Formulation of Controlled Release Pelubiprofen Tablet Using Matrix-Forming Polymers

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Purpose

Pelubiprofen (PLB) is a propionic acid derivative with analgesic and anti-inflammatory properties and is widely used in the treatment of inflammatory diseases. Because of the short half-life of PLB, it needs to be taken three times a day. Therefore, a controlled release (CR) formulation would benefit patients by elongating the dosing interval. Matrix system has many advantages such as effectiveness, wide range of drug loading and the utilization of conventional manufacturing equipment among CR systems. In this study we employed the matrix system as controlled-release system to develop PLB-containing controlled release tablets (PLB-CRT) to improving patient compliance and efficacy.

Methods

PLB-CRT 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. 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, then compressed using a rotary tablet press machine at a compression force of 10 kN using 7 mm standard concave and round-shaped punches and each tablets containing 45 mg of PLB. In vitro dissolution studies were carried out using USP36 dissolution apparatus type I with a basket rotating at 100 rpm in 900 mL medium (FaSSIF, FeSSIF and pH6.8). The temperature was maintained at 37±0.5°C. To simulate the path of the preparation in GI tract, the buffer transition method was introduced according to the USP dissolution test for delayed release (method A). The dissolution studies were carried for 8 hours (the initial 2 h at pH 1.2 and the remaining 6 h at pH 6.8). Human PK studies were performed under a randomized, open-label, 2-way crossover design. The IR tablet (Pelubi®) containing 30 mg PLB was given orally three times at 0, 6, and 12 h, and the CR tablet (K1) containing 45 mg PLB was given orally twice at 0 and 12 h.

Results

In FaSSIF medium, all tested polymers showed a rate-controlling effect for 2 h with the greatest delay with T2 (HPMC2910 10000cps), followed by T1 (HPMC2910 4000cps), T3 (HPC H), T4 (Eudragit RS PO), and T5 (Kollidon SR). However, in FeSSIF medium, formulations T1-T4 did not show delayed drug release, resulting in complete dissolution of PLB within 15 min. In general, as the ion concentration in a polymer solution increases, the solubility of polymer decreases. In this experiment, the osmolality and ionic strength of FeSSIF are about 2 times higher than those of FaSSIF. At this relatively higher ion concentration, water is less available to fully hydrate the polymer. On the contrary, formulation containing Kollidon SR showed a controlled drug release in both FaSSIF and FeSSIF media: approximately 40% at 1 h and over 70% at 2 h; the release pattern was independent of the ionic strength. Thus, Kollidon SR was finally selected for further optimization. To find the optimal content of Kollidon SR, additional CR tablets (K1-K3) were formulated which containing 12.4%, 18.4% and 24.3% of polymer, respectively. Dissolution properties were tested in pH 6.8 media. K1 showed gradual surface erosion during the dissolution test. Hixson-Crowell model has been applied to a solid dosage form, in which the dissolution profile is parallel to the diminishing tablet's dimensions. On the contrary, K2 and K3, which contained higher amount of Kollidon SR compared to K1, did not disintegrate during the dissolution test and showed the best fit to Peppas-Korsmeyer model. The values of the correlation coefficient (r2) for K1, K2, and K3 were high enough to evaluate the drug dissolution behavior (r2 > 0.95) and diffusional exponents (n) were 0.5749, 0.4523, and 0.4250, respectively. These results indicated that drug release from K1 tablet was governed by anomalous transport, and drug release from K2 and K3 tablets was governed by Fickian diffusion. Based on the drug release profiles, K1 and K2 were subjected for further dissolution studies by the buffer transition method. IR tablets showed a fast release, but both CR tablets showed a limited release less than 10 % during the two-hour acidic stage. After transition to the buffer stage, PLB release from CR tablets gradually increased: K1 released over 90% in 3 h and K2 released less than 80% in the same period. With respect to PLB absorption that mainly occurred in the upper intestine, the release pattern of K1 was more acknowledgeable than that of K2. Therefore K1 was finally selected for further in vivo PK studies. Bioequivalence was evaluated by comparing the relative ratio of AUC and 90% confidence interval (CI) for logarithmic-transformed data. The T/R ratios for AUC were 1.02 for PLB. Moreover, the 90% CI was 0.85-1.23 for PLB which was within the range of the acceptance criteria (from 0.80 to 1.25). Thus, the two formulations were considered bioequivalent in terms of the extent of bioavailability.

Conclusion

PLB-CRT containing Kollidon SR showed gradual surface erosion during the dissolution test, resulting in the best fit to Hixson-Crowell model. Comparative PK studies of IR and K1 tablets using a multiple dosing, cross-over design in human volunteers showed bioequivalence in terms of the extent of bioavailability.