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Formulation of controlled-release pelubiprofen tablet using Kollidon® SR

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ABSTRACT

To develop a matrix-type, controlled-release tablet formulation of pelubiprofen (PLB), a recently developed non-steroidal anti-inflammatory drug, polymeric excipients including hypromellose, hydroxypropylcellulose, Eudragit® RS PO, and Kollidon® SR were screened. A formulation containing 12.4% w/w Kollidon® SR (K2 tablet) was found to be the most promising and stable for 6 months in an accelerated stability test. PLB release from K2 tablet was limited at pH 1.2, but gradually increased at pH 6.8 with a surface-erosion, resulting in the best fit to Hixson-Crowell equation. Comparative human PK studies were performed using a randomized, 2-way crossover design. LC–MS/MS assay revealed that the plasma level of PLB-transOH, an active metabolite, was significantly higher than that of PLB. After multiple dosing of immediate-release tablet (R) and K2 tablet (T), the T/R ratios of *AUC* were 1.02 and 1.04 for PLB and PLB-transOH, respectively. Level A *in vitro-in vivo* correlation was established for the K2 tablet-administered group. PK profile of PLB-transOH was not influenced by food intake, while that of PLB was altered. We suggest that K2 tablet could be administered twice a day without being affected by food intake, thereby enhancing patient compliance.

1. Introduction

Pelubiprofen (PLB), 2-[4-(Oxocyclohexylidene methyl) phenyl] propionic acid, is a recently developed non-steroidal anti-inflammatory drug (NSAID) widely used for treatment of osteoarthritis and rheumatic diseases as well as pain relief. PLB acts *via* dual inhibition of cyclooxygenase (COX) activity and the TAK1-IKK-NF-κB pathway (Shin et al., 2011), in addition to its well-known anti-inflammatory property due to inhibition of prostaglandin synthesis. Like other NSAIDs, the main adverse effects of PLB are gastrointestinal irritation, dyspepsia, heartburn, edema, nausea, and vomiting (Shin et al., 2012).

PLB is rapidly absorbed from the gastrointestinal (GI) tract after oral administration, and reaches maximum plasma concentration after 15 min and 30 min in mice and rats, respectively (Takasaki et al., 1993), and 1 h and 2 h in male and female beagle dogs, respectively (Asami et al., 1995). It is mainly distributed to the liver and kidneys, but not to the central nervous system, and has high affinity (>90%) to plasma proteins (Asami et al., 1996). Absorbed PLB is rapidly metabolized to a saturated ketone and an unsaturated alcohol; the saturated ketone is further metabolized to isomeric metabolites (i.e., *trans*-alcohol form and *cis*-alcohol form) *via* a reduction process in the body. Such a metabolic process is important for the onset of the pharmacologic activity of the drug because the *trans*-alcohol form (PLB-transOH) is the most potent active metabolite (Terada et al., 1984). Since the plasma half-lives of PLB and PLB-transOH are 0.36 h and 1.5 h, respectively, frequent dosing is required. PLB is usually administered *via* the oral route in either fasted or fed condition. Food intake reduced the peak plasma concentration and the area under the curve of the parent molecule, but those of the active metabolite were not significantly affected (Matsuki et al., 1993).

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Controlled drug delivery has improved the clinical efficacy and patient compliance, e.g., it is applied to reduce the dosing frequency and the unwanted adverse effects, to maintain constant drug blood level, and to minimize the food effect (Junghanns and Müller, 2008; Betha et al., 2015). Controlled release (CR) systems generally fall into one of three broad categories: monolithic matrix, reservoir (or membrane-controlled), and osmotic pump (Ankit et al., 2011; Isha et al., 2012; Kundawala et al., 2016). In matrix systems, the drug substance is homogeneously distributed throughout a polymer matrix. Modification of drug release is attained by the use of water-swellable or erodible matrices consisting of various polymeric excipients such as hydrophilic polymers (hypromellose, hydroxypropylcellulose, polyethylene oxide, etc.) and hydrophobic polymers (ethylcellulose, Eudragit® RS and RL PO, Kollidon® SR, etc.) (Lee et al., 2015; Khairnar et al., 2014). Drug release mechanism involves either diffusion or erosion. Matrix systems are cost effective owing to their relatively short developing time and an easy-to-apply technique for formulating a wide range of drugs using conventional manufacturing equipments (Qiu et al., 2009).

In this study, in order to develop a matrix-type PLB preparation, various CR tablets were formulated with different polymeric ingredients. The *in vitro* drug release characteristics of various CR tablets were evaluated. Comparative pharmacokinetic (PK) studies on the selected CR tablet and the immediate release (IR) tablet were performed in healthy human volunteers. The food effect on PLB absorption from the selected CR tablet was also investigated in human PK studies.

2. Materials and methods

2.1. Materials and reagents

PLB (99.8% purity) was purchased from SAMOH Pharm. Co., Ltd. (Gyeonggi-Do, Korea). Hypromellose 60SH-4000 (HPMC2910 4000 cps) and 60SH-10000 (HPMC2910 10000 cps) were purchased from Shin-Etsu (Tokyo, Japan). Eudragit® RS PO was a donation from Evonik Korea Ltd. (Seoul, Korea). Lactose monohydrate (Pharmatose 200M) from DFE Pharma (Goch, Germany), magnesium stearate from FACI (Genoa, Italy), hydroxypropylcellulose (HPC) L type and H type from Nippon Soda Co., Ltd. (Tokyo, Japan), and Kollidon® SR from BASF (Ludwigshafen, Germany) were purchased and used as received. Methanol and acetonitrile of HPLC grade were purchased from J.T. Baker (Phillipsburg, NJ, USA). Commercially available IR-type tablets containing 30 mg PLB (Pelubi®) were kindly provided by Daewon Pharm. Co., Ltd. (Seoul, Korea). PLB-transOH was purchased from Estech Pharma Co. (Gyeonggi-Do, Korea). Butyl paraben and tolbutamide were purchased from Sigma Aldrich (Saint Louis, Missouri, USA). All other chemicals and reagents used were of analytical grade.

2.2. Determination of PLB solubility

The equilibrium solubility of PLB was measured in water and different media (pH 1.2, 4.0, 4.5, 6.8) by placing an excess of the bulk crystalline drug in the aqueous media and shaking at 25 °C for 24 h. Samples were placed in a micro-centrifuge tube and centrifuged at 12,000 rpm for 5 min. A portion of the supernatant was diluted sufficiently with the mobile phase and analyzed by HPLC as described below. For further evaluation, the dimensionless dose number (D_0) was calculated using Eq. (1).

$$D_0 = (M_0/V_0)/C_S \quad (1)$$

where M_0 is the highest dose strength (mg), C_S is the saturation solubility (mg/mL) of the solute, and V_0 is the volume of the medium (250 mL) (Dahan et al., 2009; Kasim et al., 2004).

2.3. Preparation of CR tablets

PLB-containing CR (PLB-CR) tablets were prepared by wet granulation method. PLB, lactose monohydrate, and HPC L were mixed and granulated in the presence of water using a high-speed mixer (SM-5C; Sejong Pharmatech, Incheon, Korea). The wet mass was passed through a 16-mesh sieve. The wet granules were dried at 55 ± 5 °C for 2 h and then passed through a 20-mesh sieve. The dried granules were blended with the selected polymeric excipient: HPMC 2910 and HPC H as hydrophilic polymers; Eudragit® RS PO and Kollidon® SR as hydrophobic polymers. The mixture was blended with magnesium stearate using a Y-mixer (AR YB5; Erweka GmbH, Heusenstamm, Germany), then compressed using a rotary tablet press machine (Piccola Euro B-10 type; Riva, Buenos Aires, Argentina) at a compression force of 10 kN using 7 mm standard concave and round-shaped punches (Young-Chang Punch Co., Gyeonggi-Do, Korea).

2.4. Physical characterization of PLB-CR tablets

Physical testing of PLB-CR tablets was performed after a relaxation period of at least 24 h. Weight variation tests were performed on 20 individually weighed tablets. The thickness and diameter of 10 tablets were measured individually and the crushing strength was determined. Weight variation tests, thickness, diameter, and crushing strength were determined using an automated tablet testing system (Smart-Test 50; Pharmatron, Solothun, Switzerland). Tablet friability was calculated as the percentage of weight loss (4 min, 25 rpm, 60 tablets) using a friabilator (FAT-1, Fine Scientific Instrument, Seoul, South Korea).

2.5. Stability assessment for PLB-CR tablets

According to the ICH guidelines, stability tests were performed under the accelerated and long-term storage conditions. PLB-CR tablets were packed into high-density polyethylene (HDPE) bottles and served as the stability test samples. For accelerated stability, samples were stored at 40 ± 2 °C and 75 ± 5% relative humidity (RH) over 6 months. For long-term storage stability, samples were stored at 25 ± 2 °C and 60 ± 5% RH over 24 months. Drug content and impurities were determined by HPLC assay as described below.

2.6. HPLC determination of PLB content and impurities

The drug content and impurities were analyzed by HPLC. For drug content determination, 20 tablets were weighed individually, crushed into a fine powder, and mixed together to give a sample containing 60 mg of PLB. The mobile phase was poured into the volumetric flask and the drug was extracted for 5 min at 60 Hz using a bath sonicator (8510-DTH; Branson, Danbury, CT, USA). After adding butyl paraben as an internal standard, PLB concentration was determined using HPLC system (Model 1260; Agilent Technologies Inc., Santa Clara, CA, USA). Chromatographic separation was performed using an ODS column (Xbridge C18, 4.6 × 150 mm, 5 μm, Waters, Milford, MA, USA) at a flow rate of 1.0 mL/min with the mobile phase consisting of methanol, water, and glacial acetic acid at a ratio of 1200:800:1 (v/v/v). The sample was injected and the peaks were monitored using a UV detector at 274 nm. For the determination of impurities, the same HPLC system and column were used and chromatographic separation was performed at a flow rate of 0.82 mL/min with a gradient elution that was performed by changing the ratio of mobile phase A