Bioavailability and in vitro oesophageal sticking tendency of hydroxypropyl methylcellulose capsule formulations and corresponding gelatine capsule formulations

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Abstract

The overall aim of the present study was to widen our knowledge about the biopharmaceutical behaviour of novel hydroxypropyl methylcellulose (HPMC)-based two-piece capsules by comparing them with the classic hard gelatine capsules. Firstly, the tendency of the HPMC capsules to stick to isolated porcine oesophageal preparation was evaluated. The force needed to detach the HPMC capsules from the oesophagus was significantly lower than that for the gelatine capsules (P<0.001), which is evidently an advantage of this new dosage form. The second aim was to investigate the possibility of preparing sustained-release capsules using different powdered HPMCs as diluents (K100, K4M and K15M) and the effect of the molecular weight of HPMC powder on the in vitro and in vivo behaviour of the capsules. In addition to peroral drug administration also rectal dosing was applied. Two groups of eight healthy volunteers participated in randomised, cross-over, single-dose studies. One group was administered capsules orally and the other rectally. There were no marked differences in the bioavailability properties of either the oral or rectal HPMC capsules containing ibuprofen as model drug as compared with corresponding gelatine capsule formulations. Using different viscosity grades of HPMC powders as diluents it was possible to control the absorption rate of the model drug both from gelatine and HPMC capsules as far as the oral route was concerned. After rectal administration there were no statistically significant differences between the formulations containing different grades of HPMC powder. Only partial correlation was observed between the results of the bioavailability studies and the in vitro dissolution studies. From a biopharmaceutical point of view these two shell materials can be regarded as interchangeable. © 2002 Elsevier Science B.V. All rights reserved.

Keywords: Adherence to the oesophagus; Bioavailability; Ibuprofen; Gelatine capsule; Hydroxypropyl methylcellulose capsule; Sustained-release

1. Introduction

Hard gelatine capsules have been used as oral dosage forms since the late nineteenth century (Jones, 1987). Recently, hard two-piece capsules made of hydroxypropyl methylcellulose (HPMC) have been introduced on the market (Ogura et al., 1998). HPMC capsules are made of plant-derived material, whereas gelatine capsules are of animal origin. In theory it is possible to transmit to patients bovine spongiform encephalopathy (BSE) agents via gelatine capsules. In this respect, HPMC capsules could be considered as a safer choice. In addition, HPMC capsules are ideal for use with formulations containing water-unstable drugs, because the moisture content of the HPMC capsules is 30–50% lower than that of gelatine capsules. Further, HPMC does not contain chemically reactive groups as does gelatine, which decreases the potential for reactions between the drug and the capsule shell.

A well-known fact is that drug products can adhere to the oesophagus (Marvola, 1982). If the product contains a drug substance having a corrosive effect on the oesophageal mucosa, it can cause serious adverse effects. Numerous studies have proven that a hard gelatine capsule has a high tendency to adhere to the oesophagus (Marvola et al., 1982, 1983; Swisher et al., 1984; Al-Dujaili et al., 1986; Bailey et al., 1987; Perkins et al., 1999). If the sticking tendency of HPMC capsule were lower, it would be a clear advantage for this new dosage form. Only one study
concerning the oesophageal sticking properties of HPMC capsules can be found in the literature (Ponchel and Degobert, 1999). The bioadhesive bond strength was determined by a modification of a classic tensile experiment and the results showed that the adhesive properties of HPMC capsules were relatively comparable to those of gelatine capsules.

In our previous study we investigated the possible differences in the bioavailability of ibuprofen form orally and rectally administered HPMC capsules compared with corresponding gelatine capsules (Honkanen et al., 2001). In that study both capsules contained lactose as the only additive. Both formulations behaved as an immediate-release drug product and after oral administration there were no statistically significant differences in the pharmacokinetic parameters of the two products. After rectal administration of HPMC capsules, the lag time in the commencement of drug absorption averaged 0.9 h compared with 0.6 h for the gelatine capsules. In addition, the parameter describing the absorption rate (C_{max}/AUC) averaged 0.3 h^{-1} for the HPMC capsules and 0.2 h^{-1} for the gelatine capsules. These were the only statistically significant (P<0.05) differences in the pharmacokinetics of the two capsule formulations differing from each other only in the shell material. It was concluded that HPMC capsules can be regarded as comparable to gelatine capsules at least as far as immediate-release oral formulations are concerned.

Sustained-release hard gelatine capsules are quite simple to produce by adding suitable hydrophilic polymer to the formulation (Marvola et al., 1991; Ojantakanen, 1992; Efentakis and Vlachou, 2000). On contact with water hydrophilic polymers hydrate and generate a gelatinous layer on the surface of the product and drug is released from the formulation by diffusion out of the gelatine layer and by erosion of the gel. Our laboratory has made experiments on sustained-release capsule formulations containing ibuprofen as a model drug and HPMC of different viscosity grades as diluents (Ojantakanen et al., 1993; Eerikäinen et al., 1996; Leino et al., 1997). These studies on healthy volunteers showed that gelatine-based capsules containing HPMC as diluent behaved appropriately as sustained-release products both after peroral and rectal administration. The rectal route, however, requires training of the dosing technique beforehand and use of a glidant to facilitate the application of the drug product.

The overall aim of the present study was to widen our knowledge about the biopharmaceutical behaviour of the novel HPMC-based two-piece capsule just by comparing with the properties of the classic hard gelatine capsule. The first interesting point was whether the tendency of HPMC capsules to stick to the oesophageal mucosa differs from that of hard gelatine capsules. In this evaluation we used the isolated porcine oesophagus method developed in our laboratory (Marvola et al., 1982). The second detailed aim was to investigate the possibility of preparing sustained-release capsules using different powdered HPMECs as diluents and the effect of the molecular weight of HPMC powder on the in vitro and in vivo behaviour of the capsules. In addition to peroral drug administration also rectal dosing was utilised, because it is known that in hospitals commercial hard gelatine capsules are sometimes used rectally although they are not—contrary to some soft gelatine capsules—officially accepted for rectal use. Ibuprofen is a suitable model drug for sustained-release formulations, because it is absorbed adequately throughout the gastrointestinal tract and its elimination half-life is only about 2 h (Davies, 1998).

2. Materials and methods

2.1. Materials

The model drug used was ibuprofen (Ph.Eur., Industria Chemica Prodotti, Italy), particle size <0.3 mm. Hydroxypropyl methylcellulose (HPMC, Methocel®, Dow Chemicals, Great Britain) of different viscosity grades, HPMC K100, HPMC K4M and HPMC K15M, was used as a diluent. The viscosities of the HPMCs (measured as a 2% aqueous solution at 20 °C) were 100, 4000 and 15000 mPa·s, respectively. The glidant used to facilitate rectal administration was hard fat, adeps solidus (Ph.Eur., Witepsol W45®, Condea Chemie GmbH, Germany).

2.2. Composition

Size 0 hard hydroxypropyl methylcellulose (Shionogi Qualicaps S.A., Spain) and gelatine (Coni-Snap, Capsugel, Belgium) capsules were used in the formulations. The amount of ibuprofen per capsule was 200 mg. The necessary amount of ibuprofen was weighed out into a measuring cylinder and hydroxypropyl methylcellulose was added so as to obtain sufficient material for a batch of 100 capsules (68 ml). The composition of the capsules is presented in Table 1. The powders were mixed manually, and the capsule bodies were filled using a Feton apparatus (Feton International, Belgium). The capsules for rectal

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Ibuprofen (mg)</th>
<th>HPMC K100 (mg)</th>
<th>HPMC K4M (mg)</th>
<th>HPMC K15M (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>H_{100}</td>
<td>200</td>
<td>145</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>H_{5M}</td>
<td>200</td>
<td>–</td>
<td>141</td>
<td>–</td>
</tr>
<tr>
<td>H_{15M}</td>
<td>200</td>
<td>–</td>
<td>–</td>
<td>143</td>
</tr>
<tr>
<td>G_{100}</td>
<td>200</td>
<td>141</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>G_{5M}</td>
<td>200</td>
<td>–</td>
<td>140</td>
<td>–</td>
</tr>
<tr>
<td>G_{15M}</td>
<td>200</td>
<td>–</td>
<td>–</td>
<td>142</td>
</tr>
</tbody>
</table>
administration were coated by dipping them into melted hard fat (Witepsol W45®, mp 35 °C) using tweezers.

2.3. Methods

2.3.1. Weight and content uniformities

The weight uniformity (n=20) and the content uniformity (n=10) were tested according to the Ph.Eur. The content uniformity was tested by dissolving the capsule contents in pH 7.2 buffer solution (USP 24). The concentration of ibuprofen was determined spectrophotometrically at 221 nm (Lambda 20 UV/VIS Spectrometer, Perkin Elmer, USA).

2.3.2. Isolated oesophageal preparation

Immediately after slaughter of a male Landrace pig, weight about 100 kg, the oesophagus was removed and taken to the laboratory in Tyrode’s solution. Segments (6–7 cm long) were cut from the oesophagus and mounted in a classic organ bath for isolated preparations as described in detail elsewhere (Marvola et al., 1982). Gelatine and HPMC capsules (n=10) were filled with lactose and placed in the oesophageal preparation for 1.5 min. The force needed to detach the product was then measured using a modified prescription balance; the force used was taken as a measure of adherence. The statistical evaluation was carried out using Student’s t-test.

2.3.3. Drug dissolution

The dissolution of ibuprofen was studied using the basket method described in USP 24. The dissolution medium was trisbasic sodium phosphate buffer (pH 7.2, 900 ml at 37±0.5 °C). The speed of rotation was 150 min⁻¹. The dissolution apparatus (Sotax AT 6, Sotax AG, Switzerland) was connected to a peristaltic pump (Watson-Marlow 503S, Smith & Nephew Watson-Marlow, UK) and to a flow-through spectrophotometer (Ultrospec II, LKB Biochrom Ltd., UK). The absorbance of the dissolution medium in 2 mm flow-through cells at 221 nm was recorded automatically at regular intervals. The absorbance measurements were controlled by a computer-run tablet dissolution software (TDS, LKB Biochrom Ltd., UK). The amount of ibuprofen released was measured in parallel from six samples.

The release kinetics of ibuprofen was evaluated with the Eq. (1) derived by Korsmeyer et al. (1983) which may be used to describe drug release from polymeric systems in which release deviates from Fickian diffusion and follows a non-Fickian (anomalous) behaviour.

\[ \frac{M_t}{M_\infty} = K \cdot t^n \]  

(1)

where \( M_t/M_\infty \) is the fractional release of the drug, \( t \) is the release time, \( K \) is a constant incorporating structural and geometric characteristic of the release device and \( n \) is the release exponent indicative of the mechanism of release, for instance, \( n=0.5 \) for zero-order kinetics and \( n=1.0 \) for for zero-order release. The release kinetics of ibuprofen from gelatine and HPMC capsules containing HPMC K100 as diluent was calculated up to 5 h when 80% of ibuprofen on average was released, whereas from other capsules it was calculated up to 24 h.

2.3.4. Bioavailability studies

Two groups of eight healthy volunteers participated in randomised, cross-over, single-dose studies carried out in accordance with the guidelines of the Declaration of Helsinki (World Medical Assembly, 1964), as revised in Tokyo (1975). A group of three men and five women weighing 52–85 kg (mean 69 kg) took oral capsules whilst another group of three men and five women weighing 53–85 kg (mean 64 kg) received the capsules via the rectal route. The age range was 20 to 30 years in both groups. The subjects were informed about the possible risks and side effects of the drug and their written consent to participate was obtained. During the study, side effect forms were filled in and collected. The study protocol was approved by the Ethics Committee of the University Pharmacy, Helsinki. The National Agency for Medicines (Finland) was duly notified.

The group taking the rectal capsules were instructed on the correct insertion technique before the bioavailability tests using capsules which contained only lactose. Two capsules of each formulation (2×200 mg) were administered at 8 a.m. prior to which (7 a.m.) the group which received the capsules rectally was served breakfast to facilitate and enable normal bowel movement. The other group receiving oral medication fasted overnight for at least 10 h. The washout period was at least one week. A standard lunch was served for both groups 4 h after drug administration. Blood samples were collected from an antecubital vein into heparinised tubes just before drug administration and 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12 and 24 h thereafter. Plasma was separated from samples approximately 0.5 h after collection by centrifugation (3000 g for 10 min) and stored at −20 °C until required for analysis within two months.

2.3.5. Plasma assay of ibuprofen

Ibuprofen plasma concentrations were determined by means of high performance liquid chromatography using a slightly modified method of Avgerinos and Hutt (1986). The system was equipped with a pump (Waters 510 HPLC Pump, Millipore, United States), a sample processor (Waters 717 Autosampler, Millipore, United States), a Waters Model 486 Tunable Absorbance Detector operating at 221 nm and a Waters Millennium Workstation. Sample separation was carried out in a Waters μBondapak™ C18 reverse-phase 10 μm column (3.9×300 mm). The guard column used was Merck’s LiChroCART® 4-4 LiChrospher® 100 C18 reverse-phase 5 μm column. The isocratic mobile phase was acetonitrile and 0.1 M sodium
acetate (35/65), pH adjusted to 6.2 with glacial acetic acid. The flow rate was 2 ml/min.

The standard curve was found to be linear over the concentration range of 1 to 80 mg/l. The linear coefficient of determination was 0.999 or higher. The accuracy and precision of the method were investigated as recommended by Shah et al. (1992) by analysing six plasma concentrations of 1, 20 and 80 mg/l. The mean values were 1.06 mg/l (CV 5.8%), 19.9 mg/l (CV 1.3%) and 80.3 mg/l (CV 0.51%), respectively. The limit of quantitation was estimated to be 1 mg/l. No interfering peaks were observed in the plasma blanks.

2.3.6. Pharmacokinetic parameters

The pharmacokinetic parameters calculated (Siphar, Simed, France) from plasma samples were maximum concentration (C<sub>max</sub>), time to peak concentration (t<sub>max</sub>), absorption time lag (t<sub>lag</sub>), area under the concentration time curve from 0 to 24 h (AUC<sub>0–24h</sub>), mean residence time (MRT) and apparent elimination half-life (t<sub>1/2</sub>). The rate of absorption was evaluated also using the ratio C<sub>max</sub>/AUC<sub>0–24h</sub>. Statistical analyses were carried out using the Wilcoxon matched-pairs rank test for t<sub>max</sub> values and Student’s paired t-test for the other pharmacokinetic parameters.

3. Results and discussion

3.1. Weight and content uniformities

All formulations fulfilled the requirements of the Ph.Eur. for weight and content uniformity. The relative standard deviation (R.S.D.) range was 0.9–2.0% for the weight and 0.5–3.6% for the content.

3.2. Isolated oesophageal preparation

The force required for detachment of gelatine capsules from isolated oesophageal preparation was almost 2.5 times greater than that for HPMC capsules (Fig. 1). The difference was statistically significant when tested with Student’s t-test (p < 0.001). Unlike HPMC capsules, some of the gelatine capsules adhered to the oesophagus so hard that they broke while detaching. The present value for HPMC capsules (mean 0.59 N) is even markedly lower than those observed for smaller (sizes 1 and 2) gelatine capsules (0.85–1.30 N) in a previous study (Marvola et al., 1982). This lower sticking tendency of HPMC capsules compared with gelatine capsules is evidently a clear advantage of this novel HPMC capsule. The results presented here are not in accordance with those obtained by Ponchel and Degobert (1999), which might be due to the different manufacturer of the HPMC capsules and the different method used in that study.

3.3. Dissolution of ibuprofen

The dissolution profiles of ibuprofen from the capsules studied are presented in Fig. 2. The same capsule formulations were administered both orally and rectally with the difference that the rectally administered capsules were coated with hard fat. The melting point of the hard fat was 35 °C, and it melted almost instantly after installing the capsules into the dissolution vessel. Thus, the coating did not affect the release of ibuprofen and the dissolution curves of the coated capsules are not shown in Fig. 2.

Table 2 contains the values of constants K and n as well as the linear correlation coefficients for each formulation fitted to the equation of Korsmeyer et al. (1983). The first conclusion from the rate constant K is that the dissolution rate for HPMC capsules was always a little lower than that for the corresponding gelatine capsule. The difference, however, is hardly of any significance in practice. On the contrary, the molecular weight of HPMC powder had a significant effect. The K values for both gelatine and HPMC capsules containing HPMC K100 powder were approximately twice as high as the constants for capsules containing the other two grades of HPMC. Increasing the molecular weight of HPMC powder from K4M grade to K15M grade had no effect on the dissolution rate.

The conclusion from the values of exponent n in Table 2 is that dissolution of ibuprofen from both gelatine and HPMC capsules containing HPMC K100 powder obeyed very well the zero-order kinetics (n values close to 1). So the mechanism of drug release might be a combination of drug diffusion through the gel formed and erosion of the gel. The values of n for capsules containing the other two grades of HPMC derived clearly from 1 (0.64–0.67),
indicating that drug release was closer to the square root of time kinetics which might be explained by non-Fickian diffusion from the gel.

3.4. Bioavailability studies

3.4.1. Oral administration

The results of oral bioavailability studies are given in Figs. 3 and 4 as well as in Table 3. The first finding is that there is only one statistically significant difference ($P < 0.01$) in the bioavailability parameters between the capsule formulation differing from each other in shell material. When the diluent was HPMC K100, $t_{\text{max}}$ was reached earlier with the gelatine capsule than with the corresponding HPMC capsule (2.19 h vs. 3.25 h). In other pharmacokinetic parameters there were no significant differences between the two capsule formulations (Table 3). Inter individual variation in drug concentration versus time curves was quite similar for both formulations (Fig. 4). Thus, it seems from a biopharmaceutical point of view that these two shell materials can be regarded as interchangeable. Also the results of dissolution tests (Fig. 2) predicted no difference between the capsules made from the two different shell materials.

The second finding is that all six formulations behaved as a sustained-release product, although, not very clearly when the diluent was HPMC K100. In our previous study with corresponding immediate-release ibuprofen capsules, $t_{\text{max}}$ was obtained at 1.19 to 1.50 h (Honkanen et al., 2001). Now the mean $t_{\text{max}}$ values varied from 2.19 to 4.25 h. Correspondingly, in the present study the mean MRT values ranged from 3.39 to 6.31 h, with capsules containing lactose as diluent from 2.26 to 2.66 h. It is also important that all the $AUC_{0-24h}$ values of the present study (101–129 mg h/l) were of the same magnitude as the corresponding AUC values of the immediate-release capsules (109–111 mg h/l). No loss in bioavailability of ibuprofen had taken place when various viscosity grades of HPMC were used as diluents in the gelatine or HPMC capsules. In addition, there were no statistically significant differences in the $AUC_{0-24h}$ values between the different formulations, indicating that the viscosity grade of HPMC powder did not affect the amount of ibuprofen absorbed from different formulations (Table 3).

When the viscosity grade of HPMC in gelatine capsules was changed from K100 to K4M or to K15M, statistically significant changes were noted in $C_{\text{max}}$, $t_{\text{max}}$ and $C_{\text{max}}$/AUC values (Table 3). When the shell material was HPMC, statistically significant changes were noted in $C_{\text{max}}$, MRT and $C_{\text{max}}$/AUC values. It is noteworthy that no changes occurred when HPMC K4M was exchanged for HPMC K15M. All these in vivo findings with different viscosity grades are in good accordance with the in vitro dissolution results (Fig. 2). They are also similar to earlier in vivo studies with ibuprofen capsules containing different viscosity grades of HPMC (Ojantakanen et al., 1993). Because both the amount and the viscosity grade of HPMC were shown to control drug release from HPMC matrices.
(Alderman, 1984), the amount of polymer in the present study was kept constant.

3.4.1. Rectal administration

The results of rectal bioavailability studies are given in Figs. 5 and 6 as well as in Table 4. No statistically significant \( P > 0.05 \) differences existed between the gelatine capsule and the corresponding HPMC capsule formulations. In addition, changing the viscosity grade of HPMC as diluent did not alter the biopharmaceutical characteristics of the formulations. This means that the dissolution tests (Fig. 2) did not predict the in vivo behaviour of the capsules when rectal drug administration was used, although good in vitro/in vivo correlation existed when the oral route was used.

It is interesting that after rectal administration the AUC_{0–24h} values were of the same magnitude as (or even higher than) after oral drug administration (Tables 3 and 4). This means that the amount of ibuprofen absorbed from the present capsule formulations is equal via both administration routes. However, from Figs. 4 and 6 it can be seen that inter individual variation in concentration versus time curves is higher after rectal administration. On the other hand, rectal administration seems to lead to a slightly more prolonged drug absorption than oral drug administration (cf. Figs. 3 and 5).

In our previous study the t_{lag} values were significantly greater \( P < 0.05 \) for the HPMC capsules than for the gelatine capsules following rectal administration (Honkanen et al., 2001). Although the t_{lag} values are of the same magnitude in the present study (0.9 h for the HPMC capsules and 0.6 h for the gelatine capsules on average), the difference is not statistically significant. This is probably due to the greater variation in the t_{lag} values of the gelatine capsules (CV 65–83%) than of the HPMC capsules (CV 24–54%). The difference in the t_{lag} values
Fig. 4. Individual plasma concentrations of ibuprofen (2 x 200 mg) following oral administration of HPMC and gelatine capsules containing different viscosity grades of hydroxypropyl methylcellulose as diluents (H refers to HPMC capsule and G to gelatine capsule).

Table 3
Calculated pharmacokinetic parameters of ibuprofen following oral administration of HPMC or gelatine capsules containing different viscosity grades of hydroxypropyl methylcellulose as diluents (H refers to HPMC capsule and G to gelatine capsule; n = 8, mean ± S.D.)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Capsule</th>
<th>AUC₀−24h (mg·h/l)</th>
<th>Cmax (mg/l)</th>
<th>tmax (h)</th>
<th>MRT (h)</th>
<th>Cₘₐₓ/AUC₀−24h (1/h)</th>
<th>t₁/₂ (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>H₁₀₀</td>
<td>129±48</td>
<td>25.5±9.6</td>
<td>3.25±0.46</td>
<td>3.39±0.65</td>
<td>0.200±0.042</td>
<td>0.729±0.46</td>
<td>2.44±2.0</td>
</tr>
<tr>
<td>H₁₅M</td>
<td>113±29</td>
<td>13.7±4.4</td>
<td>3.19±1.0</td>
<td>4.94±1.4</td>
<td>0.122±0.032</td>
<td>0.531±0.51</td>
<td>2.50±1.6</td>
</tr>
<tr>
<td>H₂₀M</td>
<td>101±42</td>
<td>12.5±5.3</td>
<td>4.31±1.9</td>
<td>5.38±1.5</td>
<td>0.124±0.010</td>
<td>0.750±0.55</td>
<td>2.94±1.9</td>
</tr>
<tr>
<td>G₁₀₀</td>
<td>119±33</td>
<td>25.2±7.2</td>
<td>2.19±0.53</td>
<td>4.06±2.5</td>
<td>0.218±0.051</td>
<td>0.362±0.30</td>
<td>2.59±2.2</td>
</tr>
<tr>
<td>G₁₅M</td>
<td>118±30</td>
<td>16.0±3.9</td>
<td>3.38±0.74</td>
<td>4.66±0.83</td>
<td>0.139±0.024</td>
<td>0.563±0.40</td>
<td>2.24±1.5</td>
</tr>
<tr>
<td>G₂₀M</td>
<td>118±25</td>
<td>14.3±3.6</td>
<td>4.25±1.2</td>
<td>6.31±3.2</td>
<td>0.122±0.014</td>
<td>0.626±0.47</td>
<td>3.86±2.5</td>
</tr>
</tbody>
</table>

Statistical significance

| H₁₀₀/G₁₀₀ | NS      | NS      | P < 0.01 | NS      | NS      | NS      | NS |
| H₁₅M/G₁₅M | NS      | NS      | NS      | NS      | NS      | NS      | NS |
| H₂₀M/H₁₀₀ | NS      | NS      | NS      | NS      | NS      | NS      | NS |
| H₁₀₀/H₁₅M | NS      | NS      | P < 0.05 | P < 0.01 | NS      | NS      | NS |
| H₁₅M/H₁₅M | NS      | NS      | P < 0.05 | P < 0.01 | NS      | NS      | NS |
| G₁₀₀/G₁₀₀ | NS      | NS      | P < 0.01 | NS      | NS      | NS      | NS |
| G₁₅M/G₁₅M | NS      | NS      | P < 0.01 | P < 0.01 | NS      | NS      | NS |
| G₂₀M/G₂₀M | NS      | NS      | NS      | NS      | NS      | NS      | NS |

NS: not significant.
has probably no meaning in practice, and the overall conclusion after rectal administration is, that the bio-
pharmaceutical properties of the novel HPMC capsule are similar to those of the classic gelatine capsule.

The correct application technique is quite significant when hard capsules are used rectally, as was shown in our previous study (Eerikäinen et al., 1996). If the capsules are not pushed deep enough in the rectum, they may stick to the mucous membrane below the upper sphincter, making the absorption impossible. Although the correct insertion technique was trained before the bioavailability test, one of the subjects failed with the first formulation and was therefore excluded from the test.

In conclusion, there were no marked differences in the bioavailability properties of either the oral or rectal HPMC capsules containing ibuprofen as model drug as compared with corresponding gelatine capsule formulations. Using different viscosity grades of HPMC powders as diluents it was possible to control the absorption rate of the model drug as far as the oral route was concerned. From a biopharmaceutical point of view these two shell materials can be regarded as interchangeable. The lower tendency of HPMC capsules to adhere to the isolated porcine oesophagus might be an advantage of this new product.

Acknowledgements

This study was financed by University Pharmacy at Helsinki University. The HPMC capsule shells used in this study were a gift from Shionogi Qualicaps S.A., Spain.
Fig. 6. Individual plasma concentrations of ibuprofen (2×200 mg) following rectal administration of HPMC and gelatine capsules containing different viscosity grades of hydroxypropyl methylcellulose as diluents (H refers to HPMC capsule and G to gelatine capsule).

Table 4
Calculated pharmacokinetic parameters of ibuprofen following rectal administration of HPMC or gelatine capsules containing different viscosity grades of hydroxypropyl methylcellulose as diluents (H refers to HPMC capsule and G to gelatine capsule; n = 7; mean±S.D.)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>AUC_0–24h (mg/h/l)</th>
<th>C_max (mg/l)</th>
<th>t_max (h)</th>
<th>MRT (h)</th>
<th>C_max/AUC_0–24h (1/h)</th>
<th>t_lag (h)</th>
<th>t_1/2 (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>H_100</td>
<td>140±34</td>
<td>16.0±6.3</td>
<td>7.14±3.6</td>
<td>6.40±3.1</td>
<td>0.115±0.044</td>
<td>0.911±0.22</td>
<td>2.38±3.7</td>
</tr>
<tr>
<td>H_4M</td>
<td>114±54</td>
<td>12.2±7.0</td>
<td>4.86±1.1</td>
<td>9.72±10</td>
<td>0.121±0.054</td>
<td>0.848±0.46</td>
<td>5.06±8.5</td>
</tr>
<tr>
<td>H_15M</td>
<td>111±57</td>
<td>12.0±3.9</td>
<td>5.00±2.1</td>
<td>7.60±6.1</td>
<td>0.136±0.070</td>
<td>0.854±0.29</td>
<td>3.90±5.6</td>
</tr>
<tr>
<td>G_100</td>
<td>125±40</td>
<td>16.4±9.7</td>
<td>6.71±3.8</td>
<td>13.0±14</td>
<td>0.132±0.070</td>
<td>0.575±0.39</td>
<td>6.81±9.0</td>
</tr>
<tr>
<td>G_4M</td>
<td>154±80</td>
<td>13.8±7.0</td>
<td>6.00±2.0</td>
<td>35.9±79</td>
<td>0.0994±0.042</td>
<td>0.651±0.42</td>
<td>23.0±55</td>
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<tr>
<td>G_15M</td>
<td>139±59</td>
<td>11.1±5.3</td>
<td>7.43±3.6</td>
<td>7.02±2.1</td>
<td>0.0784±0.012</td>
<td>0.434±0.36</td>
<td>3.76±3.1</td>
</tr>
</tbody>
</table>

There were no statistically significant differences.

References


