the manufactured tablets in beagle dogs were evaluated compared with the commercial prolonged release capsule. Generally, the tablet form containing sustained release system is easily produced and is more stable than hard capsule form because the latter is very sensitive to humidity and temperature, and involves two step procedure such as production of sustained release granules and filling in capsule shell (Cho and Choi, 2013; Lim et al., 2010).

2. Materials and methods

2.1. Materials

Tacrolimus was supplied by Shanghai Qiao Chemical Science Co. (Shanghai, China). hydroxypropyl-β-cyclodextrin (HP-β-CD), dioctyl sulphosuccinate (DOSS) and talc were kindly sent by Hanmi Pharm. Co. (Suwon, South Korea). hydroxypropyl methylcellulose 2910 (HPMC) and ethylcellulose were purchased from Duksan Chem. Co. (Ansan, South Korea). The commercial product (Advagraf®, 1 mg; in prolonged release hard capsule form) was purchased from Astellas Korea Pharm. Co. (Seoul, South Korea). All other chemicals were of reagent grade and used without further purification.

2.2. Preparation of tacrolimus-loaded fast-dissolving solid dispersions and prolonged release tablets

The tacrolimus-loaded fast-dissolving solid dispersions were obtained using a Büchi 190 nozzle type mini spray dryer (Flawil, Switzerland). Tacrolimus (0.2 g), HP-β-CD (2 g) and DOSS (0.05–0.2 g) were completely dissolved in a 75 ml methylene chloride/ethanol mixture (1:2, volume ratio). The resulting clear solution was sprayed through the nozzle (0.7 mm diameter) at a flow rate of 5 ml/min using a peristaltic pump. The sprayed products were dried at 125 °C inlet temperature and 65–70 °C outlet temperature. The dried tacrolimus-loaded solid dispersion was carried in the direction of airflow into the collecting vessel. The pressure of sprayed air was 4 kg/cm^2. The flow rate of drying air was maintained at the aspirator setting of 10, which indicated the pressure of aspirator filter vessel at −25 mbar.

The morphology of the tacrolimus-loaded solid dispersion (tacrolimus/HP-β-CD/DOSS [5:40:4]) was inspected by a scanning electron microscope (S-4100, Hitachi, Japan). The sample was affixed on a brass specimen club using double-sided adhesive tape and made electrically conductive by coating with platinum (6 nm/min) in a vacuum (6 Pa) for 300 s at 15 mA using a Hitachi Iron Sputter (E-1030, Hitachi, Japan).

The tacrolimus-loaded prolonged release tablets were manufactured using the direct compression method. In brief, the tacrolimus-loaded solid dispersion, HPMC, ethylcellulose and talc were blended thoroughly (Table 1). The resultant mixture was directly compressed with a diameter of 6 mm and a hardness of 4–5 KP using the ERWEKA tablet machine (ERWEKA GmbH; Frankfurt, Germany).

2.3. Aqueous solubility of the drug in tacrolimus-loaded fast-dissolving solid dispersions

An excess of solid dispersions (about 20 mg) was added to 10 ml of water and shaken in a water bath at 25 °C for 5 days. In preliminary investigation, tacrolimus is very stable in aqueous solution during experimental period, because tacrolimus solution is commercialised as an eye drop product (Moscovici et al., 2012). The sample was centrifuged at 3000*g* for 10 min (Eppendorf, USA) and the supernatant was filtered through a membrane filter (0.45 μm). The concentration of tacrolimus in the filtrate was measured by the HPLC method as described below in Section 2.4.

2.4. Release of drug from the tacrolimus-loaded fast-dissolving solid dispersions and prolonged release tablets

The release test of tacrolimus-loaded preparations was carried out according to USP XXII, section "tacrolimus capsules" (USP36, 2013). The hard capsules enclosing the tacrolimus-loaded fast-dissolving solid dispersion or the drug powder equivalent to 1 mg tacrolimus were introduced into a sinker. The sinker was then placed in the dissolution tester (Shinseang Instrument Co., Hwasung, South Korea). Moreover, the prolonged release tablets or commercial capsules were used for determining the in vitro sustained release property of the drug. The release test was executed at 37 ± 0.5 °C using the paddle method. The paddle rotated at 50 rpm in 500 ml distilled water containing 0.005% hydroxypropylcellulose. The pH of the dissolution medium was adjusted to 4.5 with phosphoric acid. At pre-set time intervals, 3 ml of the medium was sampled and filtered through a membrane filter (0.45 μm). Then, the titre of tacrolimus in the filtrate was quantified by HPLC (Hitachi, Tokyo, Japan) furnished with the Inertsil ODS-2 column (5 μm, 2.5 cm × 4.6 mm i.d.) and UV detector (Model L-2400). The mobile phase consisting of water and acetonitrile (1/3, v/v) was eluted at a flow rate of 1.0 ml/min. The eluent was monitored at 210 nm for tacrolimus concentration detection (Joe et al., 2010; Park et al., 2009).

2.5. In vivo study

2.5.1. Animals

All animal care procedures and experimental methods were carried out following the Guiding Principles in the Use of Animals

Table 1
Composition of tacrolimus-loaded tablets.

Ingredients (mg)	I	II	III	IV	V	VI	VII
Solid dispersion*	20	20	20	20	20	20	–
Tacrolimus	–	–	–	–	–	–	2
HP-β-CD	–	–	–	–	–	–	16.4
DOSS	–	–	–	–	–	–	1.6
HPMC	178	89	71.2	66	59.3	44.5	66
Ethylcellulose	0	89	106.8	112	118.6	133.5	112
Talc	2	2	2	2	2	2	2
Total	200	200	200	200	200	200	200

* The solid dispersion was composed of tacrolimus/HP-β-CD/DOSS at a weight ratio of 5:40:4.

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