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Biopharmaceutical Evaluation of Orally and Rectally Administered Hard Hydroxypropyl Methylcellulose Capsules

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Academic Dissertation
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Contents

Abstract

Hydroxypropyl methylcellulose (HPMC) capsules are a new type of hard two-piece capsules developed as an alternative to classic hard two-piece gelatine capsules. HPMC capsules have several technical advantages over gelatine capsules, e.g. lower moisture content, chemical inertness and an ability to maintain mechanical integrity under very low moisture conditions. In addition, HPMC capsules are made of plant-derived material, whereas the gelatine capsules are of animal origin (swine and bovine). This eliminates the problems relating to religious and vegetarian dietary restrictions.

There is not enough information available about the bioavailability of drugs from HPMC capsules to be regarded as interchangeable with gelatine capsules. Therefore, the main objective of the present thesis was to evaluate the biopharmaceutical properties of HPMC capsules made by Shionogi Qualicaps S.A. in comparison with hard gelatine capsules. Both *in vitro* drug release and *in vivo* oral and rectal bioavailability of the model drugs, ibuprofen and metoclopramide hydrochloride, were investigated. The capsules were diluted with either lactose or HPMC powders of different viscosities.

The overall conclusion of the studies reported here was that the HPMC and gelatine capsule shells could be regarded as interchangeable for both oral and rectal administration regardless of the model drug or the diluent used. However, after the rectal administration of the capsules, the time lapse to the commencement of drug absorption was always greater for the HPMC capsules than for the corresponding gelatine capsules. Therefore, the rectally administered HPMC capsules could be regarded as an alternative to gelatine capsules if rapid onset of action is not needed. In addition, the tendency of the HPMC capsules to stick to the oesophagus turned out to be high, making further investigation of this phenomenon necessary.

The orally and rectally administered HPMC and gelatine capsules diluted with HPMC powders fulfilled the basic requirements of a prolonged-release formulation. The release of the model drugs could be controlled also by changing the viscosity grade of the HPMC polymer when the capsules were administered orally, but not when the rectal route was used. The hard capsules proved to be of value as a rectal dosage form, although attention should be paid to the technique of insertion and to the time lapse to the onset of drug absorption, which was about 30 min for the gelatine capsules and about 60 min for the HPMC capsules.

List of original publications

This dissertation is based on the following publications, which are referred to in the text by the Roman numerals I-IV.

I Honkanen O., Seppä H., Eerikäinen S., Tuominen R. and Marvola M., 2001. Bioavailability of ibuprofen from orally and rectally administered hydroxypropyl methyl cellulose capsules compared to corresponding gelatine capsules. S.T.P. Pharma Sci. 11, 181-185.

II Honkanen O., Laaksonen P., Marvola J., Eerikäinen S., Tuominen R. and Marvola M., 2002. Bioavailability and in vitro oesophageal sticking tendency of hydroxypropyl mehtylcellulose capsule formulations and corresponding gelatine capsule formulations. Eur. J. Pharm. Sci. 15, 479-488.

III Honkanen O., Nordberg M., Eerikäinen S., Tuominen R. and Marvola M., 2002. Bioavailability of metoclopramide from orally and rectally administered novel hydroxypropyl methylcellulose capsules containing different diluents: a comparison with corresponding gelatine capsules. S.T.P. Pharma Sci. 12, 299-307.

IV Honkanen O., Marvola J., Kanerva H., Lindevall K., Lipponen M., Kekki T., Ahonen A. and Marvola M., 2004. Gamma scintigraphic evaluation of the fate of hydroxypropyl methylcellulose capsules in the human gastrointestinal tract. Eur. J. Pharm. Sci. (in press)

1. Introduction

Hard two-piece capsules were first invented in 1846 when Parisian pharmacist J.C. Lehuby was granted French Patent 4435 for “Mes envelopes médicamenteuses” (Jones, 1987). These capsules were made of starch or tapioca. Three additions to the original patent were granted in the following four years, extending the range of raw materials to carragheen, various gelatines (including animal gelatine) and gums. The sole use of animal gelatine for making hard two-piece capsules was first described in British Patent 11,937, which was granted to J. Murdoch in 1848. Nowadays, hard gelatine capsule is a widely popular oral dosage form due to the relative ease of manufacture and flexibility of size to accommodate a range of fill weights.

Hard gelatine capsules have some disadvantages owing to the raw material. Gelatine capsule shells have 13-15% water content and therefore may not be suitable for water-unstable drugs. They also loose their mechanical strength and become brittle when the moisture content of the capsule shell is decreased, e.g. when the capsule contains strongly hygroscopic material (Kontny and Mulski, 1989). Furthermore, some drugs react with amino groups of the gelatine protein during storage under severe conditions, causing the gelatine to cross-link and reducing the solubility of the capsule shell (Digenis et al., 1994). Gelatine for capsules is mainly of bovine origin, which creates a theoretical risk of transmitting bovine spongiform encephalopathy (BSE) via capsules (U.S. Department of Health and Human Services, 1997; EMEA, 2001). In addition, gelatine products from bovine and swine sources are sometimes avoided as a result of religious or vegetarian dietary restrictions. To overcome these problems, hard two-piece capsules made of only plant-derived materials, i.e. hydroxypropyl methylcellulose (HPMC), have been developed by Shionogi Qualicaps S.A. (HPMC capsule), Capsugel Division of Pfizer Inc. (Vcaps™), Natural Capsules Ltd. (Cellulose Capsule) and Associated Capsules Ltd. (Naturecaps).

The physicochemical properties of the HPMC capsules (Shionogi Qualicaps S.A.) compared with corresponding gelatine capsules have been sufficiently described in the literature by the manufacturer (Ogura et al., 1998). The biopharmaceutical properties of the capsules were also described in the same publication, but to a far more limited extent. No other studies on the bioavailability of drugs in humans from the two different capsule shells could be found in the literature. Thus, there was an evident need for further

biopharmaceutical studies in human volunteers before the HPMC and gelatine capsule shells could be regarded as interchangeable. The main objective of the present thesis, therefore, was to widen knowledge of the biopharmaceutical properties of the HPMC capsules made by Shionogi Qualicaps S.A. The HPMC capsules were compared with classic hard two-piece gelatine capsules of the same size and both the *in vitro* drug release and the *in vivo* drug absorption following oral and rectal administration were investigated. Rectal administration was evaluated, because it is known that in hospitals commercial hard gelatine capsules are sometimes used rectally (Storey and Trumble, 1992), although they are not – contrary to some soft gelatine capsules – officially accepted for rectal use. Both the HPMC and gelatine capsules contained two model drugs of different water solubilities, ibuprofen or metoclopramide hydrochloride, and lactose or hydroxypropyl methylcellulose powder of different viscosities as diluents to obtain immediate-release or sustained-release formulations. In addition, gamma scintigraphic method was utilised in order to gain a better understanding of the fate of the HPMC capsules in the human gastrointestinal (GI) tract.

2. Review of literature

2.1. Hydroxypropyl methylcellulose capsules

2.1.1. Manufacture

HPMC capsules (Shionogi Qualicaps S.A., Japan) are manufactured by the same dipping and forming method that is applied in the manufacture of classic hard gelatine capsules (Pat.U.S. 5,756,123). Shaped pins are dipped into an aqueous solution comprising 18-28% w/w HPMC 2910 having 28-30% methoxy and 7-12% hydroxypropoxy group and a viscosity of 2.4-5.4·10^{-6} m^2/s (measured as a 2% aqueous solution at 20°C) as a base, 0.01-0.09% w/w carrageenan as a gelling agent, and 0.05-0.6% w/w potassium and/or calcium ions as a co-gelling agent. Small amounts of carrageenan and potassium and/or calcium ions are added to the HPMC solution to enable gelling at 48-55°C, since HPMC alone gels at temperatures below 60°C. After dipping, the HPMC film is gelled, dried, trimmed and removed from the pins. The body and cap pieces are then joined. The finished HPMC capsule shells comprise 79.6-98.7% w/w of HPMC 2910, 0.03-0.5% w/w of carrageenan, 0.14-3.19% w/w of potassium and/or calcium ions and 2-5% w/w of water.

2.1.2. Physicochemical properties compared with hard gelatine capsules

HPMC capsules are odourless and flexible (Pat.U.S. 5,756,123). Their appearance corresponds to that of gelatine capsules, except that the surface of HPMC capsules is matt, whereas the surface of gelatine capsules is lustrous. The physical properties of HPMC capsules compared to gelatine capsules are presented in Table 1 (Ogura et al., 1998). The main differences in the physicochemical properties between HPMC and gelatine capsules are related to their moisture content, which is 2-5% for HPMC capsules and 13-15% for gelatine capsules (Table 1). The relationship between the brittleness and moisture content of HPMC and gelatine capsules has been demonstrated using a hardness tester (Ogura et al., 1998). The percentage of broken gelatine capsules increased to almost 100% as the moisture content of the capsule shell decreased below 10%. In contrast, HPMC capsules remained undamaged even at moisture levels of only 2%. This

difference between HPMC and gelatine capsules could be of significance in practice if the drug filled in the capsule is strongly hygroscopic.

Table 1. Physical properties of HPMC and gelatine capsules (Ogura et al., 1998).

Capsule material	***HPMC***	***Gelatine***
Moisture content	2-5%	13-15%
Water vapour permeability	Low	Low
Substrate for protease	No	Yes
Maillard reaction with drug fill	No	Yes
Deformation by heat	> 80°C	> 60°C
Water dissolution at room temperature	Soluble	Insoluble
Static	Low	High
Light degradation	No	Possible

The stability of a water-unstable drug in HPMC and gelatine capsules has been tested with acetylsalicylic acid (Ogura et al., 1998). HPMC and gelatine capsules filled with acetylsalicylic acid alone were stored at 60°C for two weeks. The drug content did not decrease to less than 95% of its initial concentration when stored in the HPMC capsules, whereas it decreased to 85% of its initial concentration when stored in the gelatine capsules, apparently as a result of hydrolysis. Thus, due to the naturally low moisture content of the HPMC capsule shells, they are more suitable than gelatine capsules for use with formulations containing water-unstable drugs.

Another notable difference between HPMC and gelatine capsule shells is that HPMC capsule shells are compatible with most filling materials, since the only incompatibility known for HPMC is the interaction between some oxidizing agents (Harwood, 2000). Gelatine, on the other hand, has chemically reactive groups. Ogura and co-workers (1998) filled HPMC and gelatine capsules with ascorbic acid and packed them in polyethylene bottles without a desiccant, and stored at 40°C/75% relative humidity for two months. The gelatine capsules were dyed brown, whereas the colour of the HPMC capsules did not change. In both cases the colour of the ascorbic acid in the capsules did not change, indicating that the discoloration was the result of a reaction between the ascorbic acid and the gelatine shell (called Maillard reaction).

The dissolution of gelatine capsule shells can be incomplete and slow if the capsules contain drugs having aldehyde groups or producing aldehydes on

decomposition, which promote cross-linking between gelatine proteins and form a thin insoluble membrane called a pellicle (Carstensen and Rhodes, 1993; Digenis et al., 1994). This has been demonstrated with spiramycin, a macrolide antibiotic known to cause insolubilisation of gelatine capsules (Ogura et al., 1998). Spiramycin was filled into HPMC and gelatine capsules and stored at 60°C/75% relative humidity for ten days. After storage, the disintegration properties of the HPMC capsules remained unaffected, whereas the properties of the gelatine capsules changed and they did not disintegrate.

Chiwele and co-workers (2000) studied the shell dissolution properties of empty gelatine and HPMC capsules after storage under humid tropical conditions (37°C/75% relative humidity) for 24 h and after storage under ambient room conditions. They used the method described by Jones and Cole (1971), which consists of placing a steel ball bearing inside the capsule, suspending the capsule body in the test solution and measuring the time for it to fall from the capsule. The dissolution medium was artificial gastric or intestinal juice (BP). The temperature of the medium was in the range of 10° to 55 °C. Storage under humid tropical conditions did not affect the dissolution properties of the gelatine capsules regardless of the dissolution medium, whereas the dissolution time of the HPMC capsule shells was unaffected only in artificial gastric juice. In artificial intestinal juice the shell dissolution times of the HPMC capsules were significantly reduced for temperatures between 10° and 30°C, whereas above 37°C the shell dissolution times were increased. It was suggested that the HPMC capsules were hydrated during storage, which might have caused the slower water penetration through the hydrated material and, thus, slower dissolution time of the capsule shell. The reason for the different shell dissolution times of the HPMC capsules in the different dissolution media and at different temperatures was not discussed. Nevertheless, the authors pointed out that care should be taken when the HPMC capsules are exposed to hot and humid conditions.

As was mentioned earlier, Ogura and co-workers (1998) did not notice any effect on the disintegration properties of the HPMC capsules filled with spiramycin when stored at 60°C and 75% relative humidity for ten days. However, they used a standard pharmacopoeial disintegration test, which is fairly drastic and does not determine the shell dissolution time and the disintegration of the powder plug separately (Chiwele et al., 2000). In the method used by Chiwele and co-workers (2000), on the other hand, the filling material (steel ball bearing) did not affect the shell dissolution time.

The study of Chiwele and co-workers (2000) further revealed that the HPMC capsule shells dissolved rapidly in water (pH 5.8) and 0.1 M hydrochloric acid

(pH 1.0) in the temperature range of 10 to 55°C. The gelatine capsule shells, on the other hand, did not dissolve at temperatures below 30°C in the same dissolution medium, and the dissolution time was dependent on the temperature.

2.1.3. In vitro drug release

Three studies (other than those included in this thesis) describing the *in vitro* drug release properties of HPMC capsules (Shionogi Qualicaps S.A.) compared to corresponding gelatine capsules can currently be found in the literature (Ogura et al., 1998; Podczeck and Jones, 2002; Wu et al., 2003). Ogura and co-workers (1998) studied the release of cephalexin from HPMC and gelatine capsules in solutions having pH 1.2, 4.0 or 6.8. The procedure applied was the paddle method described in the Japanese Pharmacopoeia (JP) and the speed of rotation was 100 rpm. There were no differences in the dissolution profiles between the HPMC and gelatine capsules when the pH of the solution was 1.2 or 4.0. When the dissolution medium was the JP "second test fluid" with pH 6.8, the dissolution times of cephalexin were approximately 5 min longer from HPMC capsules than from gelatine capsules. This was supposed to be due to the presence of potassium in the medium, which promotes the gelation of carrageenan. Thus, the HPMC capsule shell formed a persistence gel membrane around the drug fill. When the dissolution medium was changed to potassium-free buffer pH 6.8, there were no differences between the two different capsule shells. Since the cation concentration in the gut is low, it was suggested that pharmacopoeial buffer solutions that do not contain potassium ions could be considered acceptable alternatives for determining *in vitro* drug dissolution rates from HPMC capsules.

Podczeck and Jones (2002) investigated the release of theophylline from HPMC capsules compared with hard gelatine capsules. The capsules contained either the model drug only or the drug and lactose or microfine cellulose as a diluent, and different fill weights and tamping forces were utilized. The dissolution tests were carried out using distilled water at 37°C and a paddle speed of 50 rpm. The amount of theophylline released after 60 min from the different HPMC capsule formulations was always greater than from the corresponding gelatine capsules. Also the release rate was generally greater from the HPMC capsules than from the gelatine capsules. This was suggested to be due to the dissolution properties of HPMC capsule shells. HPMC capsule shells dissolve evenly and simultaneously across the whole shell, whereas gelatine capsules dissolve first from the shoulders, and only later across the whole body. Thus, the whole powder plug filled in an HPMC capsule will be subjected to the dissolution

medium earlier. The authors concluded that a change from gelatine hard shell capsules to HPMC hard shell capsules should not pose problems with respect to drug absorption and bioavailability.

Wu and co-workers (2003) studied the release of an investigational drug, BMS-309403, (poorly water-soluble weak acid) from size 0 gelatine and HPMC capsules. The capsules contained either 50 or 200 mg of the granulated drug and the total fill weights were 90 and 360 mg, respectively. It was estimated that a 90 mg fill weight only occupied a volume of about 20% of the capsule body, whereas 360 mg occupied about 80%. The dissolution tests were carried out using the USP paddle method (60 rpm). The dissolution medium was 0.5% sodium lauryl sulfate in 0.1 M sodium phosphate buffer, pH 6.8 (37°C). The results showed that when the capsule shell was gelatine, the 50 mg capsules surprisingly dissolved at a much lower rate than the 200 mg capsules. It was observed that the shells of the 50 mg gelatine capsules softened and collapsed during the first 10 min of the dissolution test, occluding the granules and retarding the drug release. This was not observed when the gelatine capsules contained 200 mg of the drug; the capsule shells burst open within the first 10 min. When the capsule shell type was changed to HPMC, the 50 mg capsules dissolved slightly faster than the 200 mg capsules and the HPMC capsule shells did not collapse onto the granulation. However, both HPMC capsule strengths dissolved more slowly during the first 10 to 20 min than the corresponding gelatine capsules, which was due to the swelling and expansion of the HPMC capsule shells without leaking much granulation during the first 10 min.

2.1.4. Biopharmaceutical properties

Studies describing the bioavailability of drugs from HPMC capsules (Shionogi Qualicaps S.A.) compared to gelatine capsules are limited to that of Ogura and co-workers (1998) determining the oral bioavailability of cephalexin from HPMC capsules compared to gelatine capsules. The study was conducted with 6 healthy volunteers under fasting conditions. Concentrations versus time curves were similar between the HPMC and gelatine capsules and there were no significant differences in the pharmacokinetic parameters (*AUC*, C_{max} and t_{max}) between these capsules.

2.2. Hydroxypropyl methylcellulose

2.2.1. Manufacture

The European Pharmacopoeia describes hydroxypropyl methylcellulose (hypromellose) as partly *O*-methylated and *O*-(2-hydroxypropylated) cellulose. The structural formula of HPMC is presented in Fig. 1.

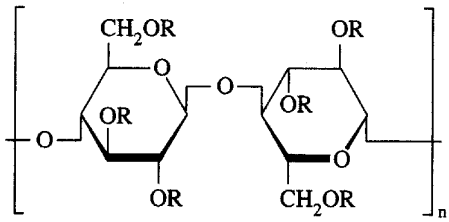

Figure 1. Structural formula of hydroxypropyl methylcellulose. The substituent R represents either a -H, -CH_3, or a -$CH_2CH(CH_3)OH$.

HPMC is an odourless, tasteless and inert hydrophilic polymer with no ionic charge. It is manufactured from purified cellulose, which is obtained from cotton linters or wood pulp (Harwood, 2000). The cellulose is first treated with sodium hydroxide solution to produce swollen alkali cellulose, which is chemically more reactive than the untreated cellulose. The alkali cellulose is then converted to methylhydroxypropyl ethers of cellulose by treating with chloromethane and propylene oxide. Finally, the fibrous reaction product is purified and ground to powder or granules.

2.2.2. Physicochemical properties

The physicochemical properties of HPMC (e.g. solubility, glass-transition temperature and viscosity) are affected by the ratio of methoxy and hydroxypropoxy groups and the molecular weight. The molecular weight of HPMC is approximately 10,000 to 1,500,000 (Harwood, 2000). There are several grades of HPMC polymers available on the market, which vary in viscosity and extent of substitution. The grades may be distinguished by a number indicative of the apparent viscosity, in mPa·s, of a 2% w/w aqueous solution at 20°C. The apparent viscosity serves as a measure of the average chain length of the polymer.

The USP presents four different types of HPMC polymers. They are classified according to their relative methoxy-group and hydroxypropoxy-group contents: HPMC 1828, HPMC 2208, HPMC 2906 and HPMC 2910. The first two numbers indicate the percentage of methoxy groups, the last two numbers the percentage of hydroxypropoxy groups, determined after drying at 105°C for two hours. The exact limits for the degree of substitution defining the respective HPMC types are given in Table 2.

Table 2. USP specifications for different types of HPMC, classified according to their degree of methoxy and hydroxypropoxy substitution.

Substitution type	*Methoxy (%)*		*Hydroxypropoxy (%)*	
	Min.	Max.	Min.	Max.
1828	16.5	20.0	23.0	32.0
2208	19.0	24.0	4.0	12.0
2906	27.0	30.0	4.0	7.5
2910	28.0	30.0	7.0	12.0

2.2.3. Applications in pharmaceutical formulation and technology

HPMC is an extremely versatile material, which is widely used in pharmaceutical products. HPMC is primarily used as a binder, film coating and as a controlled-release matrix in solid dosage forms (Rowe, 1980; Banker et al., 1981; Krycer et al., 1983a, b; Alderman, 1984; Harwood, 2000). Concentrations of 2-5% w/w may be used as a binder in either wet or dry granulation processes (Harwood, 2000). In film coating, concentrations of 2-20% are used, depending on the viscosity grade of the HPMC. In controlled-release matrix formulations, concentrations of 10-80% may be used. In liquid dosage forms HPMC is used as a suspending and thickening agent and as an emulsifier.

2.2.3.1. Hydroxypropyl methylcellulose in controlled-release formulations

Controlled-release formulations have several benefits over conventional immediate-release formulations: controlled administration of a therapeutic dose at a desired delivery rate, constant blood levels of drugs, reduction of side effects, maintenance of therapeutic concentration also during the night, minimization of dosing frequency and enhancement of patient compliance (Ritschel, 1989). On the

other hand, controlled-release formulations also have some disadvantages, e.g. loss of efficacy when one or two doses are skipped and poor dosage form for drugs with inactivation by first-pass metabolism, extremely short or long elimination half-life and instability in the gastrointestinal environment.

Hydrophilic matrix formulations are the most widely used of the numerous controlled-release dosage forms currently available and they have been employed in the pharmaceutical industry for over 40 years (Wichterle and Lim, 1960; Alderman, 1984; Ranga Rao and Padmalatha Devi, 1988; Ferrero Rodriguez et al., 2000). Of hydrophilic polymers, hydroxypropyl methylcellulose is the most popular material for the preparation of controlled-release dosage forms and it has been employed since the 1960s (Pat.U.S. 3,065,143; Lapidus and Lordi, 1966, 1968; Huber et al., 1966; Huber and Christenson, 1968; Colombo, 1993; Hogan, 1989; Ferrero Rodriguez et al., 2000). One of its most important characteristics is high swellability, which has a significant effect on the release kinetics of an incorporated drug**.** Also its ease of compression, non-toxic nature, ability to accommodate a large percentage of drugs, and the minimum influence of processing variables on the release of drugs from matrices are some of the reasons for its popularity (Vázquez et al., 1992).

When the HPMC-based matrix formulation comes into contact with a thermodynamically compatible aqueous solvent, the solvent penetrates into the free spaces on the surface between the macromolecular chains. When the solvent has sufficiently entered into the matrix the characteristic glassy-rubbery transition temperature (T_g) of the polymer is decreased to the level of the experimental temperature and relaxation of the polymeric chains takes place (Siepmann and Peppas, 2001). The HPMC swells, causing the dimensions of the system to increase and the concentrations of the polymer and drug to change markedly. Water-soluble drugs dissolve in the solvent and diffuse out of the matrix according to concentration gradients. If the drug is poorly soluble in the solvent, dissolved and non-dissolved drug coexist within the polymer matrix and the non-dissolved drug is not available for diffusion. Poorly soluble and insoluble drugs are mainly released when the outermost gel layer of the matrix is eroded. The erosion rate depends on the viscosity of the HPMC type used. The resulting drug release mechanism (Fickian, non-Fickian or Case II release) depends on the rates of drug diffusion, matrix relaxation and matrix erosion, and also on the dissolution of the drug in the gel (Lee, 1985; Colombo et al., 1999). Fickian diffusion is related to square root of time release, non-Fickian release is a combination of diffusion and polymer relaxation phenomena, and Case II release is characterised

by zero-order kinetics, i.e. the drug is released at a constant rate (Colombo et al., 1990).

Tablets are the most commonly used formulations in the design of HPMC-based controlled-release dosage forms (Alderman, 1984), but also hard two-piece capsules containing either HPMC powder (Alderman, 1984; Ojantakanen, 1992; Ojantakanen et al., 1993; Eerikäinen et al., 1996; Leino et al., 1997) or HPMC-based multiple units (Jalil and Ferdous, 1993; Cox et al., 1999; Pandey et al., 2002; De Brabander et al., 2003) have been developed. There are some differences between the HPMC-based tablets and capsules when single-unit systems are considered. The size of the tablet may influence the drug release rate and the amount of polymer needed to obtain controlled release. Usually, the smaller the tablet is the greater the polymer content required (Alderman, 1984). Further, as the tablet size is increased, the drug release rate may be decreased due to changes in surface-to-volume ratios and in the degree of initial gel formation. On the other hand, the effect of capsule size on dissolution rates is less obvious and the release of drugs from different sized capsules varies only slightly (Alderman, 1984). The amount of HPMC polymer needed to achieve controlled drug release from capsule formulations is generally a little greater than that for tablet formulations exhibiting the same dissolution times. This is probably due to lower powder density in the capsules.

A prerequisite for achieving controlled drug release from HPMC matrix formulations is fast formation of a gelatinous layer. In other words, the polymer must hydrate fast enough to form a gel layer before the contents of the formulation dissolve prematurely (Alderman, 1984; Ferrero Rodriguez et al., 2000). In tablet formulations the hydration rate of HPMC type 2208 has turned out to be adequate, whereas types 2906 and 2910 do not hydrate fast enough to prevent the rapid disintegration and dissolution of tablet formulations (Alderman, 1984; Ferrero Rodriguez et al., 2000). In capsule formulations all these HPMC types (2208, 2906 and 2910) exhibit adequate controlled drug release (Alderman, 1984).

2.2.3.2. Factors affecting drug release from hydroxypropyl methylcellulose type 2208 matrices

Hydroxypropyl methylcellulose type 2208 having 19-24% methoxy and 4-12% hydroxypropoxy content is the most widely investigated polymer among the different types of HPMCs due to its faster hydration rate. There are several factors that can affect the release rate of a drug from HPMC type 2208-based matrices, e.g. HPMC viscosity grade, HPMC/drug ratio, HPMC and drug particle size, drug

solubility and formulation additives (Table 3) (Alderman, 1984; Hogan, 1989; Nokhodchi et al., 1999). Of these factors, the viscosity grade and concentration of the HPMC are those most often used in regulating drug release.

Several studies have demonstrated that increasing the viscosity grade of HPMC type 2208 decreases the drug release rate from both tablet and hard capsule matrix formulations (Alderman, 1984; Ford et al., 1985a, b, c; Ojantakanen, 1992; Wan et al., 1992; Sung et al., 1996; Leino et al., 1997; Tros de Ilarduya et al., 1997; Li et al., 2003). This is due to the increase in the gel layer viscosity, causing the drug to diffuse slower through the gel layer. In addition, the greater the viscosity of the gel, the more resistant the gel is to dissolution and erosion. Consequently, the gel layer can be a controlling factor in drug release. In some studies, depending on the model drugs and formulations used, the release rate of the model drugs was not further decreased even though the HPMC type 2208 polymer was changed from a lower viscosity grade to a higher viscosity grade, e.g. from 4000 to 15,000 mPa·s or from 15,000 to 100,000 mPa·s (measured as a 2% w/w solution at 20°C) (Ford et al., 1985b, c; Ojantakanen et al., 1992; Sung et al., 1996). It was suggested that the HPMC matrix formulations studied have a “limiting HPMC viscosity”, i.e. the drug release rate no longer decreases when the viscosity grade is increased above a certain level, e.g. 4000 or 15,000 mPa·s (Sung et al., 1996).

The drug/HPMC type 2208 ratio in matrix formulations affects the strength of the gel layer similarly to the viscosity grade of the HPMC polymer (Alderman, 1984). When the concentration of the HPMC is increased, the viscous gel layer becomes stronger and more resistant to diffusion and erosion, causing the drug release rate to decrease. This phenomenon has been demonstrated in several studies conducted with matrix tablets containing water-soluble drugs, e.g. aminophylline (Ford et al., 1985c), potassium chloride (Salomon et al., 1979), promethazine hydrochloride (Ford et al., 1985b), propranolol hydrochloride (Ford et al., 1985c) and riboflavin (Alderman, 1984). Studies performed with hard capsule matrix formulations made of HPMC and utilising the effect of the drug/polymer ratio could not be found in the literature, probably because hard capsules are rarely used as single-unit controlled-release matrix formulations.

When the drug is poorly water-soluble, an increase in HPMC concentration in matrix tablet does not necessarily lead to a decreased drug release rate in every situation. For example Ford and co-workers (1985a) have shown that the release rate of poorly water-soluble indomethacin was independent of the drug/HPMC type 2208 ratio when the viscosity of the polymer was 100 mPa·s. However, when the viscosity of the HPMC was changed to 4000, 15,000 or 100,000 mPa·s, the

release rate of indomethacin decreased as the HPMC content increased in the formulation.

Table 3. The effect of various factors on drug release rate from HPMC type 2208-based tablet and capsule matrices.

Factor	*Effect on drug release rate*	*Reference*
HPMC viscosity grade	As the viscosity grade of the HPMC polymer increases, the drug release rate decreases from both tablet and capsule matrices.	Alderman, 1984; Ford et al., 1985a, b, c; Ojantakanen, 1992; Wan et al., 1992; Sung et al., 1996; Leino et al., 1997; Tros de Ilarduya et al., 1997; Li et al., 2003
HPMC/drug ratio	As the concentration of the HPMC polymer increases or the concentration of drug decreases, the drug release rate decreases from tablet matrices.	Salomon et al., 1979; Alderman, 1984; Ford et al., 1985b, c
HPMC particle size	The greater the particle size of the HPMC powder the greater is the drug release rate from HPMC tablet matrices.	Alderman, 1984
Drug particle size	For water-insoluble drugs, a decrease in particle size increases the release rate from HPMC tablet matrices. For water-soluble drugs the effect of drug particle size is generally insignificant.	Ford et al., 1985a, b, c; Tros de Ilarduya et al., 1997
Drug solubility	As the solubility of the drug increases, the release rate increases from HPMC tablet matrices.	Colombo et al., 1995; Ferrero Rodriguez et al., 2000
Formulation additives:		
Lactose and calcium phosphate	Addition of lactose or calcium phosphate to HPMC tablet or capsule matrices increases the release rate of drug.	Alderman, 1984; Ford et al., 1987; Sung et al., 1996; Nokhodchi et al., 1999
Sodium carboxymethyl-cellulose (NaCMC) and microcrystalline cellulose	Addition of NaCMC or microcrystalline cellulose to HPMC tablet matrices increases the drug release rate. The effect of these additives on capsule matrices is insignificant.	Alderman, 1984; Nokhodchi et al., 1999
Ionic surfactants	Ionic surfactants decrease the release rate of drugs from HPMC tablet matrices if the surfactant and the drug are ionised and have opposite charges	Feely and Davis, 1988
Sodium lauryl sulphate	Incorporation of sodium lauryl sulphate into HPMC tablet matrices increases the drug release	Nokhodchi et al., 1999

The particle size and size distribution of the HPMC type 2208 powder affect the hydration rate of the HPMC, and thus the rate of gel formation and drug release from tablet matrices (Alderman, 1984). The coarser the HPMC powder particles are, the slower the gel formation and the greater the drug release rate. The effect of the particle size of the drug on the release rate from HPMC type 2208 matrices depends on the solubility of the drug (Ford et al., 1985a, b, c; Tros de Ilarduya et al., 1997). Ford and co-workers (1985a, b, c) noticed that decreasing the particle size of freely water-soluble drugs insignificantly affected the release rate, but when the model drug was poorly water-soluble, the release rates increased as the particle size of the drug decreased. Also Tros de Ilarduya et al. (1997) discovered that decreasing the particle size of water-insoluble oxazepam increased the release rate from HPMC matrices. These results indicate that for poorly water-soluble drugs not only the viscosity grade of the HPMC and the drug/HPMC ratio are important in controlling drug release but also the particle size of the drug is significant.

Drug solubility also affects the release rate from HPMC matrices: increased solubility of the model drug results in a higher release rate from HPMC type 2208-based tablet formulations (Colombo et al., 1995; Ferrero Rodriguez et al., 2000). This is probably due to a higher concentration gradient through the gel layer, which increases the diffusion coefficient of the drug (Colombo et al., 1995). The water-solubility of drugs has an effect also on the release kinetics of drugs from HPMC type 2208 matrices (Ford et al., 1987; Ranga-Rao et al., 1990). Ranga Rao and co-workers (1990) studied the release of 23 drugs of various solubilities from HPMC type 2208 matrix tablets and reported that several sparingly, slightly and very slightly soluble drugs were released at a nearly zero-order rate from the matrices, whereas the mode of release of water-soluble drugs was non-Fickian. Ford and co-workers (1987) reported similar observations when they studied the release of seven soluble and insoluble drugs from HPMC type 2208 matrix tablets.

Formulation additives also modify the release rate of drugs from HPMC matrices. The addition of lactose or calcium phosphate to HPMC type 2208-based tablet and capsule formulations generally increases the release rate of drugs (Alderman, 1984; Ford et al., 1987; Sung et al., 1996; Nokhodchi et al., 1999). Sodium carboxymethylcellulose (NaCMC) and microcrystalline cellulose are insoluble and swellable additives often used as fillers or disintegrants. When these are incorporated into HPMC type 2208-based tablet matrices, the gelatinous layer tends to expand, causing more of the drug to be released in the early stages of dissolution (Alderman, 1984; Nokhodchi et al., 1999). On the other hand, due to

the lower density of the powder plug in capsule matrix formulations, swellable, insoluble fillers have an insignificant effect on the drug dissolution profile from capsule matrices (Alderman, 1984). Also the effect of different surfactants on the release of drugs from HPMC type 2208-based matrix tablets has been evaluated (Feely and Davis, 1988; Nokhodchi et al., 1999). Ionic surfactants (e.g. sodium dodecylsulphate, *n*-hexadecylsulphate and *n*-octadecylsulphate) retarded the drug release only when these were ionised and had opposite charges (Feely and Davis, 1988). Nokhodchi and co-workers (1999) have reported that incorporating sodium lauryl sulfate into HPMC matrices increased the drug release. This was probably due to the pores/channels that the surfactant formed in the matrix, thereby increasing the effective surface area by a method other than wetting.

2.3. Rectal administration of hard capsules

The rectal route of drug administration is feasible for the treatment of small children and very old people as well as patients who are not able to take oral medication due to nausea, vomiting, severe confusion or various GI diseases. In addition, drugs that are not suitable for oral administration could be administered rectally. For example some drugs may cause GI side effects when administered orally or they may be unstable at the pH of the upper GI tract. Orally administered drugs may also be metabolised by the various enzymes in the GI tract or during the first passage of the liver after administration. In addition, the rate of drug absorption from the rectum is not dependent on the gastric emptying rate or influenced by food.

2.3.1. General considerations

In order to understand the factors affecting rectal drug administration, it is important to be familiar with the anatomy and the physiology of the rectum. The human rectum is the distal part of the colon, forming the last 12 to 15 cm of the gastrointestinal tract (Moore, 1992). The rectal epithelium is mainly columnar or cuboidal and it is single-layered in the upper parts of the rectum and stratified in the lower parts. The epithelium contains numerous Globlet cells, but no villi or microvilli. Drugs are absorbed from the rectal mucosa via the paracellular and transcellular route and there are no active transport systems such as in the upper parts of the GI tract (Muranishi, 1984). Therefore, the main mechanism for rectal drug absorption is passive diffusion. The surface area of the rectum is about 200

to 400 cm^2, about 10,000-fold smaller than that of the small intestine, partly due to the lack of the villi in the rectal epithelium. This means that the surface area of the rectum can be a rate-limiting factor in drug absorption. Moreover, the total fluid content in the rectum is only about 3 ml and is rather viscous, which limits the dissolution of poorly soluble drugs in the rectum (de Blaey and Tukker, 1988). The pH of the fluid is approximately 7.5 and it has poor buffer capacity. The environment of the rectum is, however, quite constant with respect to the amount and viscosity of the rectal fluid, its temperature and pH. Therefore, several drugs have exhibited reproducible absorption from the rectum and also rate control in rectal drug delivery is possible by using specific formulations (de Boer et al., 1982; Breimer et al., 1985; van Hoogdalem et al., 1991a, b; de Boer and Breimer, 1997).

The rectum is drained by the superior, the middle and the inferior rectal veins (Moore, 1992). The superior rectal vein, perfusing the upper parts of the rectum, drains into the portal vein, and later into the liver, whereas the middle and the inferior rectal veins, perfusing the lower parts of the rectum, drain directly into the systemic veins. This means that it is possible to partially avoid hepatic first-pass metabolism of drugs via rectal administration, especially if the dosage form is administered to the lower parts of the rectum. However, the rectal vessels are connected with extensive anastomoses, which is a complicating factor in respect to the absorption of high-clearance drugs. The partial avoidance of the hepatic first-pass metabolism via rectal dosing has been demonstrated in humans with lidocaine (de Boer et al., 1979; de Leede et al., 1984a), metoclopramide (Hellstern et al., 1987), metopimazine (Herrstedt et al., 1996), 6-mercaptopurine (Kato et al., 1992), morphine (Babul and Darke, 1993), metoprolol (de Stoppelaar et al., 1999), propranolol (de Leede et al., 1984b), salbutamol (Kurosawa et al., 1993) and verapamil (Hammouda et al., 1996). The extent to which the first-pass metabolism can be avoided depends on several factors, e.g. the physicochemical properties of the drug and the vehicle, the absorption site in the rectum and the patient, because the venous drainage in the rectum can vary greatly between different individuals (de Boer et al., 1982).

There are also other factors than those mentioned above that can affect the bioavailability of rectally administered drugs. For example faeces can mechanically prevent contact between the drug and the absorbing mucous (de Blaey and Tukker, 1988). However, the rectum is usually empty except when the faeces are temporarily transferred from the colon and are either defecated (when also the drug is removed) or transported back to the colon depending on the voluntary control of the subject. The rectum does not have a constant internal

volume; in an upright body position the intestinal organs press against the rectum, causing it to flatten. Therefore, the spreading of the rectal formulation and the subsequent absorption of the drug could be different in humans when walking than when prone. The rectal lumen also contains a lot of metabolising micro-organisms that can affect the bioavailability of drugs, especially if the drug remains in the rectum for a relatively long time (de Boer et al., 1982). Also various properties of the drug substance and delivery system can affect the rectal bioavailability. Such properties are, for example, the solubility of the drug, the partition coefficient and particle size of the drug, the affinity and amount of the drug in the vehicle, the composition of the vehicle and the rheological, melting or dissolution properties of the vehicle (de Blaey and Tukker, 1988).

2.3.2. Hard capsules

Suppositories are the most common rectal dosage forms, but there are also rectal soft gelatine capsules on the market. So far, hard capsules have been used as a rectal dosage form only experimentally. Hard capsules have some advantages over suppositories and soft gelatine capsules. The manufacturing process for hard capsules is faster, cheaper and simpler than that for suppositories and soft capsules. Hard capsules could also be filled with solid materials in a retail or hospital pharmacy according to the specific prescription of a patient, whereas accurate dose adjustment or *ex tempore* preparation is not always possible with suppositories or soft capsules. Hard capsules could also be sealed to prevent leakage of the filling (Cadé et al., 1986), allowing greater flexibility in the choice of excipients: solids, semisolids and oily liquids could be encapsulated. Gelatine capsules become sticky when in contact with moisture, and thus the insertion of the capsules into the rectum could be difficult if the capsules are not coated with a glidant (Hannula et al., 1986; Eerikäinen et al., 1996).

In 1983, Takagishi and co-workers patented a hard two-piece capsule for rectal application which was made of enterosoluble materials selected from the group consisting of mixed esters of an alkylcellulose, hydroxyalkylcellulose or hydroxyalkyl alkylcellulose (Pat.U.S. 4,402,692; 4,405,597). These capsules could be filled also with aqueous medicines in the form of aqueous solution, aqueous suspension or emulsion, which is not possible with hard gelatine capsules. However, investigators observed considerable interindividual variation in capsule disintegration in the rabbit rectum, and therefore variation in drug absorption, when the capsules were filled with aqueous or oily substances. The problem was solved by filling the capsules with aqueous liquid that has an

osmotic pressure substantially higher than that of the rectal fluid, but not so high as to irritate the rectal membrane. The investigators evaluated these enterosoluble capsules only with test animals (e.g. rabbits) and no further studies conducted with healthy volunteers can be found in the literature.

The first hard gelatine capsule for rectal administration was patented in 1984 for indomethacin (Pat.DE 3,241,263 A1). In addition, the feasibility of hard gelatine capsules for rectal administration has been evaluated in humans with paracetamol (Hagenlocher et al., 1987), doxepin and carbamazepine (Storey and Trumble, 1992), ibuprofen (Eerikäinen et al., 1996; Leino et al., 1997; 1999) and metoclopramide hydrochloride (Leino et al., 2003). Hagenlocher and co-workers (1987) compared the bioavailability of paracetamol from hard gelatine capsules filled with amphiphilic (polyoxyethylated fats) or lipophilic (hard fat/oil mixture) excipients with a hard fat suppository and an aqueous suspension microenema, using an oral solution as a control formulation. The results indicated that the bioavailability of the model drug from both capsule formulations was comparable with that from the suppository and the microenema. It was also concluded that it is possible to achieve fast and more homogeneous *in vivo* dissolution of paracetamol from amphiphilic capsule formulations than from lipophilic capsules and suppositories. Hardy and co-workers (1987) further evaluated the mechanism of the increased absorption from the amphiphilic capsules by imaging the spreading of the capsule contents (Witepsol® and Labrafil®) in the human rectum with gamma scintigraphy. The base and the suspended non-absorbing agent, a cation exchange resin representing the drug substance, were labeled separately in order to evaluate the relative movements of the base and the “drug”. Generally, the spreading of the bases was not great and there were no differences between the two bases. Mostly the base and the resin remained together in the rectum. On the other hand, if the capsule contents were spread, it was related more to movement of the base than the suspended resin. Therefore, differences in the absorption of paracetamol from different bases in the study of Hagenlocher and co-workers (1987) probably cannot be explained by the differences in spreading.

Storey and Trumble (1992) reported the use of doxepin and carbamazepine capsules as rectal dosage forms for patients suffering from cancer. The patients were not able to take oral medication and there were no injections available. Hard gelatine capsules containing powdery drugs turned out to be clinically useful and there was no need to use long and expensive processes for making suppositories of these drugs substances.

Eerikäinen and co-workers (1996) investigated the bioavailability of ibuprofen from rectally administered hard gelatine capsules containing lactose or HPMC

K15M (15,000 mPa·s) as a diluent, using oral capsules containing only ibuprofen as a reference. They also evaluated whether the coating of the capsules and training in their administration beforehand could affect the rectal bioavailability. The results showed that dipping the capsules into liquid paraffin just before administration and training in administration beforehand significantly improved the bioavailability of ibuprofen from rectal capsules. The amount of ibuprofen absorbed from the orally administered capsules and from the rectally administered lactose-based capsules was equal and the capsules could be regarded as equivalent with respect to the bioavailability (*AUC*). However, the rate of absorption evaluated from C_{max} and t_{max} values was significantly lower for the rectal than for the oral capsules and the rectal capsules exhibited a lag time of about 30 min in the commencement of drug absorption. The capsules containing HPMC K15M as a diluent behaved as prolonged-release formulations, but the bioavailable amount of ibuprofen was decreased significantly and the capsules were considered to be unsuitable for rectal administration.

Leino and co-workers (1997) continued to develop rectal prolonged-release ibuprofen formulations from hard gelatine capsules by using the lower viscosity grades of HPMC, i.e. HPMC K100 (100 mPa·s) or HPMC K4M (4000 mPa·s). There were no differences in the pharmacokinetic parameters between the two formulations. When these capsules were compared to lactose-based capsules, a clear retardation of drug absorption was observed and adequate prolonged release was achieved at least with HPMC K100-based capsules. Also the use of polycarbophil in rectal capsules was evaluated. When the diluent consisted of 5% polycarbophil and 95% lactose, sufficiently prolonged release of ibuprofen was observed. Thus, hard gelatine capsules are useful also as prolonged-release formulations with proper diluents.

In the next study of Leino and co-workers (1999) the effect of the number of rectal hard gelatine capsules on the bioavailability of ibuprofen was assessed. The amount of ibuprofen was 400 mg and it was administered either in two size 1 capsules (200 mg per capsule) or in one size 00 capsule. The bioavailability of ibuprofen was significantly greater from the two small capsules than from the one big capsule, which was supposed to be due to wider spreading to the absorbing mucosa of the rectum by the two small capsules. They also studied the effect of sodium phosphates on the bioavailability of ibuprofen from rectal hard gelatine capsules compared with a commercial suppository and soft gelatine capsule. Ibuprofen is a weak acid, which is poorly soluble in water in an acidic environment. With a formulation containing disodium hydrogen phosphate and sodium dihydrogen phosphate in a ratio of 1/14 (the same as in the Ph.Eur. buffer

solution pH 7.5) it was possible to obtain better absorption of ibuprofen than from capsules containing only lactose as a diluent. This was most likely due to better dissolution of ibuprofen in the rectum, since the pH of the microclimate was probably increased by the presence of sodium phosphates. The bioavailability of ibuprofen from hard gelatine capsules containing sodium phosphates did not differ significantly from the suppositories or the soft gelatine capsules. In addition, the interindividual variation was lower with the hard gelatine capsules. Therefore, it was concluded that hard gelatine capsules are a notable dosage form for rectal administration.

In order to clarify the effect of the physicochemical properties of the model drug on the rectal bioavailability from hard gelatine capsules, Leino and co-workers (2003) studied the bioavailability of metoclopramide hydrochloride from capsules corresponding to those used in the studies conducted with ibuprofen (Leino et al., 1999). Unlike ibuprofen, metoclopramide hydrochloride is a weak base and readily soluble in water and physiological fluids. Two capsule formulations were studied: an immediate-release lactose-based capsule and a prolonged-release capsule containing diluents consisting of 5% polycarbophil and 95% lactose. A commercial metoclopramide suppository was used as a reference. The results showed that the bioavailability (*AUC*) and the rate of absorption (*MRT* and C_{max}/AUC) of metoclopramide were similar from the lactose-based capsules and from the suppositories. The lag time (t_{lag}) and time for maximum concentration (t_{max}) values were, however, significantly greater for the capsules than for the suppositories. Evidently, the differences in the t_{max} values could be explained by the differences in the t_{lag} values. Similar t_{lag} values were also found for ibuprofen (Leino et al., 1999), indicating that the time lag at the commencement of drug absorption was caused by the disintegration and dissolution properties of the capsule shell rather than the solubility of the model drug. The drug release from capsules containing polycarbophil was adequately prolonged when compared with lactose-based capsules and suppositories. The results obtained from corresponding prolonged-release ibuprofen capsules (Leino et al., 1999) were quite similar and it was concluded that the solubility of the model drug is not very prominent in the assessment of the biopharmaceutical characteristics of rectally administered hard gelatine capsule formulations.

The studies of Eerikäinen and co-workers (1996) and Leino and co-workers (1997; 1999) were conducted in the same laboratory as the studies presented in this thesis, and they explained the idea of studying rectal administration of the HPMC capsules.

3. Aims of the study

As was pointed out in the Introduction (Section 1) and Review of literature (Section 2) there is a real need for both *in vitro* and *in vivo* scientific evaluation in order to determine whether the novel HPMC capsule and the classic hard gelatine capsule are interchangeable in the development and clinical use of different types of capsule formulations.

The specific aims of the studies were:

- To investigate whether the change of capsule shell material causes any changes in the pharmaceutical characteristics of the capsule formulations.
- To investigate whether the change of capsule shell material causes any changes in the bioavailability parameters of the model drugs (ibuprofen and metoclopramide hydrochloride).
- To investigate whether there are equal possibilities for both capsule shell types to develop sustained-release formulations utilising HPMC powders of different viscosity grades as diluents.
- To investigate the possible effect of route of administration (oral or rectal) on the bioavailability of the model drugs from different capsule formulations.
- To investigate the possible effect of the chemical nature and water solubility of the model drugs on the *in vitro* and *in vivo* behaviour of the two capsule shell types.
- To investigate *in vitro* whether there are any differences between the two capsule shell types in their tendency to adhere to isolated porcine oesophagus.
- To investigate, by means of gamma scintigraphic investigations, the fate (movement and disintegration) of orally administered HPMC capsules containing different grades of HPMC powder in the human gastrointestinal tract.

4. Materials and methods

4.1. Model drugs

4.1.1. Ibuprofen

Ibuprofen, 2-(4-isobutylphenyl) propionic acid (Ph.Eur.), was chosen as a model drug (I and II), because it is absorbed throughout the GI tract (Parr et al., 1987; van Hoogdalem et al., 1991b). Ibuprofen is practically insoluble in acidic aqueous solutions (pK_a 5.3, M_w 206.3 g mol^{-1}), and therefore it was regarded as representative of drugs that are only sparingly soluble in water (Herzfeldt and Kümmel, 1983).

As a non-steroidal anti-inflammatory drug (NSAID), ibuprofen is used for the treatment of acute and chronic pain, e.g. dysmenorrhoea and rheumatic diseases, as single doses of 200 to 800 mg three to four times a day (Martindale, 1993). The maximum dose per day is 3200 mg. A therapeutic plasma drug concentration of ibuprofen is from 10 to 50 mg/l, and a concentration of >100 mg/l is toxic (Davies, 1998). Following administration of single doses of immediate-release preparations, the peak plasma drug concentration is observed within 3 h post-dose. The elimination half-life ($t_{1/2}$) is about 2 h. Most of the drug is metabolised to at least two metabolites and only less than 1% is excreted unchanged in urine (Mills et al., 1973).

4.1.2. Metoclopramide hydrochloride

Metoclopramide, 4-amino-5-chloro-2-methoxy-N-(2-diethylaminoethyl) benzamide (BP), as the hydrochloride, was chosen as another model drug (III). Metoclopramide hydrochloride is a weak base, which is freely soluble in water throughout the physiological pH range (pK_a 0.6 and 9.6, M_w 354.3 g mol^{-1}) (Martindale, 1993; USPDI, 1998). Thus, it was regarded as representative of freely water-soluble drugs.

Metoclopramide is a central dopaminergic antagonist and it is used for the treatment of nausea, vomiting and various gut motility disorders (Martindale, 1993; USPDI, 1998). A therapeutic dose for both oral and rectal administration is generally 10 to 20 mg three to four times a day (USPDI, 1998). There is fairly little evidence on the relationship between plasma drug concentrations and either

the efficacy of metoclopramide or the incidence of adverse effects (Bateman et al., 1979; Campbell and Bateman, 1992). However, it has been reported that central nervous system side effects of metoclopramide are likely to occur when the concentration in plasma exceeds 100 ng/ml (Bateman et al., 1979). Metoclopramide is absorbed sufficiently and rapidly throughout the gastrointestinal tract, but oral and rectal systemic bioavailability has been reported as variable, about 32-97% and 53-100%, respectively (Bateman et al., 1980; Block et al., 1981; Ross-Lee et al., 1981; Hellstern et al., 1987; Vergin et al., 1990). The great inter-individual variation and low bioavailability of metoclopramide have been shown to be caused by first-pass metabolism, which reduces the amount of drug available to the systemic circulation (Ross-Lee et al., 1981). The peak concentration for immediate-release oral formulations is reached about 1 to 2 h after administration (USPDI, 1998; Bateman, 1983). The predominant elimination route of metoclopramide is urinary excretion and the elimination half-life ($t_{1/2}$) in healthy subjects is about 3 to 5 h (Bateman et al., 1980; Wright et al, 1988).

4.2. Additives

4.2.1. Hydroxypropyl methylcellulose

Three grades of hydroxypropyl methylcellulose type 2208 having 19-24% methoxy and 4-12% hydroxypropoxy content (Ph.Eur.) (Methocel®, Dow Chemicals, Great Britain) were used in the development of prolonged-release formulations: HPMC K100 (II-IV), HPMC K4M (II-IV) and HPMC K15M (II). The nominal viscosities of the HPMCs (measured as a 2% aqueous solution at 20°C) are 100, 4000 and 15,000 mPa·s, respectively.

4.2.2. Other additives

Lactose monohydrate (Ph.Eur.) (Der Melkindrustrie, Veghel, The Netherlands) was used as a diluent in the immediate-release formulations (I and III). Hard fat (Ph.Eur.) (Witepsol W45®, mp 35°C) was used as a coating for the rectal capsules (I-III). Natural abundance samarium oxide (Sm_2O_3, purity 99.9%, Aldrich, USA) was used for radiolabelling capsules in the gamma scintigraphic study (IV).

4.3. Capsule preparation and composition

Hard size 0 HPMC (Shionogi Qualicaps S.A, Spain) and gelatine (Coni-Snap, Capsugel, Belgium) capsules were used in the formulations. All capsules were filled manually using a Feton apparatus (Feton International, Belgium). The necessary amount of ibuprofen (I and II), metoclopramide hydrochloride (III) or samarium oxide (IV) was weighed out into a measuring cylinder and lactose (I and III) or hydroxypropyl methylcellulose (II-IV) was added so as to obtain sufficient material for a batch of 100 capsules (68 ml). The powders were mixed manually, after which the capsule bodies were filled. The quality of the batches was tested according to Ph.Eur. 3th Ed. (mass and content uniformity of single-dose preparations and disintegration of capsules). The capsules for rectal administration were coated by dipping them into melted hard fat using tweezers. The compositions and routes of administration of the capsules are presented in Table 4.

Table 4. Compositions (mg) and routes of administration of the capsule formulations. Capsules for rectal administration were coated with hard fat (q.s.).

Study	Capsule material	Ibuprofen (mg)	Metoclopramide (mg)	Sm_2O_3 (mg)	Lactose (mg)	HPMC K100 (mg)	HPMC K4M (mg)	HPMC K15M (mg)	Route of administration
I	HPMC	200	-	-	157	-	-	-	oral
	HPMC	200	-	-	152	-	-	-	rectal
	Gelatine	200	-	-	171	-	-	-	oral
	Gelatine	200	-	-	157	-	-	-	rectal
II	HPMC	200	-	-	-	145	-	-	oral and rectal
	HPMC	200	-	-	-	-	141	-	oral and rectal
	HPMC	200	-	-	-	-	-	143	oral and rectal
	Gelatine	200	-	-	-	141	-	-	oral and rectal
	Gelatine	200	-	-	-	-	140	-	oral and rectal
	Gelatine	200	-	-	-	-	-	142	oral and rectal
III	HPMC	-	10	-	453	-	-	-	oral and rectal
	HPMC	-	10	-	-	245	-	-	oral and rectal
	HPMC	-	10	-	-	-	240	-	oral
	Gelatine	-	10	-	450	-	-	-	oral and rectal
	Gelatine	-	10	-	-	240	-	-	oral and rectal
	Gelatine	-	10	-	-	-	235	-	oral
IV	HPMC	-	-	6	-	260	-	-	oral
	HPMC	-	-	6	-	-	261	-	oral

4.4. In vitro studies

4.4.1. Drug release from capsules (I-III)

The release of ibuprofen and metoclopramide from HPMC and gelatine capsules was studied using the basket method described in USP 24. The dissolution medium was USP neutral potassium phosphate buffer (I) and USP neutral tribasic sodium phosphate buffer (I-III) (900 ml at 37 ± 0.5 °C). The speed of rotation was 100 min^{-1} for the metoclopramide capsules (III) and 150 min^{-1} for the ibuprofen capsules (I and II). The dissolution apparatus (Sotax AT 6, Sotax AG, Switzerland) was connected to a peristaltic pump (Watson-Marlow 503S, Smith & Nephew Watson-Marlow, United Kingdom) and to a flow-through spectrophotometer (Ultrospec II, LKB Biochrom Ltd., United Kingdom). The absorbance of the dissolution medium in 2 mm flow-through cells was recorded automatically at regular intervals. The absorbance measurements were computer-controlled by tablet dissolution software (TDS, LKB Biochrom Ltd., United Kingdom). The amount of ibuprofen and metoclopramide released was measured in parallel from six samples.

The release kinetics of ibuprofen and metoclopramide from capsules diluted with HPMC powders of different viscosities (II and III) were evaluated with the power-law equation describing fractional release from swellable devices (Korsmeyer et al., 1983; Ritger and Peppas, 1987).

$$\frac{M_t}{M_\infty} = kt^n$$

In this equation, M_t/M_∞ is the fractional amount of drug released at time t, k is the kinetic constant and n is the release exponent, indicative of the mechanism of release. The power-law equation predicts that the fractional release of drug is exponentially related to the release time. The exponent n depends on the geometry of the device. For Fickian diffusion from swellable spheres and cylinders the exponent takes the values n = 0.43 and 0.45, respectively (Ritger and Peppas, 1987). Greater values of n indicate non-Fickian release, where the drug release depends on the ratio between the polymer relaxation rate and the rate of diffusion of the drug in gel. A value of n = 1 means that the drug release is independent of time, regardless of the geometry. The release kinetics of the model drugs were calculated until 80% of the dose was released or to the end of the dissolution test if less than 80% was released.

4.4.2. Adherence to isolated oesophageal preparation (II)

An isolated porcine oesophagus method was used to determine the tendency of the HPMC capsules to stick to the oesophagus compared with corresponding gelatine capsules (II). 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). HPMC and gelatine 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.

4.5. In vivo studies

4.5.1. Bioavailability studies (I-III)

Seven groups of 7 to 8 healthy volunteers of both sexes participated in a series of randomised, cross-over, single-dose studies carried out in accordance with the recommendations of the Declaration of Helsinki (World Medical Assembly, 1964) and subsequent amendments. The ages of the subjects ranged from 20 to 32 years and their weights from 53 to 88 kg. The subjects were informed about possible risks and side effects of the drugs and their written consent to participation was obtained. During the study, side effect forms were filled and collected. The Ethics Committee of University Pharmacy, Helsinki, accepted the study protocols. The National Agency for Medicines (Finland) was duly notified. The experiments were carried out in University Pharmacy, Helsinki.

4.5.1.1. Procedure

The amount of ibuprofen in studies I and II was 400 mg, since the subjects were administered two capsules each containing 200 mg (Table 4). The amount of metoclopramide hydrochloride corresponding to metoclopramide was 10 mg and the subjects were administered one capsule (III). Orally administered capsules were taken with 200 ml of water after the subjects had fasted overnight for at least

10 h. Rectally administered capsules were taken after a standard breakfast, which was served one hour before the drug insertion to facilitate and enable normal bowel movement. A standard lunch was served to all subjects 4 h after drug administration. The blood-samples were collected from an antecubital vein at intervals. The wash-out period between the administrations of different capsule formulations was at least one week. The subjects taking rectal capsules were instructed on the correct insertion technique before the bioavailability tests using capsules containing only lactose.

4.5.1.2. Assay methods

The ibuprofen and metoclopramide concentrations in plasma were determined by means of high performance liquid chromatography using a slightly modified method of Avgerinos and Hutt (1986) for ibuprofen and Buss and co-workers (1990) for metoclopramide. The accuracy and precision of the methods were determined as recommended by Shah and co-workers (1992). Both methods fulfilled the validation criteria (I, Section 3.3.; II, Section 2.3.5.; III, Section 3.3.).

4.5.1.3. Data analysis

The pharmacokinetic parameters calculated (Siphar, Simed, France) from plasma samples were maximum concentration (C_{max}), time to peak concentration (t_{max}), absorption time lag (t_{lag}), area under the concentration time curve (*AUC*), mean residence time (*MRT*) and apparent elimination half-life ($t_{1/2}$). The rate of absorption was evaluated also using the ratio C_{max} /*AUC*. Statistical analyses ($p<0.05$ was considered as statistical significant) were carried out using Wilcoxon's matched-pairs rank test for the t_{max} values and Student's paired t-test for the other pharmacokinetic parameters. For the *AUC* values, 90 % confidence intervals with logarithmic transformation were also calculated and the gelatine capsules were the reference formulations (I and III).

4.5.2. Gamma scintigraphic studies (IV)

One group of six healthy male volunteers participated in the gamma scintigraphic studies. The ages of the subjects ranged from 19 to 28 years and their weights from 65 to 89 kg. Their body mass indices (BMI) varied from 19 to 26 kg m^{-2}. Each subject was informed about possible risks and adverse effects of taking the study formulations. Written informed consent to participation in the studies had been obtained. The investigations were carried out in accordance with the

International Conference on Harmonization (ICH), Good Clinical Practice Guidelines and the Declaration of Helsinki (World Medical Assembly, 1964) and subsequent amendments. The National Agency for Medicine (Finland) and the Ethics Committee of Helsinki University Central Hospital (HUCH) approved the study protocol. The studies were carried out in the Nuclear Medicine Division of HUCH, which has a radiation safety licence issued by STUK (Radiation and Nuclear Safety Authority of Finland). Safety requirements were set in accordance with the guidelines established by STUK. The ALARA (as-low-as-reasonably-achieveable) principle was observed, and exposure to radiation was minimised in every situation.

4.5.2.1. Procedure

Each capsule contained 6 mg of $^{152}Sm_2O_3$ (Table 4). The ^{152}Sm was activated in a thermal neutron flux to the gamma emitting nuclide ^{153}Sm ($t_{1/2}$ 46.3 h), using a 250-kW TRIGA Mark II nuclear research reactor (General Atomics, USA) at the Technical Research Centre of Finland (VTT). Gamma scintigraphic studies were carried out 48 h after neutron activation. This time period allowed decay of unwanted radioisotopes, primarily ^{24}Na. The gamma spectra and radioactivity of the ^{153}Sm were measured to determine the safety of the formulations. Safety requirements were fulfilled for every formulation (IV, Section 2.3.).

Each study subject received both ^{153}Sm-labelled formulations (Table 4), one at a time on two separate visits. A wash-out period of one week between visits cleared the radioactivity from the gastrointestinal tract. The formulations were administered in a sitting position with 180 ml of water. The subjects remained in a sitting position for at least 30 s before lying down under the gamma camera. The subjects had fasted overnight for at least 12 h. Except for the first two subjects who received extra water (180 ml) 20 min after the administration due to the adherence of the capsules to the oesophagus on the first study visit, the subjects were not allowed to drink or eat until 4 h after the administration when a standard lunch was served. Following administration, anterior and posterior images, each of 1 min duration, were recorded continuously for the first 20 min, after which six images, each of 1 min duration, were recorded every 30 min for the next 7.5 h by means of a dual-head gamma camera (ADAC Forte, ADAC Laboratories, USA). During imaging each subject lay supine beneath the gamma camera. At other times they could move freely.

4.5.2.2. Data analysis

Sequential computer-generated images were used for each subject and the regions of interest (ROI) were drawn to represent the oesophagus and the stomach (of a fixed size for paired anterior and posterior images), and counts relating to ROIs were calculated using Hermes software (version 3.7, Nuclear Diagnostics, Sweden). Geometric means of counts in paired anterior and posterior images were used. All counts were corrected for background and decay.

The gastric residence time and the large intestine arrival time were determined as the midpoint of the time interval between the last image of the capsule in the previous region and the time of first detection in the new region. The small intestine transit time of the capsules was calculated by subtracting the gastric residence time from the time at which the capsules were observed to move from the ileo-caecal junction to the large bowel.

The initial capsule disintegration time was defined as the midpoint of the time interval between the last image of the capsule with clear outlines and visually undetectable spreading of the radioactivity and the time of first detection of spreading radiation. The time for capsules to divide was defined as the midpoint of the time interval between the last image of the capsule with only one plug formation and the time of first detection of the capsule divided into two or three pieces. The complete capsule disintegration time was defined as the midpoint of the time interval between the last image of the capsule with plug formation and the time of first detection of the capsule with no plug formation. The statistical analyses were carried out using Wilcoxon´s non-parametric test ($p<0.05$ was considered as statistical significant).

5. Results and discussion

5.1. Biopharmaceutical properties of capsules diluted with lactose (I, III)

5.1.1. In vitro drug release

The release of ibuprofen from the HPMC and gelatine capsules diluted with lactose was first tested in a neutral potassium phosphate buffer, in which the release from the HPMC capsules was incomplete and highly variable compared with the gelatine capsules (I, Fig. 1). This was probably due to the presence of potassium ions in the dissolution media, which could have promoted gelation of the carrageenan in the HPMC capsule shells causing the capsule shells to form a gel membrane around the filling. Also Ogura and co-workers (1998) noticed this phenomenon and they suggested that, since the cation concentration in the gut is low, dissolution mediums that do not contain potassium could be used. Therefore, the dissolution medium was changed to the neutral tribasic sodium phosphate buffer described in the USP for enteric formulations, in which the release of ibuprofen from the HPMC capsules was complete and less variable. The same dissolution medium was used in the subsequent studies.

The release of the model drugs, ibuprofen and metoclopramide, from the HPMC and gelatine capsules diluted with lactose was fast with 100% of the drug dose being released within 15 to 20 min (I, Fig. 2; III, Fig. 1). There were no differences between the HPMC and gelatine capsules in the time when 100% of the drug dose was released. However, one difference was observed: the release of both ibuprofen and metoclopramide from the HPMC capsules started after a lag time of about 4 min, whereas the release of the model drugs from the gelatine capsules started almost immediately. Since the same phenomenon was detected for both drugs, which differ from each other in chemical nature and water solubility, it can be suggested that the physicochemical characteristics of the drug do not affect the dissolution of the capsule shells when the capsules are diluted with lactose. Also Chiwele and co-workers (2000) reported that the disintegration of empty HPMC capsule shells at 37°C takes about 4 min, whereas the disintegration of empty gelatine capsule shells takes at most 1 min. In addition, Wu and co-workers (2003) claimed that the release of an investigational drug, BMS-309403, was slower from HPMC capsules than from corresponding gelatine

capsules during the first 10 to 20 min. This kind of difference between the two capsule shells was not reported by Ogura and co-workers (1998) or Podczeck and Jones (2002) when the capsules were filled with a model drug and a diluent. On the contrary, Podczeck and Jones (2002) claimed that the release of theophylline from the HPMC capsules was faster and greater than from the corresponding gelatine capsules when the capsules contained either theophylline only or theophylline together with lactose or microfine cellulose (immediate-release formulations). It should be noted, however, that they studied only the relative amount of drug dissolved after 60 min and the mean dissolution time (MDT), not the differences in the dissolution rates between the capsules during the first 10 min.

5.1.2. Oral bioavailability

The mean **ibuprofen** concentration versus time curves after oral administration of the HPMC and gelatine capsules diluted with lactose were virtually identical, and there were no statistically significant differences in the bioavailability parameters between the two different capsule shell types (I, Fig. 3 and Table II). Similar results were obtained also when the model drug was **metoclopramide hydrochloride** (III, Fig. 3 and Table III), but there was one difference in the bioavailability parameters: the time to peak concentration (t_{max}) was significantly shorter for the HPMC capsules than for the gelatine capsules. This means that the maximum concentration of metoclopramide was reached about 20 min faster with the HPMC capsules than with the gelatine capsules. This is not in line with the *in vitro* dissolution studies, where the release of the model drugs from the HPMC capsules began more slowly than from the gelatine capsules.

The HPMC and gelatine capsules containing ibuprofen could also be regarded as bioequivalent (mean 1.0; 90% CI 0.90-1.19) (I)[i], but not the corresponding metoclopramide capsules (mean 1.09; 90% CI 0.85-1.32) (III), probably due to a greater variation in the *AUC* values. The first-pass metabolism of metoclopramide in the liver is known to cause extensive inter-individual variation in the bioavailability of metoclopramide (Ross-Lee et al., 1981). Therefore, with a greater number of subjects (n > 8) it may be possible to obtain the generally used 90% confidence interval of 0.80-1.25. Nevertheless, the change of capsule shell type did not affect the amount of metoclopramide absorbed, since there was no statistically significant difference in the *AUC* values between the capsules. There was also evidence that both the HPMC and gelatine capsules containing ibuprofen

[i] The reference formulation in Study I was accidentally HPMC capsule, not gelatine capsule as it should have been.

may have attached to the oesophagus or the upper parts of the stomach causing delayed *in vivo* disintegration of the capsules in one subject (different subject on each occasion) (I, Fig. 4). This finding led to a suspicion that also HPMC capsules could have a tendency to attach to the oesophagus or gastrointestinal mucosa, which has been recognised as a problem with gelatine capsules (Swisher et al., 1984), and further investigations concerning the sticking properties of the HPMC capsules were needed.

The overall conclusion from these results was that when the HPMC and gelatine capsules are administered orally as immediate-release formulations, the capsule shells could be regarded as interchangeable. This is in accordance with the studies of Ogura and co-workers (1998) who investigated the oral bioavailability of cephalexin from HPMC and gelatine capsules with six healthy volunteers.

5.1.3. Rectal bioavailability

Several previous studies have demonstrated that following the rectal administration of hard gelatine capsules, disintegration of the capsule shell and dissolution of powdered drug into the limited amount of fluid available in the rectum is a time consuming process, causing time lags of about 30 min in the commencement of ibuprofen and metoclopramide absorption (Eerikäinen et al., 1996; Leino et al., 1997,1999, 2003). Also the studies reported here demonstrate that the rectal gelatine capsules containing ibuprofen or metoclopramide hydrochloride as the model drugs and lactose as the diluent exhibited time lags of about 30 min. However, the rectal HPMC capsules exhibited even greater time lags, about 50 min. Consequently, the difference in the t_{lag} values between the HPMC and gelatine capsules containing either ibuprofen or metoclopramide hydrochloride was statistically significant (I, Table III; III, Table IV). These findings are in accordance with the *in vitro* results, where the disintegration of the HPMC capsules was slower than that of the gelatine capsules. Since both ibuprofen and metoclopramide exhibited higher t_{lag} values from the HPMC capsules than from the gelatine capsules, it can be assumed that the capsule shell dissolution properties rather than the physicochemical properties of drugs determine the release and absorption from hard rectal capsules.

The parameter reflecting absorption rate (C_{max}/AUC) was significantly higher for the HPMC capsules containing **ibuprofen** than for the corresponding gelatine capsules (I, Table III), indicating that after the capsules disintegrated in the rectum, the dissolution and subsequent absorption of ibuprofen was faster from

the HPMC capsules than from the gelatine capsules. However, this was not seen in other parameters reflecting the absorption rate (t_{max}, C_{max}, *MRT*). On the other hand, the great t_{lag} value of the HPMC capsules was not reflected in the t_{max} value, which was on average 3 h for both capsule shell types. This indicates that although the disintegration of the HPMC capsules in the rectum may have been slower than that of the gelatine capsules, the effect is cancelled by the slightly faster absorption of ibuprofen from the HPMC capsules. This may be explained by the differences in the dissolution properties of the HPMC and gelatine capsule shells that were noted by Podczeck and Jones (2002). They reported that the HPMC capsule shells dissolve more evenly than the gelatine capsule shells, meaning that the whole powder plug filled in the HPMC capsules may be subjected to dissolving fluid simultaneously, whereas the gelatine capsules disintegrate first from the shoulders with the other parts following only later.

Also following rectal administration of the HPMC capsules containing **metoclopramide hydrochloride**, the C_{max}/AUC values were significantly higher than those for the gelatine capsules (III; Table IV), indicating faster drug absorption from the HPMC capsules. However, the difference in the t_{lag} values between the two capsule types was so great that it was reflected in the t_{max} values, which were significantly greater for the HPMC capsules than for the gelatine capsules. Therefore, the difference in the C_{max}/AUC values is of hardly any significance in practice for metoclopramide.

The great variation of the *AUC* values for both ibuprofen and metoclopramide capsules regardless of the capsule shell material may be the reason why the rectally administered HPMC and gelatine capsules could not be regarded as bioequivalent (mean 1.0, 90% CI 0.57-1.43 for ibuprofen (I)[ii] and mean 0.90, 90% CI 0.72-1.08 for metoclopramide (III)). However, by increasing the number of subjects it may be possible to decrease the variation of the *AUC* values and, consequently, reach the 90% confidence interval of 0.80-1.25. Nevertheless, the change in the capsule shell material did not affect statistically significantly the bioavailability (*AUC*) of the model drugs and the variation in the biopharmaceutical parameters was similar for both capsule shell types. Therefore, the HPMC capsules could be regarded as a noteworthy alternative to the gelatine capsules when rapid drug action is not required. When there is need for quick onset of action after rectal administration, a rectal enema should be considered as the first choice.

When the administration route is evaluated, it can be seen that the C_{max} values of **ibuprofen** after rectal administration of the capsules were only half those

[ii] The reference formulation in Study I was accidentally HPMC capsule, not gelatine capsule as it should have been.

obtained with the corresponding oral capsules (I, Tables II and III). In addition, when the *AUC* values are compared between the rectal and oral capsules, the mean rectal bioavailability of ibuprofen was 75-85% of that recorded after oral administration. This is not in accordance with previous studies, where similar *AUC* values have been obtained for rectally and orally administered gelatine capsules containing ibuprofen and lactose (Eerikäinen et al., 1996). The reason for the decreased absorption of ibuprofen from rectal capsules in the present study could be due to poor technique for insertion of the capsules into the rectum. It has been demonstrated that training in administration beforehand and the use of a glidant to facilitate insertion increase the bioavailability of ibuprofen from rectal hard gelatine capsules (Eerikäinen et al., 1996). In the study reported here, the subjects were trained in administration and the capsules were coated with hard fat. Nevertheless, one of the subjects receiving gelatine capsules containing ibuprofen failed in insertion and no drug was recovered during the 12-hour test period. It was obvious that the capsules had stuck to the anus and had not passed the sphincters, making absorption impossible. This subject was excluded from the study. Also the degree of variation in the concentration versus time curves for the rectally administered ibuprofen capsules was clearly greater than for the corresponding orally administered capsules (I, Figs. 4 and 6). Great variation in the absorption of ibuprofen from rectal hard gelatine capsules was also reported in the previous studies (Eerikäinen et al., 1996; Leino et al., 1997, 1999). In conclusion, the rectal hard capsules made of either HPMC or gelatine could be of value for rectal administration, but attention must be paid to the insertion technique.

Unlike rectal administration of ibuprofen, rectal administration of **metoclopramide hydrochloride** turned out to be better than oral administration: the C_{max} and *AUC* values were greater for the rectal capsules than for the corresponding oral capsules (III, Tables III and IV). This indicates that the rectally administered metoclopramide at least partially avoided first-pass metabolism. The inter-individual variation was, however, slightly greater for the rectal capsules than for the oral capsules (III, Figs. 4 and 6), indicating that rectal administration did not reduce the variation even though first-pass elimination may have been partially avoided. Nevertheless, due to the better absorption, hard capsules can be regarded as valuable for rectal metoclopramide formulations if rapid onset of action is not needed.

5.2. Biopharmaceutical properties of capsules diluted with HPMC powder (II, III)

5.2.1. In vitro drug release

The capsule shell material did not seem to have any marked effect on the release profile of **ibuprofen** from capsules diluted with the HPMC powder and the release curves obtained from the HPMC and gelatine capsules containing the same polymer were almost completely overlapping (II, Fig. 2). However, the release constants, *K*, were slightly smaller for the HPMC capsules than for the corresponding gelatine capsules, especially when the capsules were diluted with the HPMC K100 powder (II, Table 2). This indicates slightly slower dissolution of ibuprofen from the HPMC capsules. The sampling interval was 15 min and, when the first sample which was obtained 15 min after starting the test was examined, the slower disintegration of the HPMC capsule shells noted with the capsules diluted with lactose (Section 5.1.1.) was no longer detectable.

The viscosity grade of the HPMC powder used as the diluent had a clear effect on the release rate of ibuprofen. Both HPMC and gelatine capsules containing the lower viscosity grade, HPMC K100, had *K* values which were almost double those for the capsules containing the higher viscosity grades, HPMC K4M or K15M (II, Table 2). The release rate of ibuprofen was not further decreased when the HPMC polymer was changed from K4M to K15M.

The capsule shell material did not affect the release mechanism of ibuprofen, whereas the viscosity grade of the HPMC polymer had an evident effect. The release of ibuprofen from HPMC and gelatine capsules diluted with HPMC K100 powder followed zero-order kinetics quite well with values of the exponent *n* close to 1 (II, Table 2). This may indicate that the drug release from these capsules was independent of time and was mainly controlled by the erosion rate of the HPMC polymer. The values of the exponent *n* for capsules containing HPMC K4M or K15M powder (0.64-0.67) indicated non-Fickian release kinetics, i.e. the release mechanism of ibuprofen may have been a combination of the polymer relaxation rate and the rate of diffusion through the gel layer. When the results presented here are compared with the results obtained with ibuprofen capsules diluted with lactose, it can be seen that all HPMC polymers used as the diluent clearly prolonged the release of ibuprofen (I, Fig. 2; II, Fig. 2).

When the model drug was **metoclopramide hydrochloride** and the capsules were diluted with HPMC K100 or K4M powder, the capsule shell material had a slight effect on the release of metoclopramide. The release rate constant *K* was

somewhat higher for the HPMC capsules than for the corresponding gelatine capsules (III, Table II), indicating that the release of metoclopramide was slightly faster from the HPMC capsules than from the corresponding gelatine capsules, which can be seen also from the release curves (III, Fig. 2). This is in accordance with the studies of Podczeck and Jones (2002), but not with the studies reported here conducted with ibuprofen. Thus, the chemical nature and water-solubility of the model drug had an effect on the release from the two different capsule shells when the capsules were diluted with the HPMC powder. This slight difference between the model drugs was not seen when the capsules were diluted with lactose (Section 5.1.1.).

As was seen with the ibuprofen capsules, also the release rate of metoclopramide was decreased when the HPMC polymer was changed from the lower viscosity grade, K100, to the higher viscosity grade, K4M (III, Table II). The release mechanisms of metoclopramide from both HPMC and gelatine capsules diluted with HPMC K100 was non-Fickian (values of exponent *n* 0.7), whereas the release of metoclopramide from capsules containing the higher viscosity grade was closer to square root of time kinetics (values of exponent *n* close to 0.5). All the capsules behaved as prolonged-release formulations when compared with the capsules diluted with lactose (III, Fig. 1 and 2).

The release behaviour of drugs from swellable polymeric systems is often described in terms of non-Fickian diffusion (Peppas, 1985). However, some studies have shown that the water-solubility of the drug may affect the release kinetics from matrix tablets prepared with various viscosity grades of HPMC type 2208, i.e. the release mechanism of freely water-soluble drugs has been reported to be non-Fickian (Ford et al., 1987; Catellani et al., 1988; Colombo et al., 1990; Ranga Rao et al., 1990; Colombo et al., 1992; Peppas and Colombo, 1997; Colombo et al., 1999; Ferrero Rodriguez et al., 2000), whereas the release mechanism of poorly water-soluble drugs has been reported to obey nearly zero-order release (Ford et al., 1987; Ranga Rao et al., 1990) when the kinetics of the model drugs have been evaluated by using the same power law equation utilised here. Also in the studies reported here, the release mechanism of the freely water-soluble metoclopramide hydrochloride from the capsules containing HPMC K100 as the diluent was non-Fickian, whereas the release of the poorly water-soluble ibuprofen from the corresponding capsules followed zero-order kinetics quite well. However, from capsules containing the higher viscosity grades of the HPMC polymers both model drugs obeyed non-Fickian release, although the release of metoclopramide tended slightly more to Fickian diffusion. It should be noted, though, that the compositions of the ibuprofen and metoclopramide capsules were

different, and they could be compared directly only if the drug/HPMC ratio was the same for both formulations. Other studies utilising the power law to evaluate the release kinetics of drugs from capsule matrices made of HPMC polymers cannot be found in the literature.

5.2.2. Oral bioavailability

5.2.2.1. Effect of capsule shell material

When the model drug was **ibuprofen**, there was only one difference between the capsules diluted with the HPMC powders and differing from each other in the capsule shell material. The t_{max} value of the HPMC capsules containing HPMC K100 as the diluent was significantly higher than that of the corresponding gelatine capsules (II, Table 3). In other words, the maximum drug concentration in plasma was reached on average an hour later from the HPMC capsules than from the gelatine capsules diluted with HPMC K100. The *in vitro* dissolution test gave an implication that the release of ibuprofen would be slightly slower from the HPMC capsules than from the gelatine capsules when the diluent was HPMC K100 powder. Nevertheless, there were no significant differences in any other pharmacokinetic parameters between the two formulations diluted with the HPMC K100 powder. The other formulations containing HPMC K4M or K15M powder as the diluent and differing from each other in the capsule shell material did not have statistically significant differences in the pharmacokinetic parameters (II, Table 3). In addition, the interindividual variation in drug concentration versus time curves was quite similar between the HPMC capsules and the corresponding gelatine capsules (II, Fig. 4).

When the model drug was **metoclopramide hydrochloride**, there were no statistically significant differences in any bioavailability parameters between the formulations differing from each other in the capsule shell material, and also the concentration versus time curves were quite similar (III, Table V and Fig. 7). Thus, the slightly faster drug release from the HPMC capsules observed *in vitro* was not reflected *in vivo*. The interindividual variation in the concentration versus time curves was slightly greater for the HPMC capsules than for the corresponding gelatine capsules (III, Fig. 8). However, this may be due to the differences in the first-pass metabolism of metoclopramide rather than to the capsule shell material, since there were no differences in the variation between the orally administered metoclopramide capsules diluted with lactose or the ibuprofen capsules diluted with lactose or HPMC polymers.

The overall conclusion about the interchangeability of the two capsule shell materials is that, from a biopharmaceutical point of view, the HPMC capsules could be regarded as a noteworthy alternative to gelatine capsules also when the capsules contain either ibuprofen or metoclopramide as the model drug and HPMC polymers of different viscosities as the diluent.

5.2.2.2. Effect of diluent

The results obtained for the orally administered **ibuprofen** capsules diluted with either lactose (I) or HPMC powders (II) are gathered in Table 5. As can be seen from Table 5, the replacement of lactose with the HPMC powder prolonged the release and subsequent absorption of ibuprofen. Following oral administration of the capsules diluted with the HPMC powder, the t_{max} and *MRT* values were increased and the C_{max} and C_{max}/AUC values were decreased, but $t_{1/2}$ remained almost unaffected, when compared with the capsules diluted with lactose. Also the t_{lag} values were increased from about 10 to 30 min, indicating fast hydration of the HPMC powder used as the diluent, which inhibits premature drug release.

Prolonged release of drugs is beneficial if, e.g. the elimination half-life of a drug is short and there is a need for decreased fluctuation and constant concentration of the drug in plasma over a long period. By prolonging the release of drug from a delivery device, it is possible to achieve a situation where the drug release *in vivo* is the rate-limiting step in drug kinetics. In other words, the very slow drug release and consequently slow absorption limit the rate of elimination of the drug and extend the apparent half-life allowing a longer interval between doses. Ibuprofen is a good candidate for prolonged-release formulations, since its elimination half-life is short, about 2 h. However, in this study the ibuprofen capsules diluted with HPMC polymers behaved as slow-release formulations rather than as extended-release formulations, since the elimination half-life ($t_{1/2}$) of ibuprofen was not extended (Table 5).

It is important to note that although the absorption of ibuprofen was slower from the capsules diluted with the HPMC polymer, there was no loss in the bioavailable amount (*AUC*) compared with the lactose-based capsules (Table 5). Also the viscosity grade of the HPMC polymer used as the diluent did not affect the amount of ibuprofen absorbed from the capsules, since there were no statistically significant differences in the *AUC* values between the different formulations (Table 5). However, the viscosity grade of the HPMC powder affected the absorption rate of ibuprofen, which was greater from the HPMC K100-based capsules than from the HPMC K4M- and K15M-based capsules. When the capsule shell was HPMC, the C_{max} and C_{max}/AUC values were

significantly greater and the *MRT* values were significantly smaller for the HPMC K100-based capsules than for the HPMC K4M- and K15M-based capsules (Table 5). When the shell material was gelatine, the C_{max} and C_{max}/AUC values were significantly greater and the t_{max} values were significantly smaller for the HPMC K100-based capsules than for the HPMC K4M- and K15M-based capsules. No changes in the pharmacokinetic parameters occurred when the HPMC polymer was changed from K4M to K15M. All these *in vivo* findings with the different viscosity grades of the HPMC polymers used as the diluent are in line with the *in vitro* dissolution results. Similar results were also obtained in previous *in vivo* studies conducted with orally administered gelatine capsules containing ibuprofen and HPMC polymers of different viscosities (Ojantakanen et al., 1993).

*Table 5. Pharmacokinetic parameters of **ibuprofen** (single dose of 2x200 mg) following **oral** administration of capsules containing lactose (I) or HPMC polymers of different viscosity grades (II) (n=8, mean ± S.D.). Parameters between the lactose and HPMC powder-based capsules were not tested statistically since the capsules were taken by two different subject groups.*

Diluent	Capsule	*AUC* (mgh/l)	C_{max} (mg/l)	t_{max} (h)	*MRT* (h)	C_{max}/AUC (h^{-1})	t_{lag} (h)	$t_{1/2}$ (h)
Lactose	HPMC	110 ± 18	39 ± 11	1.5 ± 1.0	2.7 ± 1.4	0.35 ± 0.068	0.11 ± 0.11	2.4 ± 2.5
	gelatine	110 ± 30	40 ± 7.0	1.2 ± 0.75	2.4 ± 0.79	0.38 ± 0.085	0.072 ± 0.17	2.0 ± 1.3
HPMC K100	HPMC[a]	130 ± 48	26 ± 9.6	3.3 ± 0.46	3.4 ± 0.65	0.20 ± 0.042	0.73 ± 0.46	2.4 ± 2.0
	gelatine[b]	120 ± 33	25 ± 7.2	2.2 ± 0.53	4.1 ± 2.5	0.22 ± 0.051	0.36 ± 0.30	2.6 ± 2.2
HPMC K4M	HPMC[c]	110 ± 29	14 ± 4.4	3.2 ± 1.0	4.9 ± 1.4	0.12 ± 0.032	0.53 ± 0.51	2.5 ± 1.6
	gelatine[d]	120 ± 30	16 ± 3.9	3.4 ± 0.74	4.7 ± 0.83	0.14 ± 0.024	0.56 ± 0.40	2.2 ± 1.5
HPMC K15M	HPMC[e]	100 ± 42	13 ± 5.3	4.3 ± 1.9	5.4 ± 1.5	0.12 ± 0.010	0.75 ± 0.55	2.9 ± 1.9
	gelatine[f]	120 ± 25	14 ± 3.6	4.3 ± 1.2	6.3 ± 3.2	0.12 ± 0.014	0.63 ± 0.47	3.9 ± 2.5
Statistical significance								
a/c		NS	p<0.01	NS	p<0.05	p<0.01	NS	NS
a/e		NS	p<0.01	NS	p<0.05	p<0.01	NS	NS
c/e		NS	NS	NS	NS	NS	NS	NS
b/d		NS	p<0.01	p<0.05	NS	p<0.01	NS	NS
b/f		NS	p<0.01	p<0.01	NS	p<0.01	NS	NS
d/f		NS	NS	NS	NS	NS	NS	NS

NS = not significant

Since there were no differences in the biopharmaceutical parameters of ibuprofen between the capsules containing the two higher viscosity grades of HPMC, the

HPMC K15M polymer was excluded from the next study conducted with the other model drug, **metoclopramide hydrochloride**, and only HPMC K100 and K4M polymers were evaluated as the diluents. Metoclopramide is also a good candidate for prolonged-release formulations, since its elimination half-life is only about 3 to 5 h (Bateman et al., 1980). In addition, fluctuation in plasma concentration, with high concentration peaks causing central nervous system effects, is common for metoclopramide in long-term therapy (Becket et al., 1987), and could be avoided by utilising prolonged-release formulations.

The results obtained for the orally administered metoclopramide hydrochloride capsules diluted with either lactose or HPMC powder (III) are gathered in Table 6.

*Table 6[iii]. Pharmacokinetic parameters of **metoclopramide** following **oral** administration of capsules containing lactose or HPMC polymers of different viscosity grades (III) (n=8 for the lactose-based capsules and n=7 for the HPMC powder-based capsules, mean ± S.D.). Parameters between the lactose- and HPMC powder-based capsules were not tested statistically, since there were two different subject groups taking the capsules.*

Diluent	Capsule	*AUC* (ngh/ml)	C_{max} (ng/ml)	t_{max} (h)	*MRT* (h)	C_{max}/AUC (h^{-1})	t_{lag} (h)	$t_{1/2}$ (h)
Lactose	HPMC	162 ± 72	31 ± 14	1.3 ± 0.46	4.8 ± 1.9	0.20 ± 0.030	0.27 ± 0.25	3.4 ± 1.5
	gelatine	154 ± 61	30 ± 11	1.7 ± 0.65	4.1 ± 2.1	0.20 ± 0.032	0.16 ± 0.17	2.7 ± 1.7
HPMC K100	HPMC[a]	267 ± 76	29 ± 9.9	4.2 ± 3.6	6.7 ± 2.0	0.11 ± 0.015	0.79 ± 1.1	4.1 ± 2.2
	gelatine[b]	242 ± 73	26 ± 6.0	3.4 ± 0.54	7.9 ± 2.4	0.11 ± 0.028	0.79 ± 0.50	5.4 ± 2.5
HPMC K4M	HPMC[c]	215 ± 91	19 ± 6.5	4.7 ± 1.3	7.2 ± 2.8	0.10 ± 0.030	0.91 ± 0.77	4.9 ± 2.5
	gelatine[d]	245 ± 70	22 ± 6.8	5.4 ± 1.5	8.1 ± 2.5	0.090 ± 0.017	0.96 ± 0.51	6.9 ± 4.2
Statistical significance								
a/c		NS	p<0.01	NS	NS	NS	NS	NS
b/d		NS	NS	p<0.01	NS	NS	NS	NS

NS = not significant

It is quite remarkable that although the release of metoclopramide from the capsules diluted with the HPMC K100 powder was prolonged in terms of increased t_{max} and *MRT* values and decreased C_{max}/AUC values, the *AUC* values were greater and the C_{max} values were almost unaffected when compared with the capsules diluted with lactose (Table 6). The release of metoclopramide from the HPMC K4M-based capsules was similarly prolonged and the *AUC* values were greater than those for the lactose-based capsules, but the C_{max} values were smaller.

[iii] Misprints in the Study III, Table V: the t_{max} value for the H4Moral capsules should be 4.71 h, the dimension of the *AUC* and C_{max} values should be ngh/ml and ng/ml, respectively, and the *AUC* values were calculated from 0 to 24 h.

The $t_{1/2}$ values for the HPMC powder-based capsules were also slightly greater than those for the lactose-based capsules, but not so much so that the capsules could be regarded as extended-release formulations. However, since the lactose-based and the HPMC powder-based capsules were taken by two different subject groups and the inter-individual variation is known to be great in metoclopramide medication (Bateman, 1983), it would be advisable to confirm these results by a study conducted with a single subject group.

Changing the HPMC viscosity grade from K100 to K4M had some significant effects on the absorption rate of metoclopramide. When the capsule shell material was HPMC, C_{max} was significantly smaller for the HPMC K4M-based capsules than for the HPMC K100-based capsules (Table 6). When the shell material was gelatine, t_{max} was reached significantly later with the HPMC K4M-based capsules than with the HPMC K100-based capsules. The viscosity grade of the HPMC powder did not affect the bioavailability of metoclopramide, since there were no statistically significant differences in the *AUC* values. This is in accordance with the results obtained with ibuprofen.

In conclusion, the studies conducted with the capsules diluted with the HPMC powders of different viscosity grades demonstrate that it is possible to achieve prolonged-release capsule formulations for oral administration easily and economically by filling the capsules with hydrophilic, swellable polymers. However, some optimisation of the formulations is needed. For example, the ratio of the model drugs and the HPMC polymer should be re-evaluated in order to achieve extended-release capsule formulations and thus a longer dose interval.

5.2.3. Rectal bioavailability

5.2.3.1. Effect of capsule shell material

When the rectal absorption of **ibuprofen** from the capsules diluted with the HPMC powders (K100, K4M or K15M) is examined, it can be seen that the capsule shell material did not have any statistically significant effect on the biopharmaceutical parameters of the capsules (II, Table 4). Even though the t_{lag} values of the HPMC capsules were on average 20 min longer than those for the corresponding gelatine capsules, the differences were not statistically significant. This is probably due to the wide variation in the t_{lag} values, especially for the gelatine capsules (II, Table 4). After rectal administration of ibuprofen capsules diluted with lactose, the same difference in the t_{lag} values (about 20 min) between the two capsule shell types was statistically significant (I, table III). The greater

t_{lag} values of the HPMC capsules diluted with HPMC powder probably have no importance in practice, since the capsules are intended for prolonged-release formulations. Therefore, the two capsule shell materials can again be regarded as interchangeable for rectal ibuprofen formulations.

When the model drug was changed to **metoclopramide hydrochloride**, one significant difference was observed: the t_{lag} values were significantly greater for the HPMC capsules than for the gelatine capsules (III, Table V). This difference in the t_{lag} values was not reflected in other parameters reflecting absorption rate (C_{max}, t_{max}, C_{max}/AUC). A similar difference in the t_{lag} values between the two capsule shell types was obtained also with rectal metoclopramide capsules diluted with lactose. The rectal HPMC capsules containing ibuprofen with lactose or HPMC polymers as the diluents also exhibited greater t_{lag} values than the corresponding gelatine capsules. Therefore, it can be concluded that the capsule shell material rather than the physicochemical properties of drugs or diluents affect the disintegration properties of the capsules in the rectum.

Here again, it can be assumed that, even though the absorption of metoclopramide from the rectally administered HPMC capsules diluted with HPMC K100 powder began later than from the corresponding gelatine capsules, the capsule shells could be regarded as interchangeable because there was no statistically significant difference in the amount of metoclopramide absorbed from the two capsule types. Moreover, the capsules were intended for prolonged-release formulations, where rapid onset of action is not needed.

5.2.3.2. Effect of diluent and route of administration

The results obtained for the rectally administered **ibuprofen** capsules diluted with either lactose (I) or HPMC powder (II) are gathered in Table 7. The HPMC powders used as the diluent clearly prolonged the absorption of ibuprofen *in vivo* when compared with capsules diluted with lactose. The C_{max} and C_{max}/AUC values were lower and the t_{max} values were greater for the HPMC powder-based capsules than for the lactose-based capsules (Table 7). Unlike after oral administration of the ibuprofen capsules diluted with the HPMC powders, the HPMC powders did not affect the t_{lag} values after the rectal administration of the same capsules when compared with the lactose-based capsules (Tables 5 and 7).

*Table 7. Pharmacokinetic parameters of **ibuprofen** (single dose of 2x200 mg) following **rectal** administration of capsules containing lactose (I) or HPMC polymers of different viscosity grades (II) (n=7, mean ± S.D.). Parameters between the lactose-based and HPMC powder-based capsules were not tested statistically, since the capsules were taken by two different subject groups. There were no statistically significant differences between the capsules diluted with the HPMC powders.*

Diluent	Capsule	*AUC* (mgh/l)	C_{max} (mg/l)	t_{max} (h)	*MRT* (h)	C_{max}/AUC (h^{-1})	t_{lag} (h)	$t_{1/2}$ (h)
Lactose	HPMC	83 ± 42	21 ± 9.1	3.1 ± 1.6	2.7 ± 0.75	0.27 ± 0.056	0.90 ± 0.38	1.9 ± 0.84
	gelatine	92 ± 44	19 ± 10	2.9 ± 0.93	3.3 ± 1.4	0.21 ± 0.060	0.60 ± 0.33	2.5 ± 1.1
HPMC K100	HPMC	140 ± 34	16 ± 6.3	7.1 ± 3.6	6.4 ± 3.1	0.12 ± 0.044	0.91 ± 0.22	2.4 ± 3.7
	gelatine	125 ± 50	16 ± 9.7	6.7 ± 3.8	13 ± 14	0.13 ± 0.070	0.58 ± 0.39	6.8 ± 9.0
HPMC K4M	HPMC	114 ± 54	12 ± 7.0	4.9 ± 1.1	9.7 ± 10	0.12 ± 0.054	0.85 ± 0.46	5.1 ± 8.5
	gelatine	154 ± 80	14 ± 7.0	6.0 ± 2.0	36 ± 79	0.10 ± 0.042	0.65 ± 0.42	23 ± 55
HPMC K15M	HPMC	111 ± 57	12 ± 3.9	5.0 ± 2.1	7.6 ± 6.1	0.14 ± 0.070	0.85 ± 0.29	3.9 ± 5.6
	gelatine	139 ± 59	11 ± 5.3	7.4 ± 3.6	7.0 ± 2.1	0.078 ± 0.012	0.43 ± 0.36	3.8 ± 3.1

The capsules diluted with the HPMC powders, especially those containing HPMC K4M or K15M, could be regarded as extended-release capsules, since the $t_{1/2}$ and *MRT* values were clearly increased (Table 7), which was not the case when the same capsules were administered orally (Table 5). The mean ibuprofen concentration in plasma barely exceeded the minimum therapeutic level, which is 10 mg/l (II, Fig. 5). In spite of that, the *AUC* values for the capsules diluted with the HPMC powders were greater than those for the capsules diluted with lactose (Table 7). In addition, the *AUC* values for the rectal HPMC powder-based capsules were of the same magnitude as (or even higher than) those for the same capsules administered orally (Tables 5 and 7). These findings indicate that the replacement of lactose with HPMC polymer or the use of rectal administration do not decrease the amount of ibuprofen absorbed. Therefore, it can be concluded, that the hard capsules diluted with HPMC powders have potential for rectal use as extended-release formulations, although further optimisation of the formulation is needed in order to achieve a therapeutic drug level in plasma. However, the correct technique for insertion into the rectum is essential for the success of these capsules since, as was already seen with rectal ibuprofen capsules diluted with

lactose (I), one of the subjects failed in insertion of the first study formulation in the present study (II) and was excluded from the test.

Changing the viscosity grade of the HPMC powder did not statistically significantly alter the biopharmaceutical characteristics of the ibuprofen formulations (II, Table 4). This is not in accordance with the *in vitro* dissolution tests, where the release of ibuprofen from capsules containing the HPMC K100 powder as the diluent was greater than from the capsules containing the other two viscosity grades. In other words, the *in vitro* dissolution study was not as predictive for the rectal administration as for the oral administration of these capsules.

Since the viscosity grade of the HPMC powder used as diluent had an insignificant effect on the pharmacokinetic parameters of rectal ibuprofen capsules, only the HPMC K100 polymer was utilised when the model drug was changed to **metoclopramide hydrochloride**. The results obtained for these capsules diluted with either lactose or HPMC K100 powder (III) are gathered in Table 8. The HPMC K100 polymer prolonged the release and subsequent absorption of metoclopramide when compared with the lactose-based capsules, which was seen in t_{max} and C_{max}/AUC values (Table 8). The capsules could be regarded as slow-release rather than extended-release formulations since the $t_{1/2}$ values were practically unaffected. The high $t_{1/2}$ and *MRT* value with wide variation for the HPMC capsules diluted with HPMC K100 powder (Table 8) is due to overestimation of the $t_{1/2}$ and *MRT* values: two subjects had almost the same metoclopramide concentration in plasma at 12 and 24 h post-dose.

*Table 8. Pharmacokinetic parameters of **metoclopramide** (single dose of 10 mg) following **rectal** administration of capsules containing lactose or HPMC K100 powder (III) (n=8 for the lactose-based capsules and n=7 for the HPMC K100-based capsules, mean ± S.D.). Parameters between the lactose-based and HPMC powder-based capsules were not tested statistically since the capsules were taken by two different subject groups.*

Diluent	Capsule	AUC (ngh/ml)	C_{max} (ng/ml)	t_{max} (h)	MRT (h)	C_{max}/AUC (h^{-1})	t_{lag} (h)	$t_{1/2}$ (h)
Lactose	HPMC	272 ± 153	40 ± 19	3.6 ± 0.52	7.0 ± 2.6	0.16 ± 0.021	1.1 ± 0.36	5.1 ± 2.0
	gelatine	287 ± 134	38 ± 13	2.8 ± 0.89	10 ± 7.2	0.14 ± 0.023	0.62 ± 0.17	7.4 ± 5.0
HPMC K100	HPMC	169 ± 60	15 ± 7.0	7.4 ± 3.4	23.3 ± 22	0.084 ± 0.024	1.9 ± 0.65	16 ± 16
	gelatine	206 ± 70	18 ± 5.8	6.3 ± 1.4	7.9 ± 4.2	0.089 ± 0.017	0.92 ± 0.28	5.2 ± 3.3

The t_{lag} values for the HPMC K100-based capsules are clearly greater than those for the lactose-based capsules. This is in contrast to the results obtained with

ibuprofen, where the t_{lag} values remained almost the same even though the diluent was changed from lactose to HPMC polymers of different viscosities (Table 7). This difference between the two model drugs is probably due to the differences in the drug/HPMC ratios of the capsules, which was on average 60/40% (w/w) for the ibuprofen capsules and 4/96%(w/w) for the metoclopramide hydrochloride capsules (Table 4). Several studies have shown that the drug/HPMC ratio is one of the major factors controlling the release of drugs from HPMC matrices (Salomon et al., 1979; Alderman, 1984; Ford et al., 1985b, c).

The *AUC* values for the metoclopramide hydrochloride capsules containing HPMC K100 as the diluent were clearly smaller than those for the lactose-based capsules (Table 8). In addition, the *AUC* values for the rectal HPMC K100-based capsules were smaller than those for the same capsules administered orally. This difference was statistically significant for the HPMC capsules, but not for the gelatine capsules (III, Table V). Also the C_{max} values were significantly lower and the t_{max} values were significantly higher for the rectally administered HPMC K100-based HPMC and gelatine capsules than for the corresponding orally administered capsules. One reason for these differences may be the poor drug/HPMC ratio, i.e. the amount of HPMC powder may have been too great for the metoclopramide to dissolve in the rectal fluid and to absorb completely. In addition, it should be noted that the capsules may have migrated to the upper part of the rectum which is connected with the portal vein system, and the absorbed metoclopramide was exposed to first-pass metabolism. However, the absorption profiles of metoclopramide from the HPMC K100-based capsules compared with the lactose-based capsules (III, Figs. 6 and 7) indicate that these capsules have potential for proper prolonged-release formulations if the drug/HPMC ratio is optimised, e.g. by increasing the metoclopramide dose to 20 or 30 mg.

5.3. In vitro oesophageal sticking tendency of the capsule shells (II)

Numerous *in vitro* and *in vivo* studies have shown that gelatine capsules have 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; Wilson et al., 1988; Perkins et al., 1999). The volume of water swallowed and the position of the body when swallowing are important determinants of the oesophageal transit time of gelatine capsules (Hey et al., 1982; Channer and Virjee, 1985; Bailey et al., 1987). Delayed oesophageal drug transit may have two effects. Firstly, retention of the

dosage form in the oesophagus delays drug absorption, as drugs cannot easily pass through the stratified squamous epithelium of the oesophageal mucosa (Channer and Roberts, 1984, 1985). Secondly, oesophageal disorders may develop and this has been reported for over 70 drugs (Jaspersen, 2000).

The probability of adhesion to the oesophageal mucosa is increased if the surface of the dosage form becomes sticky when in contact with water. Therefore, formulations containing gelatine or cellulose derivatives have been recognized as hazardous with respect to oesophageal attachment (Swisher et al., 1984). In the study conducted with capsules containing ibuprofen and lactose (I), both the HPMC and the gelatine capsules were suspected to have adhered to the oesophagus or to the upper parts of the stomach in one subject (different subject on each occasion). Therefore, the tendency of the HPMC capsules to stick to the oesophageal mucosa was compared to that of gelatine capsules using the isolated porcine oesophagus method developed in our laboratory (Marvola et al., 1982). The capsules were filled with lactose. The force needed to detach the HPMC capsules from the preparation was significantly ($p<0.001$) smaller than for the gelatine capsules (II, Fig. 1). In addition, some of the gelatine capsules adhered to the oesophagus so strongly that they broke up while being detached, whereas all of the HPMC capsules (n=10) remained undamaged. The lower sticking tendency of the HPMC capsules would evidently be an advantage. However, the *in vitro* method used is not fully comparable to human physiological conditions and it has been demonstrated to give unreliable results compared with human *in vivo* studies (McCargar et al., 2001). Therefore, further *in vivo* studies are needed to verify the sticking properties of the HPMC capsules.

5.4. Gamma scintigraphic evaluation (IV)

The gamma scintigraphic imaging method was utilised to obtain visual data about the fate (movement and disintegration) of the two different orally administered prolonged-release HPMC capsules in the human GI tract for 8 h. The capsules were filled with either HPMC K100 or K4M powder and samarium oxide was used as a label. The results were compared with the studies conducted with corresponding orally administered capsules containing either metoclopramide hydrochloride or ibuprofen as the model drug. The aim was to find out the main reason why the pharmacokinetic profiles of the model drugs change when the diluent was changed to a higher viscosity grade derivative, whether it is due to differences in the degradation time of the gel plugs formed in the GI tract or to

differences in the GI transit rate of these two different formulations. Special attention was paid also to whether HPMC capsules adhere to the oesophagus.

The HPMC capsules lodged in the oesophagus for 22 to 143 min on 4 of the 12 occasions (IV, Table 1). The incidence of stagnation (33%) was quite high although the subjects took 180 ml of water. In addition, they remained in a sitting position for 30 s before lying down, which should be long enough since the transit time for hard gelatine capsules has been reported to range from 7 to 24 s (Bailey et al., 1987; Wilson et al., 1988; Perkins et al., 1994, 1999). The incidence of oesophageal stagnation for hard, size 00 gelatine capsules has been reported to be 17% when ingested with 120 ml of water and 61% when ingested with only 15 ml of water (Bailey et al., 1987). In both cases the subjects were in the sitting position. In the supine position and with only 15 ml of water the incidence was 67% for the hard size 0 gelatine capsules, but if the subjects swallowed the capsule in the sitting position and immediately thereafter lay down, none of the capsules attached (Channer and Roberts, 1984). In a scintigraphic study, analogous with the present one, it was found that in one of 10 subjects a hard size 0 gelatine capsule stuck to the oesophagus for 1.75 h although the amount of water ingested was 180 ml (Säkkinen et al., 2004).

The present results on the tendency of the HPMC capsules to stick to the oesophagus do not support the results obtained with the *in vitro* oesophageal preparation (II, Section 3.2.). McCargar et al. (2001) also reported poor correlation between the results of *in vivo* human studies and the *in vitro* method utilising a porcine oesophagus. However, the *in vivo* arrangement used in the present study clearly affected the sticking incidence, since all occurrences were on the first study day. It is possible that the subjects became aware that the capsules might attach to the oesophagus and so swallowed the capsule differently on the second study day; e.g. swallowed more water with the first gulp after taking the capsule or took a gulp before putting the capsule into their mouths. Therefore, the possible differences between gelatine and HPMC capsules need further investigation with a well-planned, double-blind, cross-over human study utilising gamma imaging. Until then, it is recommended that both gelatine and HPMC capsules should be ingested with plenty of water in an upright position, then remaining in that position for several minutes.

There was no evidence of the capsules having adhered to the gastric mucosa and they were emptied from the stomach within 2 h after ingestion. There were no differences between the two viscosity grades of HPMC polymer in respect of gastric emptying time, small intestine transit time or large intestine arrival time (IV, Table 1). The small intestine transit time for HPMC K100-based capsules

averaged 2.5 ± 0.4 h, and the capsules arrived at the large intestine on average 2.8 ± 0.5 h after administration, when the oesophageal residence time was ignored (IV, Table 1). The corresponding values for the HPMC K4M-based capsules were 2.7 ± 0.8 h and 3.2 ± 0.9 h, respectively.

The viscosity grade of the HPMC polymer did not significantly affect the time at which samarium oxide started to be released from the formulations. The time for initial samarium oxide release from the HPMC K100-based capsules was on average 49 ± 20 min, and from the HPMC K4M-based capsules 53 ± 12 min (IV, Table 2). The division of the capsules into two or three pieces while drifting through the small and the large intestine also occurred at almost the same time for both capsule formulations (IV, Table 2).

The difference between the two viscosity grades was obvious when complete capsule disintegration was examined. Five of the six HPMC K100-based capsules disintegrated completely during the study, whereas all of the HPMC K4M-based capsules still exhibited plug formations in the last images taken 8 h after administration (IV, Table 2). Due to the complete disintegration of the HPMC K100-based capsules, they spread better in the ascending colon than the HPMC K4M-based capsules (IV, Fig 2). In addition, the plug formations of the capsules at the end of the test were detected in the upper parts of the ascending colon or in the transverse and descending colon. Thus, the HPMC K100-based capsule may serve better the absorption of drugs from the colon than the HPMC K4M-based capsules since the absorptive capacity of the ascending colon is greater than that of the transverse and descending colon.

When the results presented here are compared with the pharmacokinetic studies conducted with corresponding capsules containing metoclopramide hydrochloride as a model drug, it can be concluded that most of the metoclopramide dose was probably absorbed from the large intestine. The time to maximum drug concentration in plasma (t_{max}) was 4.2 and 4.7 h for the HPMC K100- and K4M-based formulations, respectively (Section 5.2.2., Table 6). When the concentration versus time curves of metoclopramide are examined, the greatest portion of the area under the concentration time curves (*AUC*) for both capsule types may have been formed when the capsules were situated in the large intestine (III, Fig. 7). The same observations were made also with ibuprofen even though the drug/HPMC ratio was different (II, Table 3 and Fig. 3). Therefore, it appears that for the capsule types tested here, under fasting conditions, the large intestinal absorption governs the success of the capsules, and these capsules may not be suitable for drugs that are absorbed only from the small intestine or are poorly absorbed from the large intestine. The faster disintegration of the HPMC K100-

based capsules compared with the HPMC K4M-based capsules explains why the maximum concentration (C_{max}) of the model drugs, metoclopramide and ibuprofen, was significantly higher for the HPMC K100-based capsules than for the HPMC K4M-based capsules (II, Table 3; III, Table V).

6. Conclusions

The main objective of the studies reported here was to evaluate the biopharmaceutical properties of the novel hard HPMC capsules in comparison with hard gelatine capsules and to determine whether the two types of capsule shell could be regarded as interchangeable from the biopharmaceutical point of view.

The following conclusions can be drawn from the present studies:

- When the capsules were diluted with lactose, the oral absorption of the model drugs, ibuprofen and metoclopramide, from the different capsule shell types was similar and the HPMC and gelatine capsules could be regarded as interchangeable. When the same capsule formulations were administered rectally, the time lapse to the commencement of ibuprofen or metoclopramide absorption was greater for the HPMC capsules than for the gelatine capsules. This result is in accordance with *in vitro* dissolution. Nevertheless, since the change in the capsule shell material did not affect statistically significantly the bioavailability (*AUC*) of the model drugs, the HPMC capsules could be regarded as a noteworthy alternative to the gelatine capsules also for rectal administration if rapid onset of action is not required.

- When HPMC and gelatine capsules filled with HPMC powders of various viscosities were administered orally, there were no differences between the HPMC and gelatine capsule shells that would have any significance in practice, regardless of the model drug. Therefore, from a biopharmaceutical point of view, the capsule shells could be regarded as interchangeable for oral use also when they are diluted with HPMC powders. When the same capsules were administered rectally, the difference between the HPMC and gelatine capsules was similar to that seen for capsules diluted with lactose: the time lapse to the commencement of ibuprofen or metoclopramide absorption was greater for the HPMC capsules than for the gelatine capsules. Nevertheless, since the bioavailability of the model drugs remained unaffected and the capsules were intended for prolonged release without need for rapid action, the HPMC capsules could be regarded as an alternative to gelatine capsules also when employing rectal administration.

- The different chemical nature and water solubility of the model drugs did not have any marked effect on the *in vitro* and *in vivo* behaviour of the two capsule shell types, which further confirms the conclusion that these capsule shells could be regarded as interchangeable from a biopharmaceutical point of view.

- Changing the diluent from lactose to HPMC powders of different viscosities prolonged the release of the model drugs after both oral and rectal administration. In addition, it was possible to control the release and subsequent absorption of the model drugs by changing the viscosity grade of the HPMC polymer, but this was valid only for oral formulations. A noteworthy observation was that changing the diluent from lactose to HPMC polymer did not reduce the oral or rectal bioavailability of the model drugs, except in the case of rectal capsules containing metoclopramide hydrochloride. In contrast, the bioavailable amount (*AUC*) from the HPMC powder-based capsules was in some cases even greater than from the lactose-based capsules, regardless of the route of administration. These findings indicate that it is possible to produce prolonged-release capsule formulations easily and economically by simply filling the capsules with a proper swellable hydrophilic polymer. However, further optimisation of the formulations containing HPMC powders is needed in order to achieve a longer elimination half-life of the drug and, consequently, to lengthen the dose interval of the formulations.

- The hard capsules turned out to be of value for rectal administration, especially when the model drug was metoclopramide hydrochloride and the diluent was lactose. Via the rectal route it was possible, at least partially, to avoid the first-pass metabolism of metoclopramide in the liver. However, the correct technique for insertion of the rectal capsules is essential for the success of this dosage form. In addition, product development is needed to minimise the time lapse to the onset of drug absorption, especially for HPMC capsules.

- The tendency of the HPMC capsules to stick to the isolated porcine oesophagus was lower than that of the gelatine capsules. However, gamma scintigraphic investigations showed that the tendency of the HPMC capsules to stick to the human oesophagus is high, although further investigations of this phenomenon are needed in comparison with gelatine capsules. Until then, it is recommended that HPMC capsules, as well as gelatine capsules, should

be ingested with plenty of water in an upright position and remaining in that position for several minutes.

- The gamma scintigraphic evaluation of the HPMC capsules containing either HPMC K100 or K4M powder as a diluent revealed that the main absorption site of drugs from these capsule formulations is the large intestine. Therefore, these capsules may not be suitable for drugs that are absorbed only from the small intestine or are poorly absorbed from the large intestine. The faster disintegration of the HPMC K100-based capsules explains why the absorption of the model drugs from these capsules was less sustained than from the HPMC K4M-based capsules.

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