Controlled Release Formulations of Pelubiprofen Employing Kollidon® SR

B.R. Chae¹, C.J. Lim¹, J.S. Bang¹, H.J. Hwang¹, S.H. Song¹, S.I. Sohn¹, H.W. Lee¹, Y.W. Choi²

¹Daewon Pharm., Seoul, KS013, Korea; ²Chung-Ang University, Seoul, KS013, Korea
hifyram@daewonpharm.com

ABSTRACT SUMMARY
Pelubiprofen (PLB), 2-[4-(Oxycyclohexylidene methyl) phenyl] propionic acid, is non-steroidal anti-inflammatory drug (NSAID), and is widely used for the treatment of osteoarthritis or rheumatic disease and for pain relief. Anti-inflammatory property of PLB is due to the inhibition of prostaglandin synthesis. PLB is absorbed rapidly from the gastrointestinal tract after oral administration and also metabolized rapidly. Commercial PLB product (Pelubi®) needs to be taken three times a day. Therefore controlled release of PLB can reduce dosing frequency and improve patient compliance. To achieve controlled release of PLB, Kollidon® SR was used as the matrix polymer, and in vitro and in vivo release was tested.

INTRODUCTION
PLB is widely used for the treatment of osteoarthritis or rheumatic disease and for pain relief. PLB is absorbed rapidly from the gastrointestinal tract after oral administration, rapidly metabolized to four metabolites. Since the half-lives of plasma PLB and the active metabolite (trans-alcohol form) are 0.36 hours and 1.5 hours, respectively, immediately-release (IR) tablet (Pelubi®) needs to be taken three times a day. Therefore the development of controlled release matrix (CRM) tablet containing PLB is required to reduce adverse effect and to improve the patient compliance.

The objective of present study is to formulate a CRM tablet containing PLB. Dissolution profiles of PLB were compared in different media and pharmacokinetic study was performed in beagle dogs after oral administration of CRM and IR tablets.

EXPERIMENTAL METHODS
CRM tablets containing PLB were prepared by wet granulation method. PLB, lactose monohydrate and HPC L type was mixed and granulated using water by high speed mixer (Sejong Pharmatech, Korea). The wet mass was passed through No. 16 sieve. The wet granules were dried at 55°C ± 5°C for 2 hours and sieved (No. 20 sieve). This granule was blended with Kollidon® SR, then the mixture was blended with magnesium stearate using Y-mixer (Erweka YB5, Germany). The final granule mixture was compressed using Piccola tablet press (Riva, Argentina) equipped with standard convex punches of 7-mm diameter (Young-chang, Korea). Each CRM tablet was containing 45 mg PLB, and the formulation ingredients (PC1-PC4) are summarized in Table 1.

The in vitro dissolution studies of CRM tablets (PC1-PC4) were carried out using USP36 dissolution apparatus type I (Agilent 708-DS, USA) with basket rotating at 100 rpm in 900 mL media. The dissolution media was pH 1.2 and pH 6.8 solutions, maintained at 37 ± 0.5 °C. Additional dissolution study was carried out by buffer transition method which changing pH of dissolution media from pH 1.2 to pH 6.8 during test. The drug release of pH 1.2 at different time intervals was measured during 2 hours. The drug release of pH 6.8 and buffer transition method was measured during 6 hours and dissolution tests were stopped when drug release was almost completed (≥ 90 %).

Table 1. Compositions of various controlled release matrix tablets containing Kollidon® SR

<table>
<thead>
<tr>
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<th>PC1</th>
<th>PC2</th>
<th>PC3</th>
<th>PC4</th>
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<tr>
<td>Pelubiprofen</td>
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<td>45.0</td>
<td>45.0</td>
</tr>
<tr>
<td>Lactose monohydrate</td>
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<td>45.0</td>
<td>45.0</td>
<td>45.0</td>
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<tr>
<td>HPC L type</td>
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<td>2.3</td>
<td>2.3</td>
<td>2.3</td>
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<tr>
<td>magnesium stearate</td>
<td>2.3</td>
<td>2.3</td>
<td>2.3</td>
<td>2.3</td>
</tr>
<tr>
<td>Kollidon® SR</td>
<td>6.4</td>
<td>13.4</td>
<td>21.4</td>
<td>30.4</td>
</tr>
</tbody>
</table>

IR (Pelubi®) and PC2 tablets were prepared for pharmacokinetic study in beagle dogs. A single IR tablet containing 30 mg dose of the PLB was given orally at 0, 6, 12 h during experiment, and a single PC2 tablet containing 45 mg dose of PLB was given orally at 0, 12 h. All subjects fasted for at least 12 h before first dosing.

RESULTS AND DISCUSSION
CRM tablets were made from various contents of polymer (6.4, 13.4, 21.4, 30.4 mg) and in vitro release was tested (Fig. 1). At pH 1.2 buffer solutions PLB was released about 12 % from PC1 and PC2 during 2 hours. PC3 and PC4 released 4.6 %, 0.1 % of drug. In contrast formulations PC1-PC3 released more than 90 % of drug in 1 hour, 3 hours and 6 hours at pH 6.8 buffer solutions, respectively. PC4 released about 75 % of drug in 6 hours. pH dependent dissolution property of CRM tablets was attributed to the pH dependent solubility of PLB. PLB is a weak acidic substance which pKa is 4.6, and highly soluble at pH 6.8, but low soluble at pH 1.2.

In pH 6.8 solution, PC1 and PC2 were disintegrated during dissolution test. On the other hand PC3 and PC4 showed no significant swelling and maintained tablets geometric shape until the end of dissolution test. Different kinetic models, (Higuchi-matrix (H-M), Hixson-Crowell (H-C)) were applied to interpret the release properties of PC2 and PC3 in pH 6.8 medium. The best fit with higher correlation (r² > 0.95) was found with the H-C model (r²=0.9522) than H-M model (r²=0.9023) for PC2, but PC3 showed higher correlation with H-M model (r²=0.9935).
than H-C model ($r^2=0.9867$). These results demonstrated main drug release mechanism of PC2 is dissolution and main drug release mechanism of PC3 is diffusion.

To estimate in vivo behavior, PC2 and PC3 were tested by buffer transition method. In acidic stage, the tablets were put into pH 1.2 buffer solution and dissolution tested for 2 hours, and then the test proceeded immediately under buffer stage. In buffer stage, buffer solution was added to finished acidic stage dissolution vessel, adjusted to pH 6.8 and dissolution tested until 6 hours (Fig. 2). During acidic stage, released drug was less than 10% in both formulations, after transition to buffer stage PC2 released about 100% of drugs in 6 hours but PC3 released only 80% of drugs in 6 hours. Therefore PC2 was chosen for in vivo study.

To evaluate in vivo properties, pharmacokinetic study of PLB from IR vs PC2 tablets was conducted in beagle dogs. The mean plasma concentration-time curves of PLB after oral administration are shown in Fig. 3. The area under the curves (AUC$_{0-24}$, ng·h/mL) of IR and PC2 tablets were 2470.4 ± 1056.5 and 2515.3 ± 400.1, respectively. Mean residence times (MRT, h) of IR and PC2 tablets were 8.3 ± 1.1 and 8.2 ± 0.8, respectively. The bioavailability and MRT of PLB from both products were similar in beagle dogs.

CONCLUSION

In this study, we found that formulation PC2 was appropriate for developing controlled-release of PLB, and pharmacokinetic study was carried out in beagle dogs after oral administration. Therefore, the developed CRM tablet of PLB is expected to be an alternative dosage form to replace IR tablet for treatment of pain through a clinical trial.