Pharmaceutical Development and Technology

RESEARCH ARTICLE

Development of a novel bi-coated combination capsule containing mosapride and probiotics for irritable bowel syndrome

Yong Il Kim1,2, Bijay Kumar Poudel1, Roshan Pradhan1, Han-Gon Choi3, Chul Soon Yong1, Jong Soo Woo1,2, and Jong Oh Kim1

1College of Pharmacy, Yeungnam University, Gyeongsan, South Korea, 2Pharmaceutical Research Centre, Hanmi Pharm. Co., Hwaseong, Gyeonggi-Do, South Korea, and 3College of Pharmacy, Hanyang University, Ansan, South Korea

Abstract

The objective of this study was to develop a novel combination product containing mosapride and probiotics for the treatment of irritable bowel syndrome. Enteric-coated hard gelatin capsules containing probiotics were prepared to protect acid-labile probiotics from the stomach by spray coating with hydroxypropylmethylcellulose phthalate, and then coated with various hydrophilic polymer solutions containing mosapride. The influence of different hydrophilic polymers on the aqueous solubility and dissolution of sparingly soluble mosapride from the capsule was investigated to select the one which imparted highest solubility to mosapride in an aqueous solution. The physicochemical properties of the hydrophilic polymer coated capsule in beagle dog was evaluated and compared to that of conventional mosapride coated capsule. Based on DSC studies, the mosapride in polymer coating underwent amorphization or molecular dispersion. In addition, the bioavailability of the mosapride-coated capsule in beagle dog was evaluated and compared to that of conventional mosapride tablet (CMT). Based on DSC studies, the mosapride in polymer coating underwent amorphization or molecular dispersion. The enteric capsule coated with mosapride/HPMC exhibited improved solubility of mosapride at acidic pH and showed significantly improved AUC (1.5-fold) and Cmax (1.6-fold) compared to the CMT. In conclusion, drug/polymer coated enteric gelatin capsule can be an alternative technique for co-delivery of sparingly water-soluble drug and acid-labile drug for enhanced solubility and bioavailability as well as for protection from acid degradation.

Introduction

Irritable bowel syndrome (IBS) is characterized by abdominal discomfort associated with altered bowel function. It is viewed as a functional disorder, and as such, no structural abnormalities as well as unique pathophysiology or etiology underlying IBS have been conclusively elucidated.1 Typical symptoms of IBS include recurrent abdominal pain, altered motility, altered stool consistency and frequency, flatulence, abdominal distension and heightened intestinal/visceral sensation. Moreover, IBS can be regarded as a biopsychosocial disorder that is associated with a significantly impaired health-related quality of life, reduced work productivity and diminished social and personal function.2,3 Recent studies have suggested IBS etiological mechanisms such as dysmotility, mucosal inflammation, enteric neuromuscular dysfunction, increased intestinal mucosal permeability, alteration of intestinal microflora, visceral hypersensitivity and enteric infection.4-8

Probiotics have been used on an empirical basis for many years in the treatment of IBS. Probiotics alone or in combination have been reported to have a statistically significant effect on IBS symptom alleviation compared to placebo.9,10 Probiotics are live or attenuated bacteria or bacterial products that, via exogenous supplementation, can maintain microbial balance in the gastrointestinal (GI) tract of an animal host including a human.11 Probiotics have been shown to reduce mucosal inflammation, thereby decreasing immune-mediated activation of enteric neurons.12,13 In addition, probiotics are known to alter the composition of GI microflora, alleviate viral, gastroenteritis and antibiotic-induced diarrhoea, decrease lactose intolerance and infant food allergic symptoms, decrease flatulence, decrease abnormal colonic fermentation, protect the integrity of the GI mucosal barrier and reduce post-infective IBS14,15. Lactic acid bacteria (Lactobacilli) are the most common microbes used as probiotics.16 The intestinal lactic acid bacteria block the attachment of pathogens to the epithelium of the digestive tract to prevent pathogen-induced disease, and produce antibiotics to kill or inhibit the diarrhoea-inducing pathogen.17-20 Probiotic products, however, tend to be destroyed by the acidic conditions in the stomach if taken orally. Although, probiotic lactobacillus strains are known to be intrinsically acid-resistant dependent on the species and strains, they exhibit a marked vulnerability at pH values below 3. As the gastric pH can reach as low as 1.2 and with salinity as much as 0.5% w/v, most probiotic organisms including lactobacillus cannot survive gastric transit to reach intestinal mucosa in viable number.21,22 In order to address this problem, a number of micro-encapsulation and enteric coating technologies...
have been developed. A simple technology for probiotics is an enteric capsule that is resistant to gastric degradation\cite{23,24}. A clinical trial demonstrated that an enteric-coated probiotics product, Medilac DS\textsuperscript{5} (Bacillus subtilis, Streptococcus faecium, Hanmi Pharm. Co., Korea) was a safe and useful probiotic agent for the treatment of abdominal pain in patients with IBS\cite{25}.

Mosapride [4-amino-5-chloro-2-ethoxy-N-((4-(4-fluorobenzyl)-2-morpholiny1) methyl) benzamide] is a selective serotonin 5-HT\textsubscript{4} receptor agonist and its primary metabolite, M1, has 5-HT\textsubscript{4} agonistic and 5-HT\textsubscript{3} antagonistic properties\cite{26,27}. Mosapride enhances the gastric emptying propulsive movement and initiates mucosal secretory reflexes by facilitating acetylcholine-release through 5-HT\textsubscript{4} receptor of intestinal myenteric plexus\cite{28–32}. Absorption of mosapride is very rapid in the GI tract in human and animals\cite{33}.

For treatment of IBS, co-administration or a combination product of probiotics and mosapride may exhibit synergistic effects as they have different mechanisms of action and alleviate different contributing etiologies. Therefore, the primary aim of this study was to develop a novel combination product of enteric-coated probiotics and absorption-improved mosapride. In this study, a novel bi-coated capsule was formulated with acid-labile probiotic surrounded by enteric mosapride coats. The influence of the hydrophilic polymer-mosapride coating on the aqueous solubility and dissolution of sparingly soluble mosapride from the capsule was investigated. The physicochemical properties of the capsule were assessed using SEM and DSC. Finally, the bioavailability of mosapride in the developed capsule was evaluated in beagle dog and compared to that of conventional mosapride tablet (CMT).

Materials and methods

Materials

Lactic acid bacteria culture (Fermalac SB, containing more than 900 000 000 units of Streptococcus faecium and 100 000 000 units of Lactobacillus subtilis per 250 mg) was purchased from Rosell Co. (Montreal, Canada) and mosapride citrate dihydrate from Dongwoo Syntech Co. (Seoul, South Korea). Hydroxypropylmethylcellulose phthalate (HPMCP) and Hydroxypropylmethyl cellulose 2910 (HPCM 2910) were purchased from Kollicoat IR – – – 24 and 30 g of acetylated monoglyceride, croscarmellose sodium and microcrystalline cellulose were supplied by Hanmi Pharm. Co. (Hwasung, South Korea) and were of USP grade. Deionized water was used and was freshly prepared using Milli-Q water purification system (Millipore, Billerica, MA). All chemicals were used as received without further purification.

Animals

Eighteen male beagle dogs weighing 9–11 kg were purchased from Sam Youk Animal Facility (Kyounghi-Do, South Korea) and were housed in individual cages in the Animal Centre of Yeungnam University (Gyeongsan, South Korea) under adequate temperature, light and humidity control. They were re-weighed prior to each study. All experimental procedures involving animals were conducted in accordance with the Guiding principles in the Use of Animals in Toxicology, as adopted by the Society of Toxicology\textsuperscript{34}, which were reviewed and approved by the Animal Care & Use committee at Yeungnam University (Approval no. 2012-03-0012/Dated 26 March 2012). The animals were fasted for 16 h prior to the experiments but were allowed free access to water.

Preparation of enteric-coated hard gelatin capsules containing probiotics

About 2500 g of Fermalac SB, 48 g of lactose, 26 g of tcalc and 26 g of magnesium stearate, finely ground and pre-sieved through 60-mesh screen were mixed using a double cone mixer (10 RPM, 30 min) for preparation of 10 000 units of capsules. About 260 mg of the homogeneous mixture was used to fill the hard gelatin capsules for preparation of the enteric-coated capsules. Then, 470 g of HPMCP and 30 g of acetylated monoglyceride were dissolved in 1200 g of ethanol and 3000 g of acetic solution mixture to prepare the enteric coating solution for 10 000 capsules. Uncoated hard gelatin capsules were warmed to 40 °C in the mini coating pan of a Sejong Pharmatech SCF-30C auto-coating machine (Seoul, South Korea). The freshly prepared coating solution was sprayed over the warmed capsules using 1.5 mm air nozzle spray gun with a pan rotation of 6 RPM, flow rate of 30 ml/min, atomizing air pressure of 3 kg/cm\textsuperscript{2}, product temperature of 35 °C and inlet temperature of 55 °C. After spray-coating, the enteric-coated capsules were dried for 60 min in the pan with inlet temperature of 40 °C. All coating solutions were continuously stirred throughout the coating process. The capsules were sealed in a closed glass container at room temperature until further study.

Preparation of mosapride-coated enteric capsule

Fifty-three grams of mosapride citrate dihydrate (equivalent to 50 g of mosapride base) and 240 g of a hydrophilic polymer such as HPMCP, HPC-L, CMC Na, Kollicoat IR and 60 g of PEG 6000 as a plasticizer were dissolved in 3000 g of water to prepare the mosapride film coating solution for 10 000 units of enteric-coated capsules containing probiotics (Table 1). Prior to spray-coating, the enteric-coated capsules were warmed to 40 °C in the mini coating pan of a Sejong Pharmatech SCF-30C auto-coating machine (Seoul, South Korea). Freshly prepared film coating solution-containing mosapride was sprayed over the warmed capsules using 1.5 mm air nozzle spray gun with a pan rotation speed of 6 rpm, flow rate of 30 ml/min, atomizing air pressure of 3 kg/cm\textsuperscript{2}, product temperature of 35 °C and inlet temperature of 60 °C. After spray coating, mosapride-coated enteric capsules (MEC) were dried for 60 min in the pan with inlet temperature 40 °C. All coating solutions were continuously stirred throughout the coating process. The capsules were sealed in a closed glass container at room temperature until further study.

Preparation of conventional mosapride tablet

A 5.3 g of mosapride citrate dihydrate (equivalent to 5 g of mosapride base), 120 g of lactose, 6 g of croscarmellose sodium and was freshly prepared using Milli-Q water purification system (Millipore, Billerica, MA). All chemicals were used as received without further purification.

<table>
<thead>
<tr>
<th>Ingredients</th>
<th>HPMC-MEC</th>
<th>HPC-MEC</th>
<th>CMC-MEC</th>
<th>KIR-MEC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mosapride citrate dihydrate (5 mg as mosapride)</td>
<td>5.3</td>
<td>5.3</td>
<td>5.3</td>
<td>5.3</td>
</tr>
<tr>
<td>HPMC</td>
<td>24</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>HPC-L</td>
<td>–</td>
<td>24</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>CMC Na</td>
<td>–</td>
<td>–</td>
<td>24</td>
<td>–</td>
</tr>
<tr>
<td>Kollicoat IR</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>24</td>
</tr>
<tr>
<td>PEG 6000</td>
<td>6</td>
<td>6</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>Water</td>
<td>300</td>
<td>300</td>
<td>300</td>
<td>300</td>
</tr>
</tbody>
</table>
and 2.0 g of magnesium stearate, finely ground and pre-sieved through 60-mesh screen, were mixed using a high-shear mixer (NMG-1L, Nara, Japan) for the preparation of 1000 tablets. Round biconvex tablets with a diameter of 5 mm and a hardness of 3–4 KP were prepared by direct compression using ERWEKA tablet machine (GmbH, Frankfurt, Germany).

Surface morphology

To evaluate the coating integrity, the surface morphology of a cross section of enteric-coated capsule and MEC coated with HPMC (HPMC-MEC) was explored using a scanning electron microscope (SEM; S-4100, Hitachi, Japan). The capsules were made electrically conductive by coating with platinum (6 nm/min) in a vacuum (6 Pa) using Hitachi Ion Sputter (E-1030) for 300 s at 15 mA.

Differential scanning calorimetry

The thermal characteristics of mosapride, CMT, physical mixture of drug, PEG 6000 and four different polymers (HPMC, HPC-L, Kollicoat IR and CMC Na) and four different mosapride-coated films (HPMC/mosapride, HPC-L/mosapride, CMC Na/mosapride and Kollicoat IR/mosapride) were investigated using a differential scanning calorimeter (DILSUS, Rheometric Scientific, Piscataway, NJ). About 2 mg of each sample, separately taken in a sealed aluminum pan, were heated at the rate of 10 °C/min in the range of 50–150 °C under nitrogen flow (10 ml/min). An empty pan was used as a reference and the machine was calibrated prior to use.

Solubility of mosapride from MEC

Twenty units of each of four different MECs were added to 100 ml of deionised water, 0.1 N HCl (pH 1.2), phosphate-buffered solution (pH 4.0) and phosphate-buffered solution (pH 6.8), respectively. The media was degassed by sonication prior to use. They were shaken in a water bath at 37 °C for 3 days and then centrifuged at 3000 x g for 10 min using a 5415C centrifuge (Eppendorf; Hauppauge, NY) and filtered through a membrane filter (0.45 μm) to obtain a clear solution. The resulting solution (20 μl) was analysed by HPLC (Hitachi, Tokyo, Japan) equipped with an Inertsil ODS-2 column (0.5 μm, 15 cm x 0.46 cm i.d.) and a UV detector (Model L-7400). The mobile phase consisted of phosphate buffer (pH 4.0, adjusted by o-phosphoric acid) and acetonitrile (50:50, volume ratio). The eluent was monitored at 274 nm with a flow rate of 1.0 ml/min at 40 °C. All standard curves showed excellent linearity with R^2 = 0.999; the relative standard deviation at different concentrations and time was less than 2.76%.

In vitro dissolution study

The dissolution test was performed using USP XXXII dissolution apparatus II with 900 ml water, 0.1 N HCl (pH 1.2), phosphate-buffered solution (pH 4.0) and phosphate-buffered solution (pH 6.8) as the dissolution media at 37 ± 0.5 °C. The speed of the paddle was adjusted to 50 rpm. The CMT and four different MECs at an equivalent dose of 5 mg mosapride base were placed into a PTWS-1200 dissolution tester (Pharmatest Co., Hainburg, Germany), respectively. At predetermined intervals, 1 ml of the medium was sampled and filtered through a membrane filter (0.45 μm). After each sampling, 1 ml of medium maintained at 37 ± 0.5 °C was immediately added to compensate for the withdrawn aliquot. The study was carried out in triplicates. The concentration of mosapride in the filtrate was analysed by the HPLC method as mentioned above.

The dissolution profiles of the MECs were compared with reference to CMT using the difference factor (f₁) and similarity factor (f₂), as defined by the following equation:

\[ f_1 = \frac{\sum_{i=1}^{n} (R_j - T_j)}{\sum_{i=1}^{n} (R_j + T_j)} \times 100 \]

\[ f_2 = 50 \log \left(1 + \frac{1}{n} \sum_{i=1}^{n} (R_j - T_j)^2 \right)^{-0.5} \times 100 \]

where n is the number of time points, Rj and Tj are the dissolution value of the reference product and the test products, respectively, at each time points j. In order to consider the similar dissolution profiles, the f₁ values should be close to 0 and values f₂ should be close to 100. In general, f₁ values lower than 15 (0–15) and f₂ values higher than 50 (50–100) show the similarity of the dissolution profiles.

In vivo pharmacokinetics

Oral administration and plasma collection

Eighteen male beagle dogs, divided into three groups, were fasted for 16 h and restrained by means of a dog sling (Alice King Chatham Medical Arts, Los Angeles, CA) during the 48-h experimental period. The beagle dogs in each group were orally administered CMT, MEC coated with HPMC (HPMC-MEC) and MEC coated with Kollicoat IR (KIR-MEC) at a dose of 5 mg/kg of mosapride base. About 1.5 ml of blood was collected from the cephalic vein at pre-determined time intervals. These samples were immediately centrifuged at 3000 x g at 4 °C for 15 min using a centrifuge (5415C; Eppendorf, Hamburg, Germany) and stored at −80 °C prior to analysis.

Blood sample treatment

Plasma (500 μl) was mixed with 25 μl of methanol solution containing lansoprazole (1.0 μg/ml) as an internal standard. Then, 3 ml of extraction solution, diethyl ether–dichloromethane (70:30) was added, followed by liquid–liquid extraction for 40 s. The organic layer was separated and removed at 30 °C in a heated centrifugal evaporator (EYELA CVE-200D; Tokyo Rikakikai Co., Tokyo, Japan). The residue was reconstituted in 500 μl of the mobile phase by vortex-mixing for 15 s, and 5 μl of this solution was injected onto the column.

HPLC–MS–MS conditions

The plasma concentrations of mosapride were quantified using an Agilent 1200 series LC/MS/MS system (Agilent, Santa Clara, CA) equipped with an electrospray ionization interface that was used in the positive ion mode ([M + H]^+). The compounds were separated on an Atlantis C 18 column (2.1 x 100 mm, 5 μm, Waters, Milford, MA) with a mobile phase that consisted of methanol and water (80:20 mixture). The column was heated to 30 °C and the mobile phase was eluted at 0.25 ml/min. The ESI-MS data were acquired in the turbo ion spray ionization mode (positive) and the conditions of MS analysis were as follows: drying gas (Nitrogen) flow rate, 10 l/min; drying gas temperature, 550 °C; capillary voltage, 5.5 kV; fragmentor, 0.3 V. Mosapride and lansoprazole (internal standard) gave mainly protonated molecules at m/z 422.2 and 370.2, respectively. Quantification was performed by multiple reaction-monitoring (MRM) of the protonated precursor ions and the related product ions, using the ratio of the area under the peak for each solution and a weighting factor of 1/y². The analytical data were processed with Analyst.
software (MassLynx, version 4.0, Waters Corporation, Milford, MA). The calibration curve was constructed over a range of 0.1–20 ng/ml ($R^2 = 0.9994$) with a lower limit of quantification (LLOQ) of 0.1 ng/ml for mosapride. For the validation, inter- and intra-day differences were conducted and the differences were found to be within an acceptable range.

**Pharmacokinetic data analysis and statistical analysis**

The area under the drug concentration time curve from zero to infinity (AUC), the elimination constant ($K_{el}$) and the half-life ($t_{1/2}$) were calculated using non-compartmental analysis (WinNonlin™; professional edition, version 2.1; Pharsight Co., Mountain View, CA). The maximum plasma concentration of the drug ($C_{\text{max}}$) and the time taken to reach the maximum plasma concentration ($T_{\text{max}}$) were directly obtained from the plasma data. Levels of statistical significance ($p<0.05$) were assessed using the Student’s $t$-test between the two means for unpaired data. All data are expressed as the mean ± standard deviation (SD) or as the median (ranges) for $T_{\text{max}}$.

**Results and discussion**

**Preparation of mosapride-coated enteric capsules**

Hard gelatin capsules containing probiotics were enteric-coated to prevent gastric degradation. The average weight of the resulting enteric-coated capsule containing probiotics was 374.2 ± 2.8 mg, while that of uncoated capsule was 324.8 ± 2.3 mg. Thus, on average 49.4 mg of film material was used in the coating, which is 15.2 (w/w) % of the total weight of the core capsule. To investigate the enteric properties of the enteric-coated capsule, visual inspection was performed after 1 h disintegration test in 0.1 N HCl (pH 1.2). The disintegration test was performed, according to the USP XXXII. Due to the enteric coating, no evidence of disintegration or cracking in 0.1 N HCl (pH 1.2) was observed in any of the 12 capsules tested. However, in phosphate-buffered solution (pH 6.8), the capsule readily disintegrated; the average disintegration time was 9.6 ± 0.8 min. The enteric-coated capsule was then coated with various mosapride-dissolved hydrophilic polymer solutions such as HPMC, HPC-L, Kollicoat IR and CMC Na (HPMC-MEC, HPC-MEC, KIR-MEC and CMC-MEC, respectively). Thus, a novel bi-coated capsule was formulated to protect acid-labile drug, solubilize sparingly soluble drug by amorphization or molecular dispersion and polymer coating, and allow co-delivery of these two drugs for IBS treatment.

**Physical characterization**

The scanning electron micrographs of MEC coated with HPMC (HPMC-MEC) is shown in Figure 1. Enteric-coated capsule showed double layers of the gelatin capsule, shell layer and the enteric layer (Figure 1A). On the other hand, HPMC-MEC showed distinct and continuous coated triple layers: gelatin capsule shell layer, enteric layer and mosapride film layer (Figure 1B). Enteric-coated capsules had some pores that can be attributed to the fast evaporation rate of the ethanol/acetone coating film. MEC coated with HPMC polymer exhibited distinct coated layers without cracks or pores.

The thermal behaviour of raw materials, CMT and MEC with various coating polymers are given in Figure 2. The thermograms of mosapride (Figure 2A) exhibited an endothermic peak at about 110 °C corresponding to its melting point, indicating its crystalline nature. Coating polymers, HPMC, HPC-L, CMC Na and Kollicoat IR are known to have no intrinsic peaks38,39. CMT (Figure 2B) and the physical mixture (Figure 2C) displayed a slightly muted melting peak for drug indicating that no crystalline change occurred. However, the endothermic peaks of the drug were absent in the MEC coated with polymers (Figure 2D–G). This suggests that crystalline mosapride underwent amorphization or molecular dispersion39, which might be responsible for improved solubility and dissolution as described later. The amorphous form of a drug has a higher thermodynamic activity than its crystalline form, leading to improved solubility. Hence, it can be safely reasoned that such improved solubility of mosapride from MEC was either due to the change of drug crystallinity to the amorphous form or due to molecular dispersion of mosapride in MEC coated with HPMC, HPC-L CMC Na and Kollicoat IR films. Moreover, another contributing factor for increased solubilization may be the hydrophilic polymer coating of amorphous drug in aqueous environment. Hydrophilic polymers such as HPMC, HPC-L CMC Na and Kollicoat IR attached to drug particles impart hydrophilicity, and also impede nucleation, crystal growth and precipitation.

**Effect of hydrophilic polymers on the solubility of mosapride**

To investigate the effect of polymers on the solubility of mosapride from different hydrophilic polymers, their solubility in pH 1.2, pH 4.0, pH 6.8 and water was evaluated (Figure 3). Compared to the solubility of mosapride powder, all the MEC formulations including CMT, demonstrated improved solubility of mosapride at acidic pH (pH 1.2 and pH 4.0) and water Figure 3A, B and D). However, at pH 6.8, no significant improvement in solubility was
Figure 2. DSC thermograms of (A) mosapride, (B) CMT, (C) physical mixture of mosapride and HPMC, (D) HPMC-MEC, (E) HPC-MEC, (F) CMC-MEC and (G) KIR-MEC.

Figure 3. Effect of hydrophilic polymers on the solubility of mosapride at (A) pH 1.2, (B) pH 4.0, (C) pH 6.8 and (D) water.
observed as shown in Figure 3(C). The highest solubility of mosapride was shown from the HPMC-MEC followed by KIR-MEC which were comparable with CMT at all pH levels.

**In vitro dissolution studies**

To evaluate whether the polymer films affected the dissolution rates of the drug, dissolution studies of CMT and different MECs were performed at pH 1.2, 4.0, 6.8 and in deionized water (Figure 4). At pH 1.2 (Figure 4A), pH 4.0 (Figure 4B) and water (Figure 4D), mosapride from MEC coated with HPMC and Kollicoat IR showed almost complete dissolution (above 70%) within 60 min, compared to HPC-L and CMC Na. However, in case of pH 6.8 (Figure 4C), the release of mosapride from the MECs were lesser than in other dissolution media, which was attributed to the inherent low solubility of the drug in pH 6.8. Nevertheless, in this pH condition, the HPMC-MEC exhibited highest dissolution rate (about 60%) in 15 min, attributed to the increased solubility of mosapride in HPMC at pH 6.8.

The $f_1$ and $f_2$ values between HPMC-MEC and CMT at pH 1.2, 4.0, 6.8 and deionized water are shown in Table 2. Except at

<table>
<thead>
<tr>
<th>Formulations</th>
<th>Dissolution medium</th>
<th>Difference factor ($f_1$)</th>
<th>Similarity factor ($f_2$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HPMC-MEC</td>
<td>pH 1.2</td>
<td>2.1</td>
<td>81.0</td>
</tr>
<tr>
<td></td>
<td>pH 4.0</td>
<td>2.7</td>
<td>78.7</td>
</tr>
<tr>
<td></td>
<td>pH 6.8</td>
<td>29.6</td>
<td>43.1</td>
</tr>
<tr>
<td></td>
<td>Water</td>
<td>1.9</td>
<td>85.0</td>
</tr>
<tr>
<td>HPC-MEC</td>
<td>pH 1.2</td>
<td>29.4</td>
<td>28.6</td>
</tr>
<tr>
<td></td>
<td>pH 4.0</td>
<td>30.7</td>
<td>29.0</td>
</tr>
<tr>
<td></td>
<td>pH 6.8</td>
<td>21.0</td>
<td>48.2</td>
</tr>
<tr>
<td></td>
<td>Water</td>
<td>30.2</td>
<td>28.4</td>
</tr>
<tr>
<td>CMC-MEC</td>
<td>pH 1.2</td>
<td>56.6</td>
<td>19.7</td>
</tr>
<tr>
<td></td>
<td>pH 4.0</td>
<td>58.5</td>
<td>20.3</td>
</tr>
<tr>
<td></td>
<td>pH 6.8</td>
<td>23.5</td>
<td>49.9</td>
</tr>
<tr>
<td></td>
<td>Water</td>
<td>57.5</td>
<td>19.5</td>
</tr>
<tr>
<td>KIR-MEC</td>
<td>pH 1.2</td>
<td>8.9</td>
<td>55.1</td>
</tr>
<tr>
<td></td>
<td>pH 4.0</td>
<td>6.8</td>
<td>59.0</td>
</tr>
<tr>
<td></td>
<td>pH 6.8</td>
<td>41.5</td>
<td>34.9</td>
</tr>
<tr>
<td></td>
<td>Water</td>
<td>8.0</td>
<td>57.5</td>
</tr>
</tbody>
</table>
pH 6.8, the HPMC-MEC gave a similar correlation of dissolution profiles to the CMT, corresponding to the $f_1$ and $f_2$ values of 2.1 and 81.0 at pH 1.2, 2.7 and 78.7 at pH 4.0, 1.9 and 85.0 at neutral pH (water), respectively. Similarly, except at pH 6.8, the $f_1$ and $f_2$ values between KIR-MEC and CMT were 8.9 and 55.1 at pH 1.2, 6.8 and 59.0 at pH 4.0 and 8.0 and 57.5 at neutral pH (water), respectively, indicating similarity of the dissolution profiles. On the other hand, the $f_1$ and $f_2$ values of HPC-MEC and CMC-MEC with reference to CMT were greater than 15 and less than 50, respectively, at all dissolution media, indicating dissimilarity of the dissolution profiles between these formulation and the CMT. The analysis of the results suggested that HPMC-MEC and KIR-MEC demonstrated dissolution profiles that are similar to the CMT at acidic pH and water, while the other two, HPC-MEC and CMC-MEC, showed no similarity. Therefore, based on the superior dissolution profiles shown by MECs coated with HPMC and Kollicoat IR, these two formulations were selected for carrying out the pharmacokinetic study in beagle dogs.

### In vivo pharmacokinetic studies

The pharmacokinetic profile of mosapride was investigated after oral administration of HPMC-MEC, KIR-MEC and CMT to beagle dogs. The changes in mean plasma concentrations after oral administration of the formulations are shown in Figure 5. The HPMC-MEC gave higher total plasma concentrations of mosapride compared to the CMT. In particular, HPMC-MEC showed significantly higher concentrations compared with those in CMT, from 0.50 h to 1.5 h ($p<0.05$). The higher plasma concentrations of mosapride in the HPMC-MEC were due to higher solubility at the acidic pH. On the other hand, KIR-MEC gave comparable plasma concentrations of mosapride compared to the CMT. The total plasma concentrations of mosapride in the KIR-MEC did not differ significantly from those in the CMT in beagle dogs.

The pharmacokinetic parameters are shown in Table 3. The mosapride plasma peak concentration times of CMT, HPMC-MEC or KIR-MEC appeared at 0.58, 0.63 and 0.50 h, after oral administration, with half-lives of 1.56, 1.64 and 2.36 h, respectively, indicating rapid absorption and elimination. The HPMC-MEC gave a significantly higher AUC and $C_{max}$ of mosapride than CMT ($p<0.05$). In particular, the AUC of mosapride from HPMC-MEC was about 1.5-fold higher than that from CMT. However, the $K_{el}$ and $t_{1/2}$ values of HPMC-MEC were not significantly different from those of CMT ($p<0.05$). Our results suggested that the higher plasma concentration of mosapride was due to the increase in solubility and dissolution of mosapride from HPMC-MEC in beagle dogs. In addition, there was no significant difference in the AUC, $C_{max}$ and $T_{max}$ values between the KIR-MEC and the CMT ($p>0.05$), suggesting that the MEC coated with Kollicoat IR might be bioequivalent to the CMT in beagle dogs. From the pharmacokinetic point of view, therefore, the MEC coated with HPMC was superior to Kollicoat IR as it showed improved AUC and $C_{max}$ in beagle dogs.

### Conclusion

In conclusion, a novel amorphous or molecularly dispersed mosapride-coated enteric capsule containing acid-labile probiotic for the treatment of IBS was formulated. The mosapride in the polymer coating underwent a crystallinity change. Among the various polymers used, the mosapride-coated enteric capsule using HPMC polymer exhibited improved drug solubility and dissolution profile at acidic pH and water and showed relatively higher values of AUC and $C_{max}$ compared to CMT. Therefore, the enteric capsules coated with drug/HPMC can be an alternative technique for co-delivery of acid-labile drug such as probiotics and sparingly water-soluble drug such as mosapride, by protecting the drug from gastric acid degradation and enhancing oral bioavailability.

### Declaration of interest

The authors declare that they have no conflicts of interest to disclose. This study was supported by a grant from the Medical Cluster R&D...

References


26. Yoshida N, Kato S, Ito T. Oral bioavailability was 8% of the dose in dogs and 14% in monkeys, suggesting the extensive first-pass metabolism of mosapride. Drugs Future 1993;18:513–515.


