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Improved oral absorption and chemical stability of everolimus via preparation of solid dispersion using solvent wetting technique

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ABSTRACT

The aim of this study was to improve the physicochemical properties and oral absorption of poorly water-soluble everolimus via preparation of a solid dispersion (SD) system using a solvent wetting (SW) technique. The physicochemical properties, drug release profile, and bioavailability of SD prepared by SW process were also compared to SD prepared by the conventional co-precipitation method. Solid state characterizations using scanning electron microscopy, particle size analysis and X-ray powder diffraction indicated that drug homogeneously dispersed and existed in an amorphous state within the intact polymeric carrier. Whereas, a film-like mass was obtained by a co-precipitation method and further pulverization step was needed for tabletization. The drug release from the SD tablet prepared by SW process at a ratio of drug to hydroxypropyl methylcellulose of 1:15 was markedly higher than the drug alone and equivalent to the marketed product (Afinitor®, Novartis Pharmaceuticals), a SD tablet prepared by co-precipitation method, archiving over 75% the drug release after 30 min. At the accelerated (40 °C/75% R.H.) and stress (80 °C) stability tests, the novel formula was more stable than drug powder and provided comparable drug stability with the commercially available product, which contains a potentially risky antioxidant, butylated hydroxyl toluene. The pharmacokinetic parameters after single oral administration in beagles showed no significant difference ($P > 0.01$) between the novel SD-based tablet and the marketed product. The results of this study, therefore, suggest that the novel SD system prepared by the solvent wetting process may be a promising approach for improving the physicochemical stability and oral absorption of the sirolimus derivatives.

1. Introduction

Everolimus (EVR), the 40-*O*-(2-hydroxyethyl) derivatives of the natural product sirolimus, has been recently prescribed for the treatment of patients with advanced renal cell carcinoma (RCC) after their disease fails to respond to sunitinib or sorafenib treatment. EVR inhibits the mammalian target of rapamycin (mTOR), a component of an intracellular signaling pathway that regulates cellular metabolism, growth, proliferation, and angiogenesis (Motzer et al., 2008; Yuan et al., 2009). In recent days, the mTOR inhibitor has been further approved for the treatment of a number of cancers, including breast cancer, neuroendocrine tumors, and renal angiomyolipoma with tuberous sclerosis complex, which indicates the increasing clinical significance of EVR as an anti-neoplastic agent. However, the oral absorption of EVR is challenging owing to its low solubility in water, unfavorable breakage of the drug in the gastrointestinal tract, and intestinal efflux by p-glycoprotein transporter (Guitard et al., 1997). The absolute oral bioavailability (BA) of the mTOR inhibitor was only 5% in the mouse, 6% in the monkey and 14–26% in the rat (EMEA, 2009). In addition, the molecule is extremely susceptible to oxidative degradation via a radical mechanism (EMEA, 2009).

To improve dissolution and oral BA of EVR, the originator (Novartis Pharmaceuticals, Basel, Switzerland) formulated an oral dosage form (Afinitor®) based on the solid dispersion (SD) system, with a hydrophilic polymer hydroxypropyl methyl cellulose (HPMC) (EMEA, 2009). In their co-precipitation method, both the drug and HPMC are dissolved in organic solvents and then vacuum or spray dried (Guitard et al., 1997). The drug molecularly dispersed in the polymer provides the high levels of particle size reduction and surface area enhancement, which resulted in improved dissolution rates (Swarbrick, 1990; Shargel, 1993; Craig, 2002). Also, the aqueous solubility and wettability of the drug may be increased by the surrounding hydrophilic carrier (Swarbrick, 1990; Shargel, 1993; Leuner and Dressman, 2000). However, the process is composed of the complex steps of mixing and dissolving

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a sirolimus derivative and a polymer in an organic solvent, evaporating the solvent, and pulverizing dry residues to obtain a particulate (Guitard et al., 1997). The process introduces residual solvent, which may create environmental issues. In addition, the marketed product contains butylated hydroxytoluene (BHT) to improve chemical stability (EMEA, 2009) of EVR, which could raise a lot of controversy with regards to the association of the anti-oxidant with hyperactivity disorder for some children and carcinogenicity (Williams et al., 1990).

The approaches used to formulate SD include the melting method, co-precipitation method, roll or co-mixing, and solvent wetting method (Ford, 1986; Leuner and Dressman, 2000; Yamashita et al., 2003). Among them, solvent wetting (SW) process requires a minimal amount of solvent in dissolving the poorly water-soluble drug and uniformly dispersing it in the polymeric carrier (Ford, 1986; Kim et al., 2006; Yamashita et al., 2003). The SW approach can provide uniform and free-flowing granules while minimizing granular changes in the polymeric carrier, and thereby it has the advantage that the pulverization step of the particulates can be omitted in comparison with the co-precipitation approach. Furthermore, we surprisingly found that the chemical stability of EVR significantly improved by dispersing the drug molecule into the carrier using the SW technique.

The aim of this study was to develop the SD system for the improvement of the physicochemical properties and the BA of poorly water-soluble EVR, using the SW approach. The physico-chemical properties of SD granule prepared by SW process were characterized by scanning electron microscopy, particle size analysis, and powder X-ray diffraction and compared to SD prepared by the co-precipitation method. We subsequently tabletized the SD powders prepared by SW process by direct compression (named SW-T) and compared the dissolution profile, chemical stability, and pharmacokinetic profiles of EVR with the marketed product (Afinitor®), a SD tablet prepared by co-precipitation method, in beagle dogs.

2. Materials and methods

2.1. Materials

EVR with and/or without BHT and sirolimus, as an internal standard for LC–MS/MS analysis, were purchased from Biocon Ltd. (India, purity over 99.0 w/w%). Hydroxypropyl methylcellulose (HPMC 2910) was kindly provided from Shin-Etsu Chemical Co., Ltd. (Tokyo, Japan). Microcrystalline cellulose (Avicel PH 112) and crospovidone (Kollidon CL) were obtained from FMC Corporation (Philadelphia, USA) and BASF Co., Ltd. (Ludwigshafen, Germany), respectively. Magnesium stearate and sodium lauryl sulfate (SLS) were obtained from Duksan Co., Ltd. (Seoul, Korea). The commercially available product (Afinitor®) was purchased from the market. All organic solvents were high-pressure liquid chromatography (HPLC) grade. All other chemicals were of reagent grade and were used without further purification.

2.2. Preparation of SD of EVR and tabletization

2.2.1. Preparation of SDs by SW method

EVR (100 mg) was dissolved in an appropriate amount of ethanol. The amount of ethanol used was the same as the weight of the polymer. After complete dissolution of the drug, solutions were dropped onto different amounts of HPMC (500, 1000, 1500 and 2000 mg). Solvents were removed under vacuum at 30 °C for 2 h.

2.2.2. Preparation of SDs by co-precipitation method

Dispersions were prepared by dissolving both 100 mg of drug compound and 1000 mg of HPMC in total 10 ml of absolute ethanol and dicholoromethan (8:2 v/v) under sonication for 15 min. The solvent was removed by evaporation under vacuum at 30 °C for 6 h. The prepared films were pulverized for 10 min and were passed them through a 500 μm sieve for further tabletization.

2.2.3. Preparation of SW-Ts

The SD granules of EVR (50 mg) obtained were blended with lactose, microcrystalline cellulose, crospovidone and magnesium stearate, by dry mixing for 10 min. The formulation containing 10 mg EVR was compressed on a single-punch tablet machine (Erweka, Germany) using an 8-mm round shaped flat punch by the direct compression technique. The total weight of the tablets was set to 500 mg at which the hardness value was 11 ± 1 kP.

2.3. In vitro characterization of SDs of EVR

2.3.1. Drug content

Each formulation containing 10 mg of the drug was dissolved in 20 ml of acetonitrile and sonicated for 10 min. Then the samples were centrifuged at 12,000 rpm for 10 min and the supernatants were analyzed by HPLC analysis. The quantitative determination of EVR was performed by HPLC using acetonitrile-phosphate buffer (KH_2PO_4 0.002 M) (40:60) as a mobile phase at a flow rate of 1.1 ml/min. The HPLC system consisted of a pump (L-2130), UV detector (L-2400), a data station (LaChrom Elite, Hitachi, Japan), and a 15 cm C_{18} column (Shiseido, Tokyo, Japan). The column eluant was monitored at 275 nm, and the peak of EVR was separated with a retention time of 7.5 min.

2.3.2. Scanning electron microscopy (SEM)

The SD powders were coated with a thin gold layer by an automatic magnetron sputter coater system (Jeol MSC201, USA). Then, SEM photographs were taken by a scanning electron microscope (Joel JSM 6510 SEM, USA) operated at an acceleration voltage of 15 kV.

2.3.3. Particle size analysis

The particle size of the SD powders was determined by using a HELOS laser diffraction analyzer (Sympatec GmbH, Germany) equipped with a RODOS vibrating trough disperser.

2.3.4. X-ray powder diffraction (XRD)

XRD observation of the SD powders was performed at room temperature with an X-ray diffractometer (X'Pert Prompt PANalytical Co., Lelyweg, Netherlands). Monochromatic Cu Kα-radiation (λ = 1.5418 Å) was obtained with a Ni-filtration and a system of diverging and receiving slides of 0.5° and 0.1 mm, respectively. The diffraction pattern was measured with a voltage of 40 kV and a current of 30 mA over a 2θ range of 3–40° using a step size of 0.02° at a scan speed of 1 s/step.

2.4. Dissolution test

Dissolution studies were performed according to the USP XXVIII paddle method using a VK 7000 dissolution testing station and VK 750d heater/circulator (Varian Industries, New Jersey, USA). The stirring speed was 50 rpm, and the temperature was maintained at 37 °C ± 0.1 °C. Each test was carried out in 900 ml of dissolution media (pH 1.2, pH 4.0, pH 6.8, distilled water and 0.4 w/v% SLS solution). Each tablet containing 10 mg EVR were put into a sinker then placed in the dissolution medium. Then, 4 ml aliquots were withdrawn at various time intervals and filtered using a 0.45 μm glass membrane syringe filter. At each sampling time, an equal volume of the test medium was replaced. Filtered samples were appropriately diluted with methanol, and the drug concentration was assayed by HPLC as described earlier.