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The value of hard gelatin capsules as a rectal dosage form in man using ibuprofen and metoclopramide hydrochloride as model drugs

by

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To my wife Kati

ABSTRACT

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Dissertationes Biocentri Viikki Universitatis Helsingiensis 16/2004, pp. 47.

There are severeal kinds of clinical situations in the hospital environment that indicate use of various rectal dosage forms. It is well known that hard gelatin capsules offer a suitable *extempore* dosage form for use in these cases. The main advantages of using hard gelatin capsules are: their ease of manufacture enabling strict adjustment of individual dose and low cost production. They offer also an alternative in serious clinical situations with children, nausea or unconsciuos patients and patients with gastrointestinal illnesses.

There is very little scientific documentation concerning rectal administration of hard gelatin capsules. For these reasons the aim of this thesis was to carry out a biopharmaceutical characterisation of hard gelatin capsules as a rectal dosage form. In the investigations two rectally well-absorbed model drugs were used: one a weak acid, ibuprofen and the other a weak base, metochlopramide hydrochloride. Both *in vitro* and human *in vivo* tests were utilised.

It was found that these compounds with different biopharmaceutical characteristics can be administered adequately in rectally administered hard gelatin capsules. The mean relative bioavailability of ibuprofen via the rectal route with eight subjects was 99 % (90 % CI 0.81-1.18) compared with oral administration. It was investigated whether it is possible to modify the drug release from rectally administered hard gelatin capsules using suitable pharmaceutical excipients and adjusting their amounts in the capsules. In this study, the adequate immediate-release and prolonged-release formulations were obtained when ibuprofen and metoclopramide hydrochloride were used as the model drugs.

In rectal hard gelatin capsules a bioavailability of ibuprofen and metoclopramide hydrochloride can be achieved which corresponds to that of oral dosage forms. So the rectal administration route with hard gelatin capsules is not only an alternative, but often also a prime choice in different clinical situations. However, a clear time lag of 0.5 to 1.5 h was noticed in the commencement of drug absorption; normally causing a slightly slower absorption phase in the administration of hard gelatin capsules.

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LIST OF ABBREVIATIONS

AUC	area under the concentration-time curve from time 0 to infinity
C_{max}	maximum concentration
t_{max}	time to peak concentration
$t_{½}$	elimination half-life
k_a	absorption rate constant
MRT	mean residence time
HPMC	hydroxypropyl methylcellulose
K15M	the viscosity grade of the HPMC, 15000 mPas measured as a 2% aqueous solution at 20 °C
K4M	the viscosity grade of the HPMC, 4000 mPas measured as a 2% aqueous solution at 20 °C
K100	the viscosity grade of the HPMC, 100 mPas measured as a 2% aqueous solution at 20 °C
DSHP	disodium hydroxide phosphate
SDHP	sodium dihydroxide phosphate
Ph. Eur.	European Pharmacopoeia
USP	United States Pharmacopoeia
NSAID	non-steroidal anti-inflammatory drug
HPLC	high-performance liquid chromatography
c.v.	coefficient of variation
CI	confidence interval
mw.	molecular weight
mp.	melting point

LIST OF ORIGINAL PUBLICATIONS

This thesis is based on the following original papers:

I Eerikäinen S., Leino J., Harjula M., Klinge E. and Marvola M. 1996. Use of a hard gelatin capsule as a rectal dosage form. *STP Pharma Sci.* **6** 435-440.

II Leino J., Haavisto H., Tomminen T., Heinilä K., Eerikäinen S., Klinge E. and Marvola M. 1997. Development of rectally administered prolonged-release hard gelatin capsules using different polymers as diluents. *STP Pharma Sci.* **7** 348-353.

III Leino J., Salmela O., Alastalo H., Eerikäinen S., Klinge E. and Marvola M. 1999. Rectal bioavailability of ibuprofen from hard gelatin capsules containing sodium phosphates as adjuvants and soft gelatin capsules or suppositories as reference. *STP Pharma Sci.* **9** 579-585.

IV Leino J., Honkanen O., Kokkonen M., Eerikäinen S., Klinge E. and Marvola M. 2003. Evaluation of hard gelatin capsules as a rectal dosage form for a freely water-soluble model-drug, metoclopramide hydrochloride. *STP Pharma Sci.* **13**, 141-145.

The studies are referred to in the text by the Roman numerals I-IV.

1. INTRODUCTION

1.1. Background

While suppositories are an old form of medication that has been known from the time of Hippocrates (Abdou 1989), hard gelatin capsules have been used in oral medication since the late 19th century (Jones B. 1987). On the other hand, the origins of gelatin manufacture can be traced back as far as 4000 B.C. (Jones R. 1987). The first recorded patent for a gelatin capsules was French Patent 5648, granted in Paris on 25th March 1834 to Dublanc and Mothes. The idea was quickly acclaimed and its use spread rapidly both inside and outside France. In 1835 capsules were being manufactured in places as far apart as Berlin and New York (Jones B. 1987).

In France, capsules were well established by the end of the 19th century. In Britain, the spread was similar but slower. In the pharmaceutical literature, several attempts were made to popularise their use, particularly for extemporaneous dispensing. *The Chemist and Druggist* in 1888 published an article on capsule manufacture (Jones B. 1987). It explained that if it were known that a dozen capsules could be made in the same time as a dozen suppositories then every pharmacist would adopt this art.

In Anglo-Saxon countries, rectal suppository administration accounts for only 1 % to 2 % of all drugs that are given for their systemic effects. On the other hand, suppositories account for approximately 15 % to 20 % of all products used in many European and Latin American Countries. During the last 10 - 20 years or so, several publications on the rectal absorption of drugs have also appeared in the US and Japan, the world`s two biggest pharmaceutical markets, where suppositories or other rectal dosage forms had not been previously well accepted from the cultural and emotional points of view (Hermann 1995).

Soft gelatin capsules are frequently used for rectal and vaginal application. A less common rectal dosage form is the rectal capsule. These are generally similar to soft gelatin capsules except that they usually have a lubricating coat to aid gliding during administration (Hardy *et al.* 1987). Moreover, for example Hannula and co-workers have studied the coating of hard gelatin capsules with a gliding coat (Hannula 1985, Hannula *et al.* 1986). Already in the 1960s Wagner investigated the effects of dosage form variation on blood levels of the drug, indoxole, and reported that a soft gelatin capsule (drug dissolved) was equivalent to the emulsion dosage form,

followed by aqueous suspension, and last was the powder-filled hard gelatin capsule (Wagner *et al.* 1966).

1.2. Physiology and biopharmaceutical characteristics of rectum

The colon consist of the ascending, transverse and descending colons which encircle the small intestine; the sigmoid colon, which turns medially and downward; the rectum; and the anal canal. The rectum is about 15-20 cm long, and the anal canal is the last couple of centimetres of the colon that surrounds the anus. Clinically, however, the terminal end of the colon is usually referred to as the rectum (Scanlon and Sander 1995).

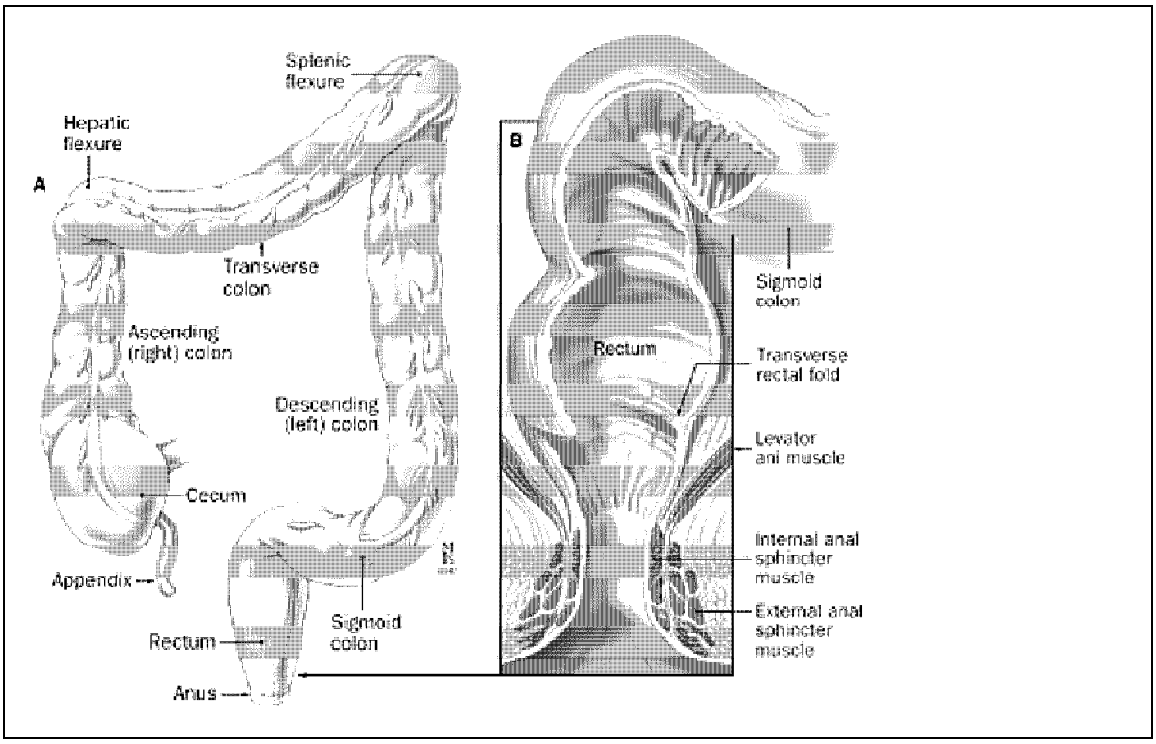


Figure 1. Anatomy of the colon (A) and the rectum (B) (The Johns Hopkins Medical Institutions, Gastroenterology and Hepatology Resource Center, Digestive Disease Library 2004).

The rectum has a good blood supply, and is characterised by absence of villi and a relatively small surface area (0.02-0.05 ml^2). Rectum contains a small volume of viscous fluid (0.5-1.25 ml) which spread over the surface, and which has a clearly limited buffer capacity. Mostly based on

these factors, many drugs which are well absorbed orally are poorly absorbed rectally, even when administered in solution. Even if well absorbed, it is quite common that blood levels may be more variable after rectal absorption (Wagner 1971, De Boer *et al.* 1982, Ziegler 1986). Since only a little fluid is present in the rectum, a greater water solubility is generally required for a compound to be absorbed rectally as compared with oral absorption. For rabbits, Nishihata *et al.* (1984) has shown that the effective rectal fluid volume available to dissolve drugs is only about 0.1 ml.

The significance of the rectal region, also as an alternative route for administration, has increased and it is, therefore, of growing interest in drug therapy. It can offer a long residence time and low luminal peptidase activity; and may have some certain advantages for the absorption of drugs with reduced permeability across the epithelial barrier and/or increased sensitivity to enzymatic degradation in the upper part of the gastrointestinal tract (Lennernäs *et al.* 1995, De Boer *et al.* 1992). There are several examples in study reports that the rectal bioavailability of drugs, even when administered in solution, appears to be drug spesific; examples of suppressed (Kitazawa *et al.* 1978, Pappenheimer and Reiss 1987, Madara *et al.* 1987), similar (Eichelbaum and Spannbrucker 1977, Sarkar and Karnes 1988, Lee *et al.* 1993) and even improved (Amidon *et al.* 1980) bioavailability relative to oral administration can be found. As an absorption process, colorectal absorption occurs by passive diffusion through the lipoidal membrane in which carrier-mediated mechanisms have showed to have no role (Eller *et al.* 1989). Since solubilities, water solubility and lipophilicity, have a reverse relationship, it is apparent that an optimal balance between these properties is required to achieve optimal absorption (Buur and Bundgaard 1987).

1.2.1. Permeability

The effective permeability of drugs across the intestinal epithelium is influenced by several physico-chemical and physiological properties and may differ in various intestinal regions (Ho *et al.* 1983). Lennernäs and co-workers (1995) have reported that the absorption of water occured at the lower degree in the rectum compared with other parts of the gastrointestinal tract. They estimated that it might be explained by a smaller pore radius, tighter epithelium, less fluidity in the rectal membrane, lower number of pores in the rectal region, and a decreased mucosal surface area (Davis *et al.* 1982, Powell 1981, Brasitus and Dudeja 1985, Chadwick *et al.* 1977). It

has been proposed that the electrolytes and water are transported transcellularly in the colon/ rectum, which is different from more high permeable tissue in which the transport of electrolytes and water has been assumed to be by the paracellular route (Allen 1983). The tighter and less fluid rectal epithelium is probably due to a change in the lipid composition, such as increased cholesterol/phospholipid molar ratio and degree of saturation of fatty acid residues (Brasitus and Dudeja 1985). Furthermore, Lennernäs with his study group also suggest that an unstirred water layer is an essential factor since it might be thicker and more coherent in the colonic-rectal region (Lennernäs *et al.* 1992) compared with what they and others have found in the jejunum in man (Levitt *et al.* 1990, Muranishi 1990).

The more pronounced effect of the absorption of drugs during an increased convective flow across the barrier is in agreement with indications that various absorption enhancers seem to be more effective in the colon/rectum compared with the small intestine (De Boer *et al.* 1992, Muranishi 1990). Bile salts such as sodium glycholate seem to bind with calcium ions and sodium caprate changes the pore size in the tight junctions of membranes. These promoters probably increase the permeability of membranes to hydrophilic macromolecules via the paracellular route. Sodium salicylate seems to increase transport by both paracellular and transcellular routes (Mizuno et al. 1992). Nishihata et al. (1982) investigated the enhancement effect of salicylate on the rectal absorption of different types of drugs; theophylline as a neutral substance; lidocaine as a basic material; cefmetazole as acidic and levodopa which exists as a zwitterion in solution. Absorption of each drug was enhanced, particularly at pH values were the substances exist primarly in their ionic form. A requirement for the observed enhancement was that salicylate was present in the rectal membrane.

1.2.2. Effect of pH

The rectum as an absorption site has a higher pH (7-8) than that of the gastro-intestinal tract. It is not a favorable site for the absorption of most of the weak organic acids which have pK_a values lower than the pH of the rectum, because most of the drug molecules exist in an ionized form in the rectum. If the pH of the drug absorption site in the rectum was temporarily lowered below the pK_a value of the drug, increased rectal absorption of drug would be expected. Yagi and his study group (1993) found that the mean areas under the plasma concentration-time curves (AUCs) following the administration of suppositories containing weak acids were larger

than both those of the suppositories containing bumetanide without weak acids (control) and those of an orally administered bumetanide suspension in rabbits. Moreover, the pH in the rectum decreased to between 2-4 for 30 minutes following the administration of the suppositories containing weak acids, like citric acid or tartaric acid.

The pH of the rectal fluid is determined by the contents of the rectum, because of the lack on buffer capacity (Coben and Lieberman 1986). Consequently, the absorption of the drug could be improved by adding acids or bases to a formulation until the balance of ionized and unionized forms of the drug is optimal. In this way it could be possible to improve the solubility of the drug in the rectal fluid and at the same time ensure sufficient permeability. On the other hand, it has been determined that under the conditions met in the study of Crommelin et al (1979): the rectum is able to secrete neutralizing agents when the luminal pH deviates from the physiological pH. The degree of the secretion depends on the magnitude of the deviation. In general, the dissociation reaction of a drug is an equilibrium reaction. Thus, if some of the undissociated form of a drug is eliminated from the system, new undissociated drug will be formed to compensate (Ritschel 1992). Consequently, the proportion of the undissociated drug need be only 1-2% in order to be absorbed.

1.2.3. Question of first-pass metabolism

Rectal administration has been recommended as a non-invasive alternative for drugs which are largely metabolized by the liver or excreted in the bile and for those subject to degradation in the gastrointestinal tract (Jonkman *et al.* 1979). Also, drug administration in the lower part of the rectum is useful as an almost non-hepatic route for high-clearance drugs such as lidocaine, propranolol, nitroglycerin and certain narcotic analgesics like morphine (De Boer *et al.* 1979).

Although partial avoidance of first-pass elimination may in principle occur in the lower part of the rectum (De Boer *et al.* 1979), many human rectal bioavailability studies have clearly demonstrated presystemic eliminination, usually equal to (Jonkman *et al.* 1979, Westerling *et al.* 1982, Moolenaar *et al.* 1979A, 1981, 1983) but sometimes even exceeding that (Moolenaar *et al.* 1978, 1979B) after oral dosing. In this respect it should be emphasized that rectally administered

fluids do not remain in the lower part of the human rectum, but they spread upward to a region where veins draining into the portal circulation predominate (Moolenaar and Schoonen 1980).

The possible liver-based first-pass metabolism in the rectum is assumed to happen mainly in a two different ways. When the drug is absorbed in the inferior or middle rectal veins, it probably reaches the superior rectal veins by way of the numerous connections (anastomoses) between them. Another possibility is that the dosage form quickly reaches the higher parts of the rectum and thus the drug is directly absorbed into the superior rectal veins (Jonkman *et al.* 1979).

To test the hypothesis that first-pass metabolism is at least partially avoided when a drug is given rectally, since part of the rectal drainage is directly into the vena cava, de Boer and co-workers (1982) administered lidocaine to six volunteers intravenously, perorally (gelatin capsules) and rectally (aqueous solution) in a cross-over design. Corrected for dose size differences, the oral bioavailability was 31 ± 11% (S.D.) and the rectal bioavailability was 63 ± 23% (S.D.). In a follow-up study (De Boer *et al.* 1982b) in the same six subjects the mean oral bioavailability was 27% and the rectal bioavailability 67%, indicating good agreement between the individual data of the two studies.

Many drugs are metabolized at the absorption site, in the colorectal area, in many cases by the enteral bacteria (e.q. atropine, steroids, polypeptide drugs, indomethacin, sulphasalazine, l-dopa,) (Fara 1985). Furthermore, there are peptidase enzymes in the membrane of the rectum which metabolize proteins and peptides, so the rectum is not only the physical barrier but also the metabolic barrier (De Boer *et al.* 1990).

1.2.3.1. Existence of efflux proteins

Increasing interest is focused on the role of the efflux proteins.in scientific literature during the last decade. These proteins like P-glycoprotein and other multidrug resistance proteins form a group of ATP-binding cassette transporters that act as energy-dependent efflux pumps transporting a wide variety of low molecular weight compounds out of cells. Transporters can recognize and efflux numerous substrates with varied chemical structures, including many anticancer drugs. While the molecular mechanisms underlying the broad substrate spesificity of efflux proteins are generally unknown; it appears that in the intestinal tract *epithelia* the drug is

effluxed by flipping the drug from the inner to the outer leaflet of the bilayer membrane (Kondratov *et al.* 2001). This model is consistent with the ability of compounds to penetrate lipid and the common denominator is that the P-glycoprotein substrates are hydrophobic and amphipathic in nature.

A wide variety of drugs suffer from incomplete, variable and non-linear absorption. Similarly, at the blood-brain barrier a range of drugs have limited brain penetration due to P-glycoprotein-mediated-efflux, which can limit therapeutic effectiveness of CNS agents (Ayrton and Morgan 2001). For absorption, a clear role has emerged for P-glycoprotein in limiting permeability across the gastrointestinal tract. The drugs that can be effluxed from the cell by glycoprotein include e.g. cyclosporin A, digoxin, erythromycin, antibiotics, cimetidine. Inhibition of P-glycoprotein improves intestinal absorption and tissue distribution while reducing the metabolism of the substrate and its elimination (Varma *et al.* 2003). P-glycoprotein can often be the mechanism for significant pharmacokinetic drug interactions when two or more drugs are competing for the P-glycoprotein transport site (Johnson 2002).

Together with drug-metabolising enzymes, transmembrane transporters are important determinants of drug metabolism and clearance by the liver (Faber *et al.* 2003). An overwhelming proportion of clinically relevant drug interactions where the intestine has been implicated as a major contributor to first-pass metabolism involves drugs that undergo cytochrome P450(CYP) 3A4-mediated biotransformation and are substrates for the efflux transporter P-glycoprotein (Doberty and Charman 2002). These two integrated and complex systems exist, among other places, in the tips of the villi of the intestinal tract: P-glycoprotein is expressed in a variety of normal human tissues including the liver, brain, adrenal gland, kidney and intestinal tract epithelia. Thus, P-glycoprotein might have a potential role in transformation of the oral bioavailability of many clinically important drugs, it is obviously of no biophamaceutical importance in rectum because of the absense of the villi. Most of the study reports concerning the efflux proteins focus on the upper parts of the intestinal tract.

1.3. Rectal drug administration

Over a long period of time the rectal route was used only for the administration of local anasthetics, anti-haemorrhoidal, vermifugal and laxative agents. Now the majority of natural and

synthetic drugs are also formulated in the different kinds of rectal dosage forms to produce a systemic effect (Hermann 1995). Absorption following rectal administration is often said to be unreliable, but this route can be adequate to patients who are vomiting or nauseous, or who are unable to take medication by mouth (e.g. postoperatively). The rectal dosage forms are used to administer diazepam to children who are in *status epilepticus* in whom it is difficult to establish intravenous access. Study reports concerning the rectal administration of diazepam have shown that, being a lipophilic drug, it is better absorbed from hydrophilic than lipophlic suppositories (Marvola *et al.* 1981, Redgon *et al.* 1994). Often, though, the reasons for avoiding the rectal route appear to be more cultural than pharmacological.

Many reserchers have concentrated their efforts in rectal drug absorption on those drugs which currently must be injected parenterally to provide effective therapy. Those drugs may be divided into two categories: antibiotics (e.g. streptomycin, cefazolin) and polypeptides (heparin, interferon, insulin, gastrin) (Nishihata *et al.* 1982, Caldwell *et al.* 1984, Muranishi 1984, Ritschel and Ritschel 1984, Davis *et al.* 1985, Beskid *et al.* 1988, Bahia and Giuedes 1991, De Muynck *et al.* 1994, Nishihata *et al.* 1984b). The suppository or some other rectal dosage form may be useful as a sustained-release formulation for the long-term treatment of chronic diseases like essential hypertension, asthma, diabetes, AIDS, anaemia, *etc.* (Kurosawa 1985, Kawaguchi *et al.* 1991, Morgan *et al.* 1992, Reynolds 1993, Hsyu *et al.* 1994). Furthermore, there is a growing interest in the possibility of rectal administration in the treatment of post-operative pain and malignant pain (Moolenaar *et al.* 1984, Leow *et al.* 1992, Saruki *et al.* 1992, Koja *et al.* 1994).

Storey and Trumble (1992) have investigated the rectal absorption of carbamazepine and doxepin when the drugs were administered in hard gelatine capsules. The study was established, because many cancer patients, who needed the medication, were not able to take it orally and there were no injectable products on the market at that time. As a result, all patients benefited from the rectal administration of hard gelatine capsules. The general status of the patients, who have had pains and attacks, was notably improved.

1.3.1. Advantages of using a hard gelatin capsule as a rectal dosage form

It is generally known that hard gelatin capsules, either manufactured *extempore* or commercial brands, are used in some clinical cases in hospitals, although the commercial ones, unlike for

example some soft gelatin capsules, are not officially accepted for rectal use. There are many clinical applications or situations where the use of rectal dosage forms is preferable; as can be seen from the following detailed arguments concerning hard gelatin capsules administered rectally:

1. Can be manufactured *extempore* in the hospital and/or retail pharmacies
2. Enable strict individual adjustment of the dose; better than e.g. suppositories and soft gelatin capsules
3. Simple and low-cost production
4. A relatively great variation of drugs can be employed; from antibiotics and NSAIDs to polypeptides
5. Possibility to avoid, at least partially, first-pass metabolism; especially with high-clearance drugs
6. Offer an alternative way in different and/or serious clinical situations with children, nauseous or unconsciuos patients, aged people, patients with certain gastrointestinal illnesses, etc.
7. As a dosage form, relative easy to formulate; presumably when immediate or slow release profile is required
8. Possible to employ acid labile, stomach-irritating or bad tasting drugs
9. Food intake does not have a direct effect on the drug administration; unlike in oral medication
10. Offer a relatively steady environment and long residence time for drugs to be absorbed
11. Replace in some cases the use of other administration routes, e.g. parenteral dosage forms

According to the pharmaceutical literature, one of the main reasons for the unpopularity of rectal dosage forms, beside the incovenience, is the lack of reliable *in vitro/in vivo* correlation in the evaluation of their therapeutic effectiveness (Abdou 1989). It is also possible that factors which are not directly dependent on the dosage from; like unfamiliar and partly difficult administration technique, compliance and spesific character of the absorption region, can cause problems in rectal administration of hard gelatin capsules. Our laboratory group made experiments on immediate relese and sustained release capsule formulations containing ibuprofen as a model drug and HPMC of different viscosities as diluents (Ojantakanen *et al.*

1993). Furthermore, it has been shown that e.g. sustained release hard gelatin capsules, for oral or rectal administration, are relatively uncomplicated to produce by adding suitable hydrophilic polymer to the formulation (Ojantakanen *et al.* 1993, Marvola *et al.* 1991, Ojantakanen 1992, Efentakis and Vlachou 2000).

2. AIMS OF THE STUDY

As shown in the review of literature, there is very little scientific documentation concerning rectal administration of hard gelatin capsules. However, some special indications exist where administration of hard gelatin capsules via the rectal route would be justified. For these reasons the overall aim of the present study was to carry out a biopharmaceutical characterisation of hard gelatin capsules as a rectal dosage form. In the investigations two rectally well absorbable model drugs were used: one a weak acid (ibuprofen), the other a weak base (metochlopramide hydrochloride). Both *in vitro* and human *in vivo* tests were utilised. The detailed aims of the study were:

1. To study whether training in rectal administration (I) or dipping of capsules into liquid paraffin (I, II, III) or coating them with hard fat (III, IV) would affect drug bioavailability from the capsule or facilitate drug administration.
2. To determine the relative bioavailability of rectally administered capsules compared with that after oral dosing of the corresponding capsule (I).
3. To determine the relative bioavailability of the rectal capsule compared with a corresponding soft gelatin capsule (III) or commercial suppositories (III, IV).
4. To study the effect of the type of diluent (water-soluble, water-insoluble or gel-forming agent) on the bioavailability of the model drugs (I-IV).
5. To test whether long-acting rectal formulations could be developed using different grades of hydrophilic polymers as a diluent (II, IV).
6. To study whether it would be possible to enhance the bioavailability of the model drug by regulating the ionisation degree of the model drug with pH-regulating inorganic salts as additives (III).
7. To evaluate whether it would be possible to predict the *in vivo* behaviour of the formulations based on the results gained in the *in vitro* dissolution tests (I-IV).

3. MATERIALS AND METHODS

3.1. Model drugs

3.1.1. Ibuprofen

Ibuprofen (Ph. Eur., Industrial Chemica Prodotti, Italy, particle size < 0.3 mm) was used as a model drug in hard gelatin capsules (I, II and III). Ibuprofen (mw. 206.3) is a non-steroidal propionic acid derivative with anti-inflammatory, analgesic and antipyretic properties. Its pharmacological mechanism is based on inhibition of cyclo-oxigenase thus preventing prostanoid synthesis.

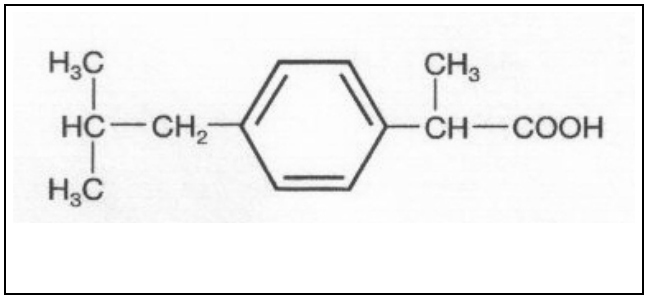
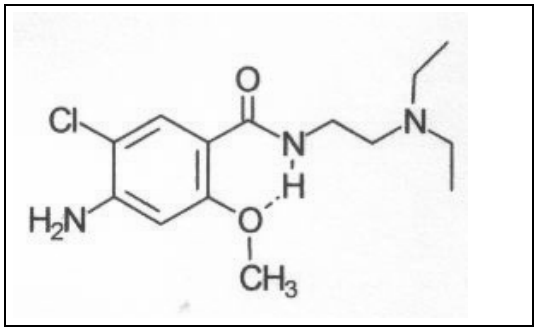


Figure 2. Chemical structure of ibuprofen.

Ibuprofen is regarded as a representative of drug that is well absorbed throughout the gastrointestinal tract (Wilson *et al.* 1989, Van Hoogdalem *et al.* 1991). It is also widely used and safe (Van Hoogdalem *et al.*1991.). Ibuprofen is a weak acid with a pK_a of 5.3 and it is sparingly soluble in water (Herzfeldt and Kummel 1983). Its solubility change in the physiological pH range, as reflected by the volume required to dissolve a dose, ranges from 12 l to 100 ml as the pH increases from 1 to 7.4 (Corrigan 1997). After an oral dose, ibuprofen enters the systemic circulation mainly in its unchanged form (Mills *et al.* 1973). It has a short elimination half-life of only about two-hours and the therapeutic plasma drug concentration is 5 to 50 mg/l. The pharmacokinetics of ibuprofen is non-linear, thus, the bioavailability of ibuprofen does not increase correspondingly with the dose (Lockwood *et al.* 1983). This is explained by the intense and non-linear protein binding of ibuprofen, *in vitro* over 99 %. The HPLC technique for determination of ibuprofen from plasma samples is fairly easy (3.4.2.).

3.1.2. Metoclopramide hydrochloride

Metoclopramide hydrochloride (particle side < 300 um, BP 93, Dolder, Switzerland) was used as a model drug in hard gelatin capsules, reported in paper IV. Metoclopramide (mw. 300.0) is the methoxychlorinated derivative of procainamide (Buss *et al.* 1995) and further metoclopramide hydrochloride is a water-soluble salt form of the lipid-soluble metoclopramide. The pharmacological effects of the drug in man relate to at least two actions: a dopamine receptor-blocking effect (Pinder *et al.* 1976) and an effect on cholinergic mechanisms possibly increasing acetylcholine release (Hay 1977). Metoclopramide is a widely used drug in the treatment of vomiting and disorders of gastrointestinal motility. It is one of the least toxic antiemetics and its commonest side effect is drownsiness. Metoclopramide is rapidly and well absorbed in the gastrointestinal tract (Bateman1983) and in man it undergoes variable first-pass metabolism (oral bioavailability 32 to 100%).



3. Figure. Chemical structure of metoclopramide.

A single dose of 20 mg metoclopramide *per os* produces peak plasma concentration of approx. 40 ng/ml within 1 hour with interindividual variation due to first-pass hepatic metabolism. The usual therapeutic dosage of metoclopramide in adults is 10 mg four times daily. The elimination half-life is 2.6 to 5 hours in healthy volunteers (Harrington *et al.* 1983). Single-dose studies have suggested that the elimination of metoclopramide is dose-dependent in man after both *i.v.* (Graffner *et al.* 1979) and oral administration (Bateman *et al.* 1980). The half-life, for example, after a single 10 mg oral dose was 3.28 ± 1.32 hours and after a 20 mg oral dose 5.29 ± 1.61 hours ($p<0.05$). The bioavailability of metoclopramide was found to be significantly correlated to the ratio of free/conjugated metoclopramide in urine. Since metoclopramide N-4 sulphate is the major metabolite in man, these data suggest that sulphate conjugation (phase II) at the first pass through the gut wall or liver is the factor governing the bioavailability (Bateman *et al.* 1980).

3.2. Pharmaceutical excipients

3.2.1. Gel-forming additives

Hydroxypropylmethylcellulose and polycarbophil were used to control the drug release from the hard gelatin capsules. HPMC is widely used in peroral controlled-release dosage forms (Smal *et al.* 1994; Sirkiä *et al.* 1994 b, Halsas *et al.* 1998). Three viscosity grades of HPMC (Methocel^{R} K100, K4000; Dow Chemical, United Kingdom and K15M; Colorcon, United States) were used in the study (I, II). The viscosity grade of the polymer depends on the number of substituents in the structure of the polymer and the length of the cellulose chain.The viscosities of the HPMCs were 100, 4000 and 15000 mPas measured as a 2% aqueous solution at 20 ^{o}C.

Polycarbophil (Noveon^{R} AA-1, BF Goodrich company, United States) was used in studies II and IV. It is a synthetic hydrophilic resin of the polyacrylic acid type, a co-polymer of acrylic acid loosely cross-linked with divinyl glycol able to contain a considerable amount of water without dissolving. Carbopol resins are used e.g. in controlled-release dosage forms and to bioadhere in buccal, vaginal, opthalmic, intestinal, nasal, vaginal and rectal applications. Carbopol homopolymer resins are called in pharmaceutical literature as Carbomer, carboxyvinyl polymer, carboboxy polymethylene and polyacrylic acid. The Noveon^{R} series of carbopol resins are generically known as polycarbophil (Product Information, BF Goodrich). Polycarbophil is used to control drug release from oral formulations as well as to improve the rectal bioavailability of model drugs in both humans (Hosny E. 1988.) and dogs (Hosny and Robinson 1991, Hosny and Al-Angary 1995; Hosny *et al.* 1995).

3.2.2. Other excipients

Disodium hydrogen phosphate (DSHP; Friedel-De Haen AG, Germany) and sodium dihydrogen phosphate (SDHP; Friedel-De Haen, Germany) were used in the formulations according to the proportions of the phosphate buffer solution 7.5 in Ph. Eur. (III). Sodium phosphates are used as buffering agents in pharmaceutical technology.

Lactose (I, II, III, IV; Der Melkinindustrie Veghel, the Netherlands) and dicalcium phosphate (I; Oriola Oy, Finland) were used in the hard gelatin capsules as diluents. They are commonly used

in tablet and capsule formulations. Liquid Paraffin (I, II, III; Fina Europe, Belgium) was used to adjust the administration of the capsules. The Hard Fat, adeps solidus, (III, IV; Witepsol^{R} W45, Condea Chemie GmbH, Germany) was used for coating the capsules in order to facilitate the insertion.

3.3. STUDY FORMULATIONS

Three sizes of hard gelatin capsules were used in the formulations. Size 0: Studies I, II (Posilok, Elanco) and IV (Coni-Snap, Capsugel) and sizes 1 and 00: Study III (Coni-Snap, Capsugel). The amounts of the model drugs and the compositions of the products are presented in Table I.

Table I.

Model Drug	Study I				Study II						
	a	b	c	d	e	f	g	h	i	j	k
Ibuprofen	200	200	200	200	200	200	200	200	200	200	200
Excipient											
HPMC K15M	-	-	-	136	-	-	-	-	-	-	-
HPMC K4M	-	-	-	-	-	-	101	-	-	-	-
HPMC K100	-	-	-	-	-	103	-	-	-	-	-
Polycarbophil	-	-	-	-	-	-	-	68.8	32.9	15.8	5.1
Lactose	-	195	-	-	195	-	-	-	96.5	89.3	96.9
Dicalcium phosp.	-	-	178	-	-	-	-	-	-	-	-
Capsule size	0	0	0	0	0	0	0	100/00	75/250	85/150	95/50

Model Drug	Study III					Study IV	
	l	m	n	o	p	q	r
Ibuprofen	200	400	400	400	400	-	-
Metoclopramide HCL resp. metoclopramide	-	-	-	-	-	20	20
Excipient							
DSHP	-	-	-	28	47	-	-
SDHP	-	-	-	2	3	-	-
Polycarbophil	-	-	-	-	-	-	19
Lactose	71	100	65	29	25	391	356
Capsule size	1	00	00	00	00	0	0

The necessary amounts of the model drugs were weighed in a measuring cylinder and the excipients added in such a way as to obtain sufficients material for a batch of 100 capsules. The total volume was 50 ml for size 1 capsules (III), 68 ml for size 0 capsules (I, II, IV) and 95 ml for size 00 capsules (III). The powders were mixed manually, and the capsule bodies were filled

using a Feton apparatus. Some of the capsules were dipped in liquid paraffin before administration (I, II) or their were coated by dipping them into melted hard fat (mp. 35 °C) using tweezers (III, IV).

Three commercial products were used as reference formulations: a suppository product (Burana^{R} 500 mg, Orion, Finland) and a soft gelatine capsule product (Burana-Caps^{R} 400 mg, Orion, Finland) for the studies concerning ibuprofen (III) and a suppository product (Metopram^{R} 20 mg, Leiras, Finland) for metoclopramide (IV).

3.4. Dissolution studies

A number of *in vitro* dissolution techniques for determination of the dissolution rate of drug substances from suppositories and other rectal dosage forms are described in the literature. The techniques can be divided roughly into two groups; those not using membranes and those that do use membranes (Bornshein *et al.* 1985).

In the studies reported here, the dissolution of the model drugs was studied using the basket method described in USP 22-24. The dissolution medium was a phosphate buffer, pH 7.2 (I, II, III) for the ibuprofen formulations, except pure water for the ibuprofen formulations contained phosphate-buffers (III). Water was also used as the medium for the metoclopramide hydrochloride formulations (IV). The speed of rotation was 150 rpm (I, II, III) or 50 rpm (IV). 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 absorbances of the dissolution medium in 2-mm flow-through cells at 221 nm for ibuprofen (I, II, III) and at 275 nm for metoclopramide (IV) were controlled and recorded at the regular intervals by a computer dissolution system (TDS, LKB Biochrom Ltd., United Kingdom; I, II, III, IV). The amount of model drug released was measured from parallel in six samples.

3.5. Bioavailability studies

3.5.1. Experimental procedure

Six to eight healthy volunteers (age 19 to 40 years and weight 50 to 85 kg), who had given their written consent, participated in randomized, cross-over, single-dose studies. The studies were carried out in accordance with the provisions of the Declaration of Helsinki (World Medical Assembly, 1964) and its subsequent revisions. The volunteers were informed about the possible risks and side-effects of the drugs. The subjects trained in rectal administration before the study using exercise capsules containing only lactose as a diluent. During the study, side effect forms were filled out and collected. The study protocol was approved by the Ethics Committee of the University Pharmacy (Helsinki). The National Agency for Medicines (Finland) was duly notified.

Drug administration took place at 8 a.m. (Studies I, II) after overnight fast for at least 10 hours and afterwards in Studies III and IV, breakfast (7 a.m.) was permitted to facilitate and enable the normal bowel movement. A standard lunch was served 4 hours after drug administration. The wash-out period was at least one week. Blood samples were collected from an antecubital vein into heparinized tubes before drug administration and then 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12 (I, III) and 24 hours (II, IV) thereafter. Plasma was separated approximately 0.5 hour after collection by centrifugation (3000 g for 10 min) and stored at - 20 °C until analysis.

3.5.2. Plasma assay

The model drug plasma concentration was determined by means of high-performance liquid chromatography using a slight modification of the method of Avgerinos and Hutt (1986) for ibuprofen (I, II, III) and a slight modification of the method of Buss *et al.* (1990) for metoclopramide (IV). Each plasma sample was analysed in duplicate and the mean value was recorded.

The system was equipped with a pump and its controlling unit (Waters, Millipore, United States), a sample processor (Waters, Millipore, United States), a Waters Model 486 Tunable Absorbance Detector operating at 221 nm for the ibuprofen studies (I, II, III) and at 275 nm for the metoclopramide study (IV), and a Waters workstation. Sample separation was carried out in a

Lichrosorb RP-18 reverse phase column in the ibuprofen studies and a cyano column (Hibar Lichrosorb CN) in the metocloparmide study (IV). The isocratic mobile phase was acetonitrile and 0.1 M sodium acetate (35/65, pH 6.2, flow rate 2 ml/min) for the ibuprofen studies (I, II, III) and acetonitrile and 0.02 M potassium dihydrogen phosphate (40/60, pH 3.0, flow rate 1 ml/min) for the metoclopramide study (IV).

All the standard curves were found to be linear over the concentration ranges. The linear coefficient of determination were 0.998 or higher. The accuracy and precision of the method were investigated as recommended by Shah et al. (1992) by analysing six plasma concentrations 1, 20, 40 mg/l (I, II, III) and 5, 20, 80 ng/ml (IV). The detailed mean values are given in the original papers. The limit of quantitation was estimated to be 1 mg/l (I, II, III) and 5 ng/ml (IV). No interfering peaks were observed in the plasma blanks.

3.5.3. Pharmacokinetic parameters

In all the absorption studies the following pharmacokinetic parameters were assessed (Siphar, Simed, France): maximum plasma concentration (C_{max}), time to peak concentration (t_{max}), area under the concentration-time curve (AUC), mean residence time (MRT), apparent elimination half-life ($t_{1/2}$; only in Study IV) and lag-time (t_{lag}; only in Study III). The rate of absorption was evaluated also using the ratio C_{max}/AUC. For AUC values, 90%-confidence intervals with logarithmic transformation were calculated. The data were analysed using Student`s t-test or paired t-test; $t_{max}$-values were analysed with Wilcoxon`s matched-pairs rank test.

4. RESULTS AND DISCUSSION

4.1. Dissolution studies

Traditionally there are two classic cases in which release is limiting the absorption: these are immediate-release dosage forms containing drugs that are poorly soluble and controlled-release dosage forms (Dressman 2000). The USP dissolution method used was not only carried out to control the batch quality, but predominantly to investigate drug release mechanism with robust drug release profiles and to get supportive data for interpretation of bioavailability studies. It can be mentioned that three kinds of study formulations were tested in the dissolution studies: formulations containing rapidly dissolving diluents like water-soluble lactose (I, II, III, IV) or sparingly water-soluble dicalcium phosphate (I), or gel-forming diluents like hydroxypropylmethylcellulose (I, II) and polycarbophil (II, IV) and, finally, sodium phosphates as pH-regulative agents.

The **lactose-based** capsules were used as a model for immediate release formulation, but also as a reference for the controlled-release formulations in the *in vitro* and *in vivo* studies. The release of ibuprofen from the lactose capsules occurred completely in 10 minutes in all studies where the medium pH 7.2 was used (I, II). The dissolution profile of ibuprofen was similar when plain ibuprofen or dicalcium phosphate as a diluent was used in the capsules. These results are in accordance with the findings with tolfenamic acid studied by Eerikäinen and co-workers (1989) and with ibuprofen studied by Ojantakanen *et al.* (1990). The rate-limiting step in the dissolution process was the rupture of the capsule shell and penetration of water into the capsule. The dissolution of ibuprofen from lactose-based capsules was also studied in the medium containing pure water (III). This was the medium used for the ibuprofen capsules containing sodium phosphates as diluents where lactose-based capsules were employed as a reference product. The dissolution of ibuprofen from lactose-based capsules in pure water was still under 20% after 4 hours (III, Fig. 1.). This was clearly due to the low aqueous solubility of ibuprofen.

The dissolution of the water-soluble hydrochloride salt-form of metoclopramide in pure water was relative fast, more than 80% was released at 10 minutes (IV, Fig. 1.). Thus, the dissolution of metoclopramide hydrochloride occured at a slightly slower rate than the dissolution of sparingly

water-soluble ibuprofen in pH 7.2 phosphate buffer from lactose-based ibuprofen capsules but was, however, fair fast-releasing, reflecting the good immediate-release character *in vivo*.

Gel-forming excipients such as hydrophilic polymers hydrate on contact with water form a gelatinous clump over and within the powder bed (drug/diluent) from which the drug is released by diffusion and erosion mechanisms. This normally produces a slowly-disintegrating powder bed resulting in a sustained-release profile for the drug.

Three different viscosity grades of **hydroxypropyl methylcellulose** were studied (I, II): HPMC K100, K4M and K15M. Various studies have reported (Ojantakanen *et al.* 1992 and 1993, Smal et al., 1994, Ford *et al.* 1985a and 1985b) that the *in vitro* release rate of the drug from HPMC (and NaCMC-based) capsules is depended on the molecular weight (viscosity grade) of the polymer diluent and is further greatly affected by the drug/polymer ratio in the formulation. The amounts of HPMC used in capsules reported in this thesis were about the same as the amounts used by Ojantakanen *et al.* (1993) thus describing the same drug/polymer ratio. The K15M formulation liberated ibuprofen from the capsules relative slowly, with only 75% of ibuprofen being dissolved at 24 hours (I). Formulations based on K100 and K4M with lower viscosity characteristics liberated ibuprofen considerably faster: 100% of ibuprofen was dissolved in 4 hours with the K100-based capsules and in 16 hours with the K4M-based capsules (II, fig. 1.). It was noted that the tight mass was formed in the capsules when the viscosity of the HPMC rose. The K15M and K4M capsule formulations behaved as prolonged-release capsule formulations. The dissolution behaviour was in agreement with the results of a study by Ojantakanen (1992).

The dissolution of ibuprofen from capsules containing 100% of another type of gel-forming agent, polycarbophil (Noveon AA-1), was still incomplete after 24 hours. When the amount of **polycarbophil** in the capsules was decreased, the liberation of ibuprofen from the capsule mass and thereafter the dissolution of ibuprofen was accelerated. The ibuprofen was completely dissolved in two hours when the polycarbophil portion of the adjuvant mixture was 15%. Further when the polycarbophil portion was decreased to 5%, the ibuprofen was dissolved in 75 minutes (II, Fig. 1.). Thus the dissolution results showed that even a small amont of polycarbophil in the diluent mass retarded the dissolution of ibuprofen. These findings are in accordance with the results of the study by Hosny (1992) where propranolol hydrochloride and indomethacin were almost completely released in two hours or more quickly when the amount of polycarbophil in the matrix tablets decreased from 20 to 5%.

The dissolution of water-soluble metoclopramide hydrochloride from the capsules containing 5% of polycarbophil was biphasic (IV). Most of the drug (80 %) was released in 30 minutes and then the rate apparently decreased so that dissolution was still incomplete after 6 hours (IV, Fig. 1.). The terminal part of the dissolution curve was obviously due to the hydration effect of the polycarbophil prolonging the drug release. This kind of dissolution behaviour was not observed in our previous studies with ibuprofen. In conclusion, however, it was clearly noted that using different gel-forming excipients as diluents in capsules the release-rate of drugs, in this case a weak acid, ibuprofen, and a salt-form base, metoclopramide hydrochloride, can be modified and even controlled *in vitro*.

There are, at least in theory, three cases in which pH regulators or antacids may enhance the absorption of an acidic drug: enhancing the disintegration rate of the dosage form, enhancing the dissolution rate of the dosage form or, finally, enhancing the gastric emptying rate (Hannula *et al.* 1991). Two different **sodium phosphate-based** formulations were tested (III). The capsules contained 0 mg, 30 mg or 50 mg of a sodium phosphate mixture according to Ph. Eur. 7.5 phosphate buffer solution. Thus the ratio of disodium hydrogen phosphate to sodium dihydrogen phosphate was 14:1. The medium in the dissolution test was water because of the strong buffer capacity of medium pH 7.2 (Ph. Eur.). From the lactose-based hard gelatin capsules containing 0% of sodium phosphates, 17% of the ibuprofen dissolved in 4 hours in the water medium. Phosphates caused an increase of dissolved drug: from the formulation containing 30 mg of phosphates 27% of the ibuprofen dissolved in 4 hours and from the one with 50 mg of phosphates 31% of the ibuporfen dissolved in the same time (III, Fig. 1.).

Takubo *et al.* (1973) reported that addition of buffer reagents to the suppository is one way of enhancing the dissolution and absorption rates of sulfonamides and possibly other sparingly soluble drugs. Furthermore, Hannula *et al.* (1991) reported that the absorption of ibuprofen from sodium bicarbonate-based hard gelatin capsules was found to be significantly faster than that from capsules containing either lactose or dicalcium phosphate as diluent. The main reason for this was assumed to be the rapid *in vivo* disintegration of the sodium bicarbonate capsules. However, it may also be due to the enhanced dissolution of ibuprofen resulting from the rise of pH in the stomach. It is concluded that for rapid absorption of ibuprofen from capsules the water solubility and carbon dioxide formation of the additive are the most important factors. An increase in pH leading to an enhanced dissolution rate may potentiate this effect (Hannula *et al.* 1991). The dissolution findings reported in this thesis concerning sodium phosphates as

pH-regulators showed that they also act in such a way as to increase the dissolution rate of the acidic drug, ibuprofen.

4.2. Bioavailability studies

Bioavailability studies were performed in four phases, which are reported correspondingly in Studies I, II, III and IV. These studies with healthy volunteers were based on the *in vitro* studies carried out before the bioavailability study in question. Study design and the procedure including the plasma assay were always the same in the studies.

4.2.1. Evaluation as a rectal dosage form (I)

The primary aim for the bioavailability studies reported in this thesis was to evaluate the value of hard gelatin capsules in rectal administration in man. Ibuprofen was chosen as the model drug, because it is a safe and widely used drug which is known to be absorbed well throughout the gastrointestinal tract, including the colon (Parr *et al.* 1987, Wilson *et al.* 1989). In the first step two common diluents were selected as diluents in the capsules, *i.e.* water-soluble lactose and sparingly water-soluble dicalcium phosphate (I, Fig. 1.). The ibuprofen levels in plasma were just on the therapeutic level in most volunteers (over 10 mg/l), but the amounts of absorbed drug were comparatively low with proportionately large indivual variations (I, Fig 2.). On three occasions with lactose-based capsules and two with dicalcium phosphate based capsules, no drug was detectable during the 12-hour test period. The volunteers with no observed ibuprofen levels reported difficulties in the application. The difficulties could be caused by normal bowel movement or, for example, sticking of the capsule to the outer sphincter of the rectum. When these capsules were compared with the similar capsules given orally (Ojantakanen 1990), it was noticed that the bioavailability of the rectally administered capsules was only 55-60% of that with oral capsules. These findings was thought to be due to the difficult administration technique.

On the basis of these results our aim was next to investigate whether it is possible to improve the bioavalability of ibuprofen by training in the administration technicue and also by facilitating the insertion of the capsules. The capsules were dipped into liquid paraffin before application. The subjects also practised the administration technique using pure lactose capsules before participating in the bioavailability studies. A bioavailability test was then carried out with capsules containing ibuprofen but no diluent. It was observed that the bioavailability of ibuprofen improved to the same extent as with the same oral capsules and ibuprofen suppositories (Ojantakanen *et al.* 1990; Eerikäinen *et al.* 1994). The bioavailability of the non-dipped capsules

compared with the dipped ones was about 87%. Training alone improved the reproducibility of ibuprofen absorption by approximately 35%. Further, the use of a glidant facilitated the administration, increased the amount of drug absorbed and decreased the variations in AUC and C_{max} (I, Fig. 4., Table III). After this positive finding the subjects in the extension studies practised the administration beforehand and used liquid paraffin to facilitate the application, thereby improving the compliance.

Next, a bioavailability test was carried out in order to compare oral (plain ibuprofen) and rectal routes (lactose-based capsules) for the administration of ibuprofen in hard gelatin capsules. In this phase an additional aim was to investigate whether it is possible to modify the release of ibuprofen with hydrophilic polymer (HPMC K15M). HPMC K15 M was chosen because it was found to be an ideal polymer for sustaining the oral absorption of ibuprofen from hard gelatin capsules (Ojantakanen 1993).

The mean relative bioavailability of the rectal route with eight subjects was 99% (90% CI 0.81-1.18) compared with oral administration. The conclusion was that the bioavailabilty of ibuprofen was not dependent on the two administration routes studied (which had the same bioavailabilities) but rather on the diluents in the capsules. This means that these routes could be considered bioquivalent to ibuprofen. This was also recently confirmed with ibuprofen HPMC capsules studied in our laboratory by Honkanen (2001), where $AUC_{0\text{-}24h}$ values for rectal administration were of the same magnitude or even higher than after oral drug administration.

However, it was seen that there was a typical time lag of 0.5 to 1 hour at the beginning of the rectal absorption phase, which was seen also in other pharmacokinetic parameters (I, Table IV), indicating a lower rectal absorption rate of ibuprofen. This was probably due to the longer disintegration time of the capsule and subsequent dissolution of the ibuprofen. Hagenlocher *et al.* (1987) have reported that the hard gelatin capsule is only a fast-dissolving drug container in the rectum and has no effect on the absorption characteristics of the drug. On the other hand, Eller *et al.* (1989) reported that the absorption of rectally administered ibuprofen from solution was, even though it was relatively well absorbed in healthy volunteers, still slower than after oral administration. Interestingly, in three subjects the kinetics of absorption switched from first order to zero order in Eller`s study. This may be due to the large dose and limited surface area, thus saturating the ability of the rectal membranes to allow ibuprofen to pass through. These

might be, among the other things like lag-time, the main reasons for the slightly more prolonged release of ibuprofen in rectal administration compared with peroral administration.

When HPMC K15M polymer was used in the capsules as a diluent, the absorption of ibuprofen was clearly lower and the bioavailability was 68% of that for lactose-based capsules. The formulation behaved like a prolonged-release product, although the bioavailability was reduced too much for it to be acceptable. Nevertheless, this convinced our study group to investigate in more detail the possibility of developing a slow- or prolonged-release formulation of hard gelatin capsules for rectal administration.

4.2.2. Development of slow- or prolonged-release formulations using ibuprofen as a model drug (II)

The first part of the study showed that hard gelatin capsules are of value as a rectal dosage form in man. However, proper attention must be paid to training in the application technicue, and the use of a glidant is also important. Another important observation was that it is possible to control the absorption rate and thereafter the extent of the bioavailability of ibuprofen by using different diluents in hard gelatin capsules for rectal administration. This is contrary to the results for the different oral capsule formulations studied earlier in our laboratory (Ojantakanen *et al.* 1990 and 1993, Hannula *et al.* 1991). Then it was observed that the diluents used in peroral capsules had no effect on the extent of the bioavailability of ibuprofen, but only on the absorption rate of ibuprofen. This phenomen is obviously due to the extraordinary absorption site in the rectum compared with the other parts of the gastrointestinal tract.

4.2.2.1. Hydroxypropyl methylcellulose-based capsules (II)

Ojantakanen and Smal studied in our laboratory the possibility of formulating the prolonged-release hard gelatin capsule preparations for oral administration in man (Ojantakanen *et al.* 1993) and dogs (Smal *et al.* 1994) using different HPMC-grades as excipients. In this section we investigated whether it is possible to produce an adequate prolonged-release ibuprofen formulation for rectal administration using HPMC K100 and K4M as diluents in the capsules.

Because of the findings of our previous studies with HPMC K15M (I), lower viscosity grades of HPMC were chosen as excipients in the capsule formulations in order to control the release of ibuprofen. Testing showed that there were no substantial differences in bioavailability between these two HPMC-viscosity grades (II, Fig 2., 3.). It was noticed when comparing with lactose-based capsules, that absoption phase was prolongened. The bioavailability of the K100 capsules was 0.97 (90% CI 0.79-1.14) and 0.83 for the K4M capsules (90 % CI 0.65-1.00). On the basis of bioavailability tests and individual variations (II, Fig. 3.), it can be said that the K100 capsules behaved acceptably as prolonged-release capsules and were bioequivalent to the reference capsules. However, no statistical differences were found between the pharmacokinetic parameters of these two lower HPMC-grades. The behaviour of the absorption curves was roughly similar to the corresponding oral formulations in the study of Ojantakanen *et al.* (1993), but at a slightly lower degree In the earlier study (I), it was discovered that the bioavailibility of HPMC K15M-based capsules was only 50% compared with the reference capsules (I).

A recent study in our laboratory (Honkanen *et al.* 2001) concerning the differences between two different capsule shells, gelatine and HPMC, showed that there were no statistically significant ($p>0.05$) differences between the capsules. In addition, changing the viscosity grade of the HPMC diluent did not alter the biopharmaceutical characteristics of the rectal formulations. This means that the dissolution test did not predict *in vivo* behaviour of the capsules when a rectal dosage form was used, although good *in vitro/in vivo* correlation existed when the oral route was used. However, on the basis of the results reported in this thesis it can be assumed that with certain reservations the lower HPMC grades can be used to modify the release of ibuprofen in rectal hard gelatin capsules in preference to the higher HPMC grades. The *in vitro/in vivo* correlation was not satisfactory.

4.2.2.2. Polycarbophil-based capsules (II)

It has been reported that the rectal administration of ibuprofen with polyacrylic acid gel base has been shown to be an effective method of administration (Hirano *et al.* 1980). Polyacrylic acid gel base, a carboxyvinyl polymer, can be adjusted to a suitable pH and viscosity, and unpleasantness during rectal administration is minimal (Morimoto *et al.* 1980). Concequently, when flurbiprofen, ketoprofen and indomethacin gel preparations with a polyacrylic acid aqueous gel base were administered to rats, the control of plasma concentration against time was relatively easy.

Furthermore, this gel base was effective in the rectal administration of polypeptides such as insulin and calcitonin. Also, gel preparations were highly useful as preparations administered rectally with reduced side-effects and prolonged action. (Morimoto *et al.* 1983, Kazuhiro Morimoto 1987.).

Hydrophilic polymers that bind to the gastric mucin or epithelial cell surface might be useful in drug delivery for the purposes of retaining a dosage form in the gastrointestinal tract and increasing the intimacy and duration of contact of the drug with the absorbing membrane. Polycarbophil has previouly been shown to have such bioadhesive properties in the rat stomach and small intestine. However, it has been reported that although covalent binding of polymers to the mucin epithelial surface is a possible strategy for bioadhesive dosage forms, the desirability of this approach is reduced by concern over potential toxicity and the difficulties involved in preparing suitable dosage forms. Thus, polymers that adhere through electrostatic interactions, dispersion forces and other non-covalent interactions are preferred for drug delivery purposes (Longer *et al.* 1985).

The effect of amount of polycarbophil on the bioavailability of ibuprofen was studied (II). The lactose to polycarbophil ratio in the capsules varied. Figure 4. (II) shows that with the capsules which contained only polycarbophil as a diluent (100%) no plasma levels were detected. With the capsule formulation containing 15% of polycarbophil the bioavailability was 35% (CI 90%). Further, when the polycarbophil to lactose ratio was only 5:95, the bioavailability of the hard gelatin capsules increased to 98% (90% CI 0.71-1.25). This formulation best fulfilled the requirements for a prolonged-release formulation also in respect of the different pharmacokinetic parameters (C_{max}, t_{max}, MRT, C_{max}/AUC). So when the amount of polycarbophil was decreased and the proportion of lactose raised, the bioavailability of ibuprofen increased. Further, it was considered that by clarifying the *in vitro/in vivo* characteristics of the polymers and adjusting their amounts in the capsules, it is possible to produce prolonged-release formulations for rectal administration when ibuprofen is used as the model drug. However, the *in vitro* behaviour of the capsules gave a relatively weak prediction of the rectal absorption of ibuprofen in man.

These findings concerning the dose adjustment of polycarbophil are in agreement with findings with polyethylene suppositories containing polycarbophil as gel-forming polymer and indomethacin as the drug (Hosny and Al-Angary 1995). They reported that higher

concentrations of polycarbophil (5 to 8%), improved the sustaining action of the polycarbophil but decreased blood levels and bioavailability, whereas lower concentrations (0 to 5%) improved blood levels and bioavailability, but did not significantly improve the sustaining effect. They concluded that the major thing in the formulation of suppositories is to use the optimum concentration of polycarbophil, which achieves an improvement in blood levels, sustaining action and bioavailability.

4.2.3. Effect of sodium phosphates (III)

It is typical of rectal administration that there is a time lag of 0.5 to 1 h at the commencement of absorption phase compared with oral administration. This is also most evident in the administration of hard gelatin capsules. There are several reasons for the rectal time lag: e.g. lack of buffer capasity and limited amount of fluids in the *rectum* (Newton 1987). It was also assumed that the rate-limiting step in the absorption process in the rectum would be the dissolution of the drug. Therefore the aim of this part of the study was to investigate whether it is possible to increase the dissolution rate of ibuprofen by adding small amounts of sodium phosphates as buffering additives in the capsules. Several studies have been reported on the possibility of facilitating the liberation and absorption of a drug using pH-adjusting agents as additives in suppositories (Takubo *et al.* 1973, 129; Moolenaar *et al.* 1984). These mechanisms can be categorized as increasing the dissolution rate of the drug or the proportion of the undissociated form of the drug. An explanation for the favourable rectal absorption of codeine base (pKa=8.1) from an alkalized suppository was that most of the drug was in the non-ionized form thus resulting in a favourable driving force for absorption (Moolenaar *et al.* 1983.)

Three different amounts of the adjuvants (0, 30 or 50 mg per 400 mg of ibuprofen) were administered in lactose-based capsules (III, Table I) to volunteers. It was noticed that time lag at the commencement of the absorption phase was diminished by approx. 12-18 minutes with phosphate capsules. The decrease was greater with the formulation containing 50 mg of phosphates. Also the bioavailability of the ibuprofen was slightly increased *in vivo* when the phosphates were used in the capsules (III, Fig. 2.-3.). The absorption rate and, evidently, the dissolution of ibuprofen was improved with the phosphate capsules (compared with the reference capsules) as described by the pharmacokinetic parameters: t_{max} (4.3 to 3.3-3.1 h), C_{max}/AUC (0.18 to 0.21-0.23) and MRT (4 to 3.4-3.5 h). The bioavailability of the 30 mg

phosphate formulation was 1.19 (90% CI 0.90-1.41) compared with the reference capsules. It was interesting that the bioavailability of the formulation containing 50 mg of phosphates was 95% (90% CI 0.67-1.23). However there were no statistically significant differencies between the AUC values. The phosphates had no diminishing effect on individual variations.

The *in vivo* results showed that the bioavailability was highest with the formulation containing 30 mg of phosphates. That result differed from the *in vitro* results. Thereafter it was considered that part of the ibuprofen must be in a molecular form in order to be absorbed from the rectum to the blood circulation. The unionized form of ibuprofen was probably diminished considerably more in the formulation containing 50 mg of phosphates and therefore the portion of ibuprofen absorbed was reduced (III, Fig. 2. and Table II). However, it was concluded that the primary mechanism was an increase in the dissolution rate. This caused a decrease in the lag time and also might be dued to an improvement in the bioavailability of ibuprofen when 30 mg of sodium phosphates were used as additives in the capsules. These observations concerning the dissociation reactions of the capsule diluents are in agreement with the findings of Hannula *et al.* (1991).

4.2.4. Number of capsules (III)

In our earlier studies reported in this thesis the drug dose of 400 mg was administered in two 0-size capsules of 200 mg. Now the aim was to investigate if there is any difference in the bioavailability when ibuprofen is administered either in one larger 00-size capsule (0.95 ml) or in two smaller ones (0.50 ml). The old comprehension exists that the main thing in drug therapy is the amount of drug in a single-dose. Other factors, like the number of dosage forms given at the time, are less significant. This was considered to be of special importance in rectal administration, because of the challenging absorption circumstances in the rectum. Schoonen *et al.* (1979) stated that as far as slowly dissolving drugs are concerned in the fatty suppository vehicle, increasing the drug concentration in the vehicle or enlarging the volume of the vehicle chosen may influence the rectal absorption rate in different ways.

On the basis of bioavailability studies, it was seen that the bioavailability of ibuprofen was 25 % greater after administration of two smaller capsules (III, Fig. 4. and 5., $p<0.05$). No statistically significant differences were obtained in the pharmacokinetic parameters describing the

absorption phase: C_{max}, MRT and t_{max} values (Table III). The individual variations were slightly greater after the administration of one bigger 00-size capsule than after administration of two smaller capsules.

This finding with hard gelatin capsules is in agreement with recent results with paracetamol suppositories (Närvänen *et al.* 1998). Närvänen *et al.* found that a greater total mass of suppositories, two 500 mg suppositories weighting 4,06 g, leads to improved spreading of the melting mass in the rectum compared with one suppository (2,90 g). In addition, using two separate suppositories or, analogically, hard gelatin capsules instead of one means that the second dosage form pushes the first one deeper into the rectum so that the absorption area increases.

This finding might have some clinical importance, for example when using drugs with a narrow therapeutic window. However, most of the subjects preferred the administration of one 00-size capsule, because the application was simpler. Better compliance constituted a more important argument, with further studies indicated particularly because of the comparatively unfamiliar manner of administration.

4.2.5. Comparison to commercial ibuprofen products (III)

The last question considered in Study III, was the relative bioavailability of the hard gelatin capsule formulation containing 30 mg of sodium phosphates *versus* a commercial suppository (Burana^{R}) or a soft gelatin capsule (Burana-Caps^{R}) administered rectally. In this case, the hard gelatin capsules were pre-coated with hard fat (Witepsol W45) instead of being dipped into liquid paraffin just prior to administration (III, IV). The melting point of the hard fat was 35 ^{o}C, and it melted almost instantly after inserting the capsules into the dissolution vessel. Thus, the coating did not affect the release of the ibuprofen. The capsule size 00 (0.95 ml) was chosen for the study because of the easier application and better compliance.

The dose corrections were made after the bioavailability test by simple calculations in order to compare the results between the products. The bioavailability of the commercial suppository was 99% (90% CI 0.78-1.21) compared with the hard gelatin capsules. The bioavailability of rectally administered soft gelatin capsules was 87% (90% CI 0.68-1.06) compared with the hard gelatin

capsules as reference. For the hard gelatin capsules the t_{max}-value was 2.6 hours, while for the soft capsules it was only 1.4 hours (III, Table IV.). The mean peak plasma levels of the formulations were about the same, varying between 27.1 mg/l for the suppository, 27.1 for the soft gelatin capsules and 27.8 for the hard gelatin capsules. These levels are in agreement with the reports concerning oral commercial ibuprofen products: 23.3 and 30 mg/l for tablets (Karttunen *et al.* 1990) and 31.4 mg/l for capsules (Gillespie *et al.* 1982).

The time lag was absent at the commencement of concentration time curves for the soft gelatin capsules, the reason for this was evidently that the ibuprofen was dissolved in the capsule liquid. On the basis of the absorption (Figs. 6. and 7.), it can be also stated that there was no visible time lag for the suppository product either. This was probably due to the formulatory factors of the product The bioavalability test showed that the precoated hard gelatin capsule formulation was nearly bioequivalent to the commercial suppositories. Furthermore, the bioavailability of the hard gelatin capsules was higher compared with the commercial soft gelatin capsules. From this point of view the hard gelatin capsules once again proved to be a worthy rectal dosage form for the administration of ibuprofen in man.

4.2.6. Development of modified-release formulations using metoclopramide hydrochloride as a model drug (IV)

The previous studies in this thesis have shown that ibuprofen can be adequately administered rectally in hard gelatin capsules (I, II, III). However, there have existed a clear time lag at the beginning of the absorption curve in the bioavalability studies. Further, it was possible to shorten this delaying phenomen by using small amounts of buffering additives in the capsules (III). It was also shown that it is possible to prepare an adequate prolonged-release formulation using hydrophilic polymers as diluents in rectally administered hard gelatin capsules (II). The main aim of the final phase (IV) of the thesis was to clarify what happens if an acidic drug, ibuprofen, with spraringly water-soluble characteristics is replaced with a freely water-soluble hydrochloride of a basic drug, metoclopramide hydrochloride. The more specific aim was to determine whether it is possible to develop both immediate-release and slow-or prolonged-release rectal formulation from hard gelatin capsules containing metoclopramide hydrochloride as the active ingredient. A commercial suppository was used as a reference product. The study formulations are presented in Table I (IV).

4.2.6.1. Development of an immediate-release formulation

The mean bioavailability of metoclopramide for the hard gelatin capsules was 0.93 (90% CI 0.78-1.07). Thus the normal criterion for bioequivalence, 0.80-1.25, was not fulfilled. There were also clear time lags of 0.5 to 1.5 hours with hard gelatin capsules, this was not obtained with the metoclopramide suppositories. Due to the lag, a mean transition of 1.5 hour in t_{max} values existed between the two products (Table III). The t_{max} value, however, was slightly lower for the metoclopramide capsules compared with the ibuprofen capsules containing 30 mg of phosphates (III). The reason for this was evidently the rapid dissolution of the freely water-soluble salt form of the drug. Hermann reported that in passive absorption processes it is necessary for a drug to reach rapidly a high concentration in the rectal mucous membrane compartment. This is obviously the reason why, for instance, certain salts of organic acids which are fairly soluble in water are absorbed faster than their undissociated free acids. Once again, the time lag is presumably due to several factors in the rectum: slower disintegration of capsule shell, liberation and dissolution of the drug from the powder bed and subsequent spreading characteristics in an absorption environment containing only a couple ml of fluid and covering a relatively small area. Comparing the absorption rate of metoclopramide from the hard gelatin capsules with the reference product by the pharmacokinetic parameters MRT and C_{max}/AUC which describe the absorption rate without time lag, there were no real differences. (IV, Table III, Fig. 2.). The interindividual variation was greater with the hard gelatin capsules. The C_{max} values of these two formulations were similar (approx. 50 ng/ml) and also the AUC values were about the same. Thus it could be suspected that the acceptable confidence interval for bioavailability might be reached with a greater number of subjects.

The peak drug concentrations in plasma of this study correspond to the findings of Block *et al.* (1981); where C_{max} values were approximately 60 ng/ml wfor suppositories (dose 40 mg), 70 ng/ml for tablets (dose 26.7 mg) and 65 ng/ml for oral drops (dose 26.7 mg). However, compared with our study, their AUC values were slightly higher for the oral formulations, but lower for the suppositories. In Block`s study the rectal bioavailability of the metoclopramide hydrochloride in suppository was slightly lower (53 %) than for the different oral dosage forms (76-79%) compared with *i.v.* administration. The study showed that the rectal absorption was incomplete, although several reports indicate also variable oral bioavailabilities (Bateman *et al.* 1979 and 1980). Block *et al.* concluded that, in order to achieve a similar therapeutic effect, a higher dose is required for rectal than for oral application. On the contrary, Vergin *et al.* (1990)

reported a bioavailability of 70 % for metoclopramide suppositories, thus corresponding closely with that following oral administration of immediate-release tablet formulations (Harrington *et al.* 1983, Ross-Lee *et al.* 1981, Bateman 1983, Vergin *et al.* 1983, Berner *et al.* 1984, Block *et al.* 1981). The reduction in the amount of metoclopramide available to the systemic circulation after rectal administration is believed to be due the first-pass metabolism rather than poor absorption when compared with intravenous total plasma clearance: this would be analogous to findings following oral application (Vergin *et al.* 1990). Thus Block`s conclusion that in rectal administration of metoclopramide hydrochloride a higher dose of drug is required for a similar therapeutic effect than with oral administration, is slightly contradictory.

4.2.6.2. Development of slow- or prolonged-release formulation

Metoclopramide as a high-clearance drug causes considerable interindividual variation after oral medication (Ross-Lee *et al.* 1981, Bateman *et al.* 1979, Bateman 1983). It is, however, predominantly absorbed throughout the gastrointestinal tract and would therefore give an opportunity for the develoment of new rectal dosage forms (Vergin *et al.* 1990). The development of retard forms of metoclopramide could also be important due to the necessity of constant blood levels (Bateman *et al.* 1979).

In order to obtain a slow- or prolonged-release product, a formulation with the 5% replacement of lactose with polycarbophil was prepared analogously with the studies on ibuprofen. The absorption curves showed that the polycarbophil-based formulation clearly sustained the absorption of metoclopramide (IV, Fig. 2.). This was also evident when considering the pharmacokinetic parameters reflecting the absorption rate, like t_{max}, MRT and C_{max}/AUC; e.g. transition of t_{max} values was over 2.5 hours compared with the lactose-based capsules. Also the half-life of the terminal elimination phase ($t_{1/2}$) was 1.5 hour longer than fot the other two products, thus indicating that polycarbophil-based capsules behaved as a true prolonged-release formulation, not only as a slow-release product. However, there was a clear increase of the mean time lag from 0.75 to 1.5 hour, which can be considered a negative point. This fact, however, is probably not of major clinical significance in long-term drug therapy. Once again it was seen that the *in vitro* results did not predict adequately the *in vivo* behaviour of the rectally administered hard gelatin capsules. This was also probably due to the high-clerance character of metoclopramide, not just the rectal route. There are several studies reporting difficulties in

finding a dissolution procedure that would correlate with the *in vivo* data with ibuprofen (Dash *et al.* 1988, Vidgren *et al.* 1991). The biphasic dissolution character of polycarbophil-based metoclopramide capsules was not seen in the *in vivo* absorption curves (IV, Fig. 2). It was seen that polycarbophil can be used as a suitable polymer in an adjusted ratio in hard gelatin capsules to control the release of metoclopramide hydrochloride.

Polycarbophil-based and lactose capsules containing metoclopramide hydrochloride were bioquivalents in respect of the AUC values (1.00; 90% CI 0.86-1.18). The mean bioavailability was 0.94 (90% CI 0.78-1.08) compared with the reference suppository. When ibuprofen was used as the model drug, the bioavailability of suppository was 0.99 (CI 0.78-1.21) compared with the hard gelatin capsules. Although there are clear differences in solubility between these two model drugs, the findings were about the same: there is a clear lag time at the commencement of drug absorption with hard gelatin capsules, it is possible to modify the release of these drugs with different solubility characteristics by using different additives in the capsules and the absorption profiles of the model drugs are similar (t_{lag}, t_{max}). It can thus be concluded that the solubility of the model drug is not so dominating in the rectal absorption process with hard gelatin capsules. The mean bioavailability is not dependent on the administration route, while the peak drug levels in plasma and the areas under the concentration-time curves corresponded to the studies on oral ibuprofen and metoclopramide formulations. The success of rectal administration using hard gelatin capsules proved to depend entirely on biopharmaceutical factors including, for example, proper administration technique, choice of adequate drug, employment of suitable excipients and adjustment of their amounts together with other formulatory factors.

5. CONCLUSIONS

1. In rectally administered hard gelatin capsules, compounds with different biopharmaceutical characteristics can be administered adequately. Hard gelatin capsules are of value as a rectal dosage form and offer a simple and effective means of drug therapy. However, attention must be paid to the right administration technique, including training in application.

2. It is possible to modify the drug release from rectally administered hard gelatin capsules using suitable pharmaceutical excipients and adjusting their amounts in the capsules. In this study, adequate immediate-release and prolonged-release formulations were obtained using ibuprofen and metoclopramide as model drugs.

3. The solubility of the drug in the rectum is an essential factor for it to dissolve in the rectal fluid and to permeate through the mucosal barriers into the systemic blood circulation. However, the solubility is not so dominating, the formulatory factors of the dosage form also proved to be of particular importance in the absorption of the sparingly water-soluble ibuprofen and freely water-soluble metoclopramide hydrochloride.

4. The bioavailability of ibuprofen and metoclopramide hydrochloride in rectal hard gelatin capsules can be kept comparable with that of peroral dosage forms. So the rectal administration route with hard gelatin capsules is not merely an alternative, but also a prime choice in certain clinical situations. However, a clear time lag of 0.5 to 1.5 hour was noticed at the commencement of drug absorption; this normally causes a slightly slower absorption phase in the administration of hard gelatin capsules.

5. It is known that a poor *in vitro*/*in vivo* correlation is a problematic issue in rectal administration. This was also confirmed with the hard gelatin capsules. *In vitro* studies are not enough in the development of drug formulations, but can offer essential supportive data.

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