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DEVELOPMENT AND BIOPHARMACEUTICAL EVALUATION OF PRESS-COATED TABLETS TAKING ACCOUNT OF CIRCADIAN RHYTHMS OF DISEASE

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Academic Dissertation
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Abstract

Many functions of the human body vary considerably during a day. These variations cause changes both in pathological state of diseases as well as in drug plasma concentrations. This fact needs to be taken into account in developing dosage forms. Nocturnal symptoms also result in problems as regards timing of drug administration. Plasma levels of a drug should be highest when symptoms are most severe. In asthma and rheumatoid arthritis, for example, symptoms are usually worst from 04:00 to 06:00.

The main objective of the studies described was to develop a time-controlled release formulation based on a press-coating technique. The intention was that the formulation is administered in the evening at 22:00, which provides treatment for diseases in which symptoms are experienced in the early morning hours (i.e. chronopharmacotherapy).

The coats contained a hydrophilic polymer (sodium alginate or hydroxypropylmethylcellulose (HPMC)) to control drug release. Cores were immediate-release formulations containing all or most of the drug dose. Two model drugs were used, ibuprofen (a weak acid) and pseudoephedrine (a weak base) as the hydrochloride. Drug release was studied in vitro. Bioavailability of the formulations and variation in pharmacokinetics of ibuprofen with the time (i.e. chronopharmacokinetics) were studied on healthy volunteers. Effect of a light meal on bioavailability was also studied.

The time-controlled release dosage form containing HPMC allows time to peak plasma level to be adjusted to 6 to 8 hours after administration. Amount of HPMC used, HPMC viscosity grade and the combination of viscosity grades selected were most important factors controlling drug release and absorption from the dosage form. The dosage form functions with both ibuprofen, which is sparingly soluble in water, and pseudoephedrine hydrochloride, which is the freely soluble in water. In vitro/in vivo correlation studies show that time to peak concentration values are approximately predictable from a dissolution parameter. Amount of bioavailability tests could be reduced when the present formulation is developed.

Peak plasma level of ibuprofen from a press-coated test formulation was obtained earlier after the morning dose than after the evening dose. Time related variation in ibuprofen pharmacokinetics was found to depend on the press-coated formulation, not only of the drug substance as such. Rate and extent of bioavailability was decreased when the formulation tested was administered with a light meal. An evening meal is recommended to be eaten at least two hours before any evening dose of time-controlled release formulations, to guarantee that food intake has no effect on drug absorption.

In developing time-controlled release formulations to be used in treatment of nocturnal symptoms it is crucial that bioavailability tests are also conducted in the evening. The present dosage form is a potential choice when a drug is aimed for chronopharmacotherapy According to present study, drug formulation can cause circadian variation in drug plasma levels. The term "chronobiopharmaceutics" is suggested to describe this kind of phenomenon.

List of original publications

This dissertation is based on the following studies:

I Halsas M., Ervasti P., Veski P., Jürjenson H. and Marvola M. 1998. Biopharmaceutical evaluation of time-controlled press-coated tablets containing polymers to adjust drug release. Eur. J. Drug Metabol. Pharmacokinet. 23, 190-196.

II Halsas M., Simelius R., Kiviniemi A., Veski P., Jürjenson H. and Marvola M. 1998. Effect of different combinations of HPMC on bioavailability of ibuprofen from press-coated time-controlled tablets. S.T.P. Pharma Sci. 8, 155-161.

III Halsas M., Hietala J., Veski P., Jürjenson H. and Marvola M. 1999. Morning vs evening dosing of ibuprofen using conventional and time-controlled release formulations. Int. J. Pharm. 189, 179-185.

IV Halsas M., Penttinen T., Veski P., Jürjenson H. and Marvola M. 2001. Time-controlled release pseudoephedrine tablets: bioavailability and in vitro/in vivo correlations. Accepted for publication in Die Pharmazie.

The studies are referred to in the text by the Roman numerals I-IV.
Some unpublished results are also reported.

1. Introduction

The goal in drug delivery research is to develop formulations to meet therapeutic needs relating to particular pathological conditions. Variation of physiological and pathophysiological functions in time has brought a new approach to the development of drug delivery systems. Research in chronopharmacological field has demonstrated the importance of biological rhythms in drug therapy. Optimal clinical outcome can not be achieved if drug plasma concentrations are constant. If symptoms of a disease display circadian variation drug release should also vary over time. Utilisation of different technologies in development of time-controlled, pulsed, triggered and programmed drug delivery devices has been undergoing recent years. Formulations should be justified by biopharmaceutical and pharmacokinetic study in order to choose the best hour for administration. Another point raised by circadian variation of physiological function is that drug pharmacokinetics can also be time-dependent (i.e. chronopharmacokinetics). Both variations in a disease state and in drug plasma concentration need to be taken into consideration in developing of drug delivery systems intended for treatment of disease with adequate dose at appropriate time.

1.1. Chronobiology and chronopharmacotherapy of disease

Up to now design of drug delivery systems has been governed by the homeostatic theory. This theory is based on the assumption of biological functions that display constancy over time. However, chronobiological studies have established circadian rhythm for almost all body functions, e.g. heart rate, blood pressure, body temperature, plasma concentration of various hormones, gastric pH and renal function. It has become apparent that rhythmic processes are indispensable for treatment of human diseases. As well as physiological functions vary over time pathological state of disease have circadian rhythms. Epidemiological studies document the elevated risk of disease symptoms during 24-hour cycle (Fig. 1).

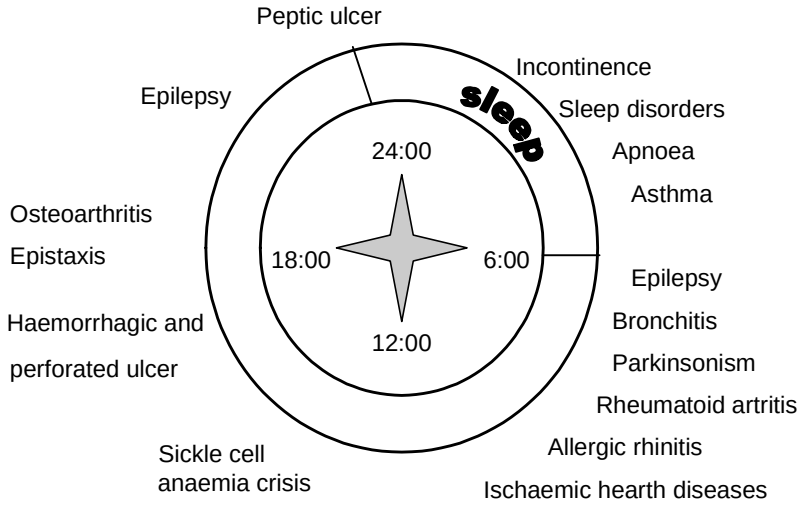

Figure 1. Diseases displaying circadian rhythm (Modified from Smolensky and Labrecque 1997)

Many of circadian dependent diseases display symptoms in early morning hours or in the morning at awakening. It is well known that patients with asthma experience symptoms at night. Dyspnoea and peak of expiratory flow (PEF) values have been found to become worse during the night (Barnes 1985, Dethlefsen and Repges 1985). Most asthma attacks occur at 04:00 to 06:00 hours. Nocturnal asthma is a complex interaction of several coincident circadian rhythms e.g. hydrocortisone and adrenalin secretion. Symptoms of allergy, e.g. runny nose, stuffy nose, wheezing and sneezing are also most frequent in the morning before breakfast (Smolensky et al. 1981). Ischaemic hearth diseases, such as angina, myocardial infarction and stroke manifests itself several times more frequent from 09:00 to 11:00 hours than any other time of the day of night (Fox and Mulcahy 1991, Cohen et al. 1997). Rapid increase in blood pressure is largely responsible for these attacks. In both hypertensive and normotensive individuals blood pressure arises notably before awakening (Millar-Craig et al. 1978). In most patients with essential hypertension blood pressure generally declines from mid-afternoon and reaches a minimum between midnight and 03:00 hours. Morning stiffness in observed rheumatoid arthritis is one of the diagnostic criteria of the disease. Joint size and stiffness and pain are greatest on awakening and in the early morning hours when grip strength is lowest (Kowanko et al. 1982). Circadian rhythm of levels of interleukin-6 might correspond to the rhythm of symptoms of rheumatoid arthritis (Arvidson et al. 1994).

In chronopharmacotherapy (timed drug therapy) drug administration is synchronised with biological rhythms to produce maximal therapeutic effect and minimum harm for the patient. By basing drug delivery on circadian patterns of diseases drug effect can be optimised and side effects can be reduced. If symptoms occur at daytime a conventional dosage form can be administered just prior the

symptoms are worsening. If symptoms of a disease became worse during the night or in the early morning the timing of drug administration and nature of the drug delivery system need careful consideration.

1.2. Chronopharmacokinetics

Chronopharmacokinetics involves study of temporal changes in drug absorption, distribution, metabolism and excretion. Pharmacokinetic parameters, which are conventionally considered to be constant in time, are influenced by different physiological functions displaying circadian rhythm. Circadian changes in gastric acid secretion, gastrointestinal motility, gastrointestinal blood flow, drug protein binding, liver enzyme activity, renal blood flow and urinary pH can play role in time dependent variation of drug plasma concentrations (Kumar 1986, Lemmer and Nold 1991, Bruguolle and Lemmer 1993). Numerous chronopharmacokinetic studies have been conducted over the last 20 years. The results of these studies demonstrate that time of administration affects drug kinetics.

Studies in man have been reported, particularly in relation to cardiovascular active drugs, non-steroidal anti-inflammatory drugs (NSAIDs), local anaesthetics, anticancer drugs, psychotropic drugs, antibiotics and anti-asthmatic drugs (Lemmer 1991). Most of the drugs seem to have higher rate or extent of bioavailability when they are taken in the morning than when they are taken in the evening. For example, with cardiovascular drugs such as nifedipine, oral nitrates and propranolol a plasma peak concentrations are twice as high and times to peak concentrations are shorter after morning dosing as after evening dosing (Bruguolle and Lemmer 1993, Lemmer and Bruguolle 1994). Such variation was not detected when sustained release dosage forms (nifedipine and isosorbide mononitrate) were used. The underlaying mechanisms of their chronopharmacokinetic pattern involve a faster gastric emptying time and a greater gastrointestinal perfusion in the morning. Shiga et al. (1993) documented that atenolol, in contrast to propranolol, is not absorbed more rapidly after morning administration compared than after evening administration. This confirms that the absorption rate of a lipophilic, but not hydrophilic, drugs are faster after morning dosing (Lemmer and Portaluppi 1997).

Studies on NSAIDs, e.g. indomethacin and ketoprofen, have also shown that the drugs have greater rate and/or extent of bioavailability when they are given in the morning than when they are given in the evening. Markedly higher ketoprofen plasma peaks were observed after administration at 07:00 than after administration at other times (Ollagnier et al. 1987). Earlier and higher peak concentrations were obtained when indomethacin was given at 07:00 or 11:00 than at other times of the day or night (Clench et al. 1981). Better morning absorption has also been observed with controlled release indomethacin and ketoprofen formulations (Guissou et al. 1983, Reinberg et al.1986). The clinical relevance of such variation is that high plasma concentrations correlate with the high incidences of adverse effects. It has been suggested that morning absorption for these drugs is better than nighttime absorption (Bruguolle and Lemmer 1993). Greater blood flow of the gastrointestinal tract in the morning than in the evening can explain this phenomenon. Circadian changes in renal function, plasma protein binding or hepatic blood flow could also explain temporal variations in drug plasma levels.

Many variables are known to influence pharmacokinetics. Time of day has to be regarded as an additional variable to influence the kinetics of a drug. In chronopharmacokinetic studies it is important to strictly control the time of drug administration. When symptoms of the disease are circadian dependent or drug used has a narrow therapeutic range a chronopharmacokinetic study should be performed (Bruguolle and Lemmer 1993). The studies should be conducted under controlled conditions, including fasting times, composition of meals and posture.

1.3. Time-controlled release dosage forms

Controlled-release formulations have many advantages over immediate-release formulations. With these formulations a less frequent drug administration is possible, lower plasma peak concentrations can be obtained to avoid adverse effects, and patient compliance can correspondingly be improved. The category of controlled release formulations can be divided into subgroups of rate-controlled release, delayed-release and pulsed-release formulations. Delayed-release formulations include time-controlled release and site-specific dosage forms. When constant drug plasma levels need to be avoided, as in chronopharmacotherapy, time-controlled or pulsed release formulations are preferable, especially in the treatment of early morning symptoms.

By timing the drug administration, plasma peak is obtained at an optimal time. Number of doses per day can be reduced. When there are no symptoms there is no need for drug. Saturable first pass metabolism and tolerance development can also be avoided (Vyas et al. 1997). Various technologies to develop time-controlled peroral drug delivery systems have been extensively studied recent decades. Some of these systems are discussed below.

1.3.1. Enteric-coated systems

Enteric coatings have traditionally been used to prevent the release of a drug in the stomach. Enteric coatings are pH sensitive. Drug is released when the pH is raised above 5 in the intestinal fluid. Although enteric-coated formulations are used mainly in connection with site-specific delivery such formulations can be utilised in time-controlled drug administration, when a lag time is needed. Because of the unpredictability of gastric residence, such systems can not be the first choice when a time controlled release is wanted.

In the treatment of nocturnal asthma a salbutamol formulation containing a barrier coating which is dissolved in intestinal pH level above about 6, has successfully been used (Bogin and Ballard 1992). Enteropolymers in time-controlled drug delivery has been used e.g. in the Chronotopic® drug delivery system (Gazzaniga et al. 1994, 1995; Sangalli et al 1999). The system contains a core which is film-coated with two polymers, first with HPMC and then with a gastroresistant polymer (Eudragit® L30D). In this system the duration of the lag phase in absorption can be controlled by the thickness of the HPMC layer.

1.3.2. Layered systems

To allow biphasic drug release a three-layer tablet system has been developed (Conte et al. 1989). Two layers both contain a drug dose. An outer drug layer contains the immediately available dose of drug. An intermediate layer, made of swellable polymers, separates the drug layers. A film of an impermeable polymer coats the layer containing the other dose of drug. The first layer can also involve a drug-free hydrophilic polymer barrier providing delayed (5 h) drug absorption (Conte et al. 1992a). The Conte et al. group has also studied a multi-layer tablet system (Geomatrix®). It consists of a hydrophilic matrix core containing the drug dose. One or two impermeable or semipermeable polymeric coatings (films or compressed) applied on both sides of the core (Conte and Maggi 1996). This kind of three-layer device has been used in the L-dopa/benserazide treatment of parkinsonian patients (Ghika et al. 1997). Night-time problems and early-morning symptoms of Parkinsonism can be avoided by use of a dual-release Geomatrix® formulation, which allows daily doses of drug to be reduced and leads to extent of bioavailability 40% greater than when a traditional controlled release formulation is employed.

Time controlled explosion systems (TES) have been developed for both single and multiple unit dosage forms (Ueda et al. 1994a,b). In both cases, a core contains drug plus an inert osmotic agent and suitable disintegrants. Individual units can be coated by a protective layer and then by a semipermeable layer, which is the rate controlling membrane for the influx of water into the osmotic core. As water reaches the core, osmotic pressure is built up. The core ultimately explodes, with immediate release of the drug. The explosion of formulation can also be achieved through use of swelling agents. A four layered time-controlled explosion system consisting of a core, drug, swelling agent and an insoluble polymer membrane has been developed by Ueda et al. (1994a). Lag time was controllable by varying the thickness of outer ethylcellulose membrane. In bioavailability studies in man a 3-hour lag time and time to peak concentration at 5 hours was obtained. These values would make the system suitable for use in treatment of nocturnal symptoms of diseases (Hata et al. 1994).

Pellet type multiple unit preparations, sigmoidal release systems (SRS) containing an osmotically active organic acid have been coated with insoluble polymer to achieve different lag-times (Narisawa et al. 1994, 1995, 1996). By different coating thicknesses lag times in vivo can be up to 5 hours. Release rates from SRS after the lag time has found to be independent of the film thickness. A good in vitro in vivo correlation with beagle dogs has been observed at early stage of drug (teophylline or propranolol hydrochloride) release.

1.3.3. Press-coated systems

Press-coating of dosage forms has a long history. The first patent for a press-coating machine was granted in at the end of the 19th century (Noyes 1896). Between 1950 and 1960, interest in press-coated tablets became widespread. Press-coated formulations can be used to protect hygroscopic, light-sensitive, oxygen-labile or acid-labile drugs, to separate incompatible drugs from each other, or to achieve sustained release (Ritschel et al. 1990). Intermittent release can also be achieved by incorporating one portion of a drug in the core and the other in the

coat. Press-coating is relatively simple and cheap. Compression coating can involve direct compression of both the core and the coat, obviating needs for separate coating process and use of coating solutions. Materials such as hydrophilic cellulose derivates can be used. Compression is easy on laboratory scale. On the other hand, for large-scale manufacture special equipment is needed. The major drawbacks of the technique are that relatively large amounts of coating materials are needed and it is difficult to position the cores correctly (Gazzaniga et al. 1994).

In recent years, various controlled release, especially time-controlled release, drug delivery systems based on compression coating technology have been studied. Most such formulations release drug after a lag phase, followed by a rapid dissolution of a core. Conte et al. (1992b, 1993) have developed a press-coated device in which the inner core contains the drug and the outer coat is made of different types of polymers. The outer barrier, controlling drug release can be either swellable or erodible. Lag times can be varied by changing the barrier formulation or the coating thickness. To achieve time-controlled delivery a press-coated formulation containing a swellable core and a less water permeable coat has been developed (Ishino et al. 1992). The core contains drug and disintegration agent. The outer shell delays commencement of drug release. A melted blend of hydrogenated castor oil and polyethylenglycol 600 has been used for coating. After a lag time of one to 10 hours release in vitro is rapid. Lag times depend on the composition of the blend used for coating.

Matsuo et al. (1995) have developed a diltiazem hydrochloride formulation intended for use in treatment of time-related symptoms of ischaemic heart disease and hypertension. The tablet consists of a core, containing drug, and a coat formed by compressing hydroxyethylcellulose. Diltiazem is rapidly released after a delay of several hours. Lag time can be controlled, primarily by changing the thickness of the outer polymer shell.

Marvola and Sirkiä (1995) have developed a press-coated tablet formulation. Most of the total amount of drug is in the tablet core. Hydrophilic polymers such as hydroxypropylmethylcellulose and sodium alginates have been used in the coat to control drug release. The extent of bioavailability of furosemide, ibuprofen and salbutamol sulphate from the system developed have been found to be satisfactory (Sirkiä et al. 1992, 1994a,b,c).

1.3.4. Other systems

Elementary osmotic pumps can be useful for delivering drugs that need pattering based on chronotherapeutic requirements. One type of elementary osmotic pump can deliver salbutamol, initially at a constant delivery rate, then as a final pulse dose (Magruder et al. 1988). Such a system could deliver a dose during a nocturnal asthma attack.

The first chronotherapeutic system for treatment for hypertension and angina pectoris, a controlled onset extended-release (COER-24) verapamil formulation has been developed and registered, e.g. in U.S.A (Cutler et al. 1995, Anwar and White 1998). This formulations has been tailored to the circadian rhythm of blood pressure and hearth rate to better cover early morning symptoms of cardiovascular diseases. COER-24 is an osmotically controlled single unit system. Around the device, which consists of a drug layer and a push layer, are two membranes. The first is a semipermeable insoluble membrane, the second a release delaying hydrophilic

polymer coat. Gastrointestinal fluid penetrates the semipermeable membrane. As fluid enter the drug layer and push layer via the hydrated coat (within 4 to 5 hours) the push layer expands, pressing against the drug layer and causing drug release at a constant rate for 18 hours. If taken at bedtime, the system provides optimal drug concentrations when the patient wakes up and during daytime. Haemodynamic effects are less during sleep when demand is less.

PULSINCAP™ is a delivery system which releases drug contents at a predetermined time or at a specific within the gastrointestinal tract (Junginger 1993, Hedben et al. 1999). Each capsule is composed of a water insoluble body and a water-soluble cap. Capsule contains the drug dose and it is sealed with a hydrogel plug. At a predetermined time after ingestion the swollen plug is ejected from the capsule. Drug is then released into the small intestine or colon. The dimensions of the plug and its position in the capsule can be varied. The dosage form can also be film coated. These properties allow the system to deliver drug at an exact time, one to 10 hours after drug administration to various regions of the gut.

1.4. Effect of food on bioavailability of solid dosage forms

The bioavailability of a drug from a formulation depends on many factors, including the properties of the formulation, gastric emptying time, duration of intestinal residence, and site of absorption. The contents of a formulation may be dispersed throughout large volume of food. Presence or absence of food in the stomach is the most important factor affecting the gastrointestinal transit of dosage forms (Davis et al. 1984). Food is a major factor controlling the time between dosing and the commencement of absorption. Food can also decrease or enhance extent of bioavailability. Time of dosing with respect to food intake is accordingly important.

The normal fasting pH in the stomach is about 1.8. Stomach pH exhibits a circadian rhythm, independent of meals. The rate of gastric acid secretion is greater in the evening than in the morning (Moore and Englert 1970). Food normally elevates pH in the stomach up to between 3 and 5 (McLaughlan et al. 1989). Because the majority of drugs are weak acids or bases, dissolution is dependent upon the pH of gastrointestinal fluids. Drug release from a dosage form can also be pH-dependent, e.g. when a formulation contains pH-sensitive polymers.

Stomach regulates emptying of gastric contents into the intestine. The interdigestive myoelectric complex can produce contractions in the gastrointestinal tract that will sweep indigestible material into the duodenum. If a non-disintegrating dosage form is administered with food, in particular with a high fat meal, it may remain in the stomach for 12 hours (Khosla et al. 1989). In the fasting state large single units can remain in the stomach from only several minutes to 4 hours (Smith and Feldman 1986, Davis et al. 1988, Meyer et al. 1989). The stomach can eject solid units at different times even though they have been ingested simultaneously. Drug pharmacokinetics can markedly be affected by meals (Wilson et al. 1989). The position within the gastrointestinal tract will not necessarily results alterations in pharmacokinetic parameters if the drug is well absorbed throughout the gastrointestinal tract (Borin et al. 1990).

1.5. In vitro/in vivo correlations

In vitro/in vivo correlation has been defined in relation to pharmaceutical products as the establishment of a relationship between a biological property produced by a dosage form, and the physicochemical characteristics of the same dosage form (USP 23). Typically, there is a relationship between in vitro dissolution rate and in vivo input rate. More weight is placed on the cumulative dissolution of a dosage from. Up to now dissolution tests have been considered useful mainly in process and quality control of drug products. Dissolution tests have also been conducted routine in the pharmaceutical development of new drug formulations. However, results of in vitro tests will be of practical value only if a correlation exists between in vitro and in vivo characteristics. In vivo performance is typically assessed in man by rate and extent of bioavailability. In the case of controlled release dosage forms the cumulative absorption vs. time profile is desirable in the assessment of in vivo performance. In vitro/in vivo correlation is classified into levels A, B, C (Leeson 1995). Level C is the lowest level and level A the highest level.

Level C correlation establishes a one point relationship between a dissolution parameter (e.g. drug released at certain time point) and a pharmacokinetic parameter (e.g. time to peak concentration). It does not reflect the whole plasma concentration/time curve, which is the important factor in the assessment of controlled-release products (Malinowski et al. 1996).

Level B correlation the mean in vitro dissolution parameter is compared to the in vivo parameter, mean residence time or mean dissolution time. It is not considered as a point-to-point correlation because it does not reflect the whole in vivo curve. Different plasma curves can have the same mean residence time.

Level A correlation involves a point-to-point relationship between in vitro dissolution and in vivo profile, i.e. the shape of the plasma concentration time curve is fully reflected. A plasma concentration/time profile can be deconvoluted to give an absorption/time profile. The most common examples of deconvolution are the Wagner-Nelson method (Wagner and Nelson 1963) and the Loo-Riegelman equation (Loo and Riegelman 1968). Correlation may be evaluated by superimposing cumulative curves of both in vitro and in vivo performance. Level A correlation can be also described by linear fitting of drug released in vitro to drug absorbed in vivo. It can be defined with two formulations but three or more products with different release rates are recommended (Malinowski et al. 1996). If one of the formulations does not show the same relationship between in vivo and in vivo data as the other formulations, the correlation can be utilised without the deviating formulation. It is recommended that during the formulation screening dissolution testing can be carried out using several dissolution conditions. Although level A correlation serves primarily as a tool in quality control, it can also be applied as a surrogate for bioequivalence tests when minor changes are made to drug products. If level A correlation is established bioavailability studies can be reduced in extent since in vitro data can be used to predict in vivo properties of a formulation developed.

2. Aims of the study

The main objective of the present studies reported here was to investigate whether compression coating could be used to produce tablets providing maximum drug plasma concentrations 6 to 8 hours after an evening dose taken at approximately 22:00. The basic idea behind the dosage form developed is that polymer coat should control drug release from a core containing drug.

In detail, aims of the study were:

- To determine a suitable amount of a hydrophilic polymer (HPMC or sodium alginate) as coat forming material in the tablets.

- To determine the effects of viscosity grade of HPMC on the behaviour of the product, and whether combinations of different viscosity grades of HPMC could be used to optimize the drug release and absorption characteristics.

- To determine how incorporating some drug in the coat affects tablet properties.

- To determine how model drugs having different aqueous solubility in physiological pH values behave in the tablet. Model drugs studied were a weak acid (ibuprofen) and a weak base (pseudoephedrine, as the hydrochloride).

- To determine whether the bioavailability of a dosage form developed depended on timing of drug administration and timing of food intake.

- To determine whether there were in vitro/in vivo correlations between results of dissolution tests in vitro and bioavailability studies with the formulations.

3. Materials and methods

3.1. MODEL DRUGS

3.1.1. Ibuprofen

Ibuprofen (Ph. Eur.) was used as a model drug in press-coated tablets (I, II and III). It was selected for this purpose because it is absorbed throughout the gastrointestinal tract (Wilson et al. 1988). It is a propionic acid derivate with a pK_a of 5.3 (Herzfeld and Kümmel 1983). It is sparingly soluble in acidic aqueous solutions. Ibuprofen has a short elimination half-life of only about two hours (Ritschel 1992). As a non-steroidal anti-inflammatory drug (NSAID) it is used to treat chronic and acute pain e.g. in rheumatic diseases as single dose of 200 - 800 mg. Therapeutic plasma drug concentration of ibuprofen is 5 to 50 mg/l. Most of the drug dose is metabolized to at least two metabolites (Mills et al. 1973). Only less than 1% is excreted unchanged to urine. Biliary elimination is less than 1% (Schneider et al. 1990).

3.1.2. Pseudoephedrine hydrochloride

Pseudoephedrine (BP), as the hydrochloride, was chosen as another model drug (IV). As salt of a weak amine base it is readily soluble in water over the physiological pH values. Pseudoephedrine, a stereoisomer of ephedrine, is a sympathomimetic drug and is commonly used as oral preparations for nasal congestion. Peroral single doses of 60 - 120 mg are used. It is completely absorbed from the gastrointestinal tract after oral administration, with no presystemic metabolism (Kanfer et al. 1993). Peak concentration for immediate-release formulations is reached 0.5 to 2 hours after administration. The predominant elimination route of pseudoephedrine is urinary excretion. Its half-life is relatively short, approximately 6 hours (Dickerson et al. 1978, Nieder and Jaeger 1988).

3.2. Polymers

Polymers were used to control drug release from the press-coated formulation. Hydrophilic polymers, which have the ability to form gels in aqueous circumstances, were chosen on the basis of previous studies on the press-coated formulation (Sirkiä et al. 1994b,c).

3.2.1. Hydroxypropylmethylcellulose

Hydroxypropylmethylcellulose (HPMC) is widely used in peroral controlled release dosage forms. HPMC is described as partly O-methylated and partly O-(2-

hydroxyproplated) cellulose. It is an inert hydrophilic polymer with no ionic charge. The viscosity grade of the polymer depends on the number of substituents on the polymeric backbone and the length of the cellulose chain. Two viscosity grades of HPMC (Methocel K100 and K4000, Dow Chemical Company U.S.A.) were used in this study (I, II, III and IV). These grades have particle sizes and particle size distributions suitable for use in controlled release formulations (Alderman 1984). Methocel K grade contains 22% methoxy and 8.1% hydroxypropoxy groups. The viscosity of Methocel K100 is 100 mPa s in 2% aqueous solution at 20 °C and the viscosity of Methocel K4000 in the same conditions 4000 mPas s.

3.2.2. Sodium alginate

Alginates are polysaccharides extracted from seaweed. Alginates are polyelectrolytes and form salts with di- or polyvalent metals and alkali metals. Alginates are biocompatible and inert. Alginic acid consists of α-L-guluronic acid (G) and β-D-mannuronic acid (M) units. Three kinds of polymer segments are present in alginic acid chains, blocks consisting of M, of G or of MG. The relative proportions of M and G -blocks determine the properties of the polymer. Sodium alginates which contain many G -chains form more viscous gels than those with many M -chains (McDowell 1986). The former sodium alginate (Manugel DPB, Kelco Ltd., U.K.) was used studies reported in study I. The viscosity in 1% aqueous solution of Manugel DPB at 20 °C is 500 mPa s.

3.3. Other excipients

Anhydrous β-lactose was used in the core tablets as a filler (Pharmatose DCL 21, DMV International, The Netherlands). Pharmatose 21 is a spray dried lactose with good flow and direct compression characteristics. Base, potassium carbonate (p.a., Merck, Germany), was added to the core to facilitate the dissolution of sparingly soluble ibuprofen. Magnesium stearate (Ph. Eur.) and talc (Ph. Eur.) were used in the core and in the coat as lubricants. Polyvinylpyrrolidone (PVP K25, Fluka, Switzerland) was used as a binder when granulating the sodium alginate.

3.4. Tablet structures and compositions

The press-coated tablet formulation included a core tablet and a compressed coat (Fig. 2). The coat contained polymer to control drug release. The core was an immediate release tablet formulation. The total amount of drug in each tablet was 100 mg.

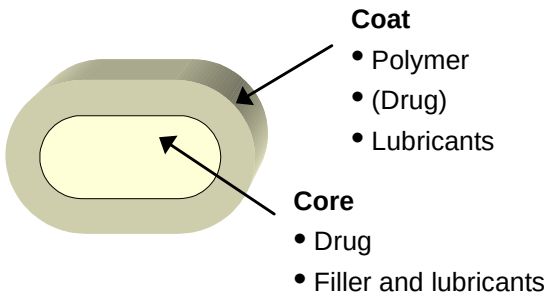

Figure 2. Cross-section through press-coated formulation.

Into the core was incorporated 50, 67, 80% or the whole of drug dose. The rest of the drug was in the coat. The amount of polymer varied from 180, 240, 300 to 360 mg. The compositions of the tablet formulations studied are shown in Table 1.

Table 1. Compositions of press-coated tablets.

Ingredients	Study I	Study I	Study II , III	Study IV
Core				
Ibuprofen	80/100 mg	50/67/80/100 mg	80/100 mg	
Pseudoephedrine HCl				80/100 mg
Lactose	40 mg	40 mg	40 mg	60 mg
Potassium carbonate	20 mg	20 mg	20 mg	
Magnesium stearate	1%	1%	1%	1%
Talc	2%	2%	2 %	2%
Coat				
Ibuprofen	20/0 mg	50/33/20/0 mg	20/0 mg	
Pseudoephedrine HCl				20/0 mg
Sodium alginate	360 mg			
PVP	q.s.			
HPMC K100			0/23/45/68/90/ 180 mg*	180/0 mg
HPMC K4000		180/360 mg	180/157/135/ 112/90/0 mg	0/180 mg
Magnesium stearate	1%	1%	1%	1%
Talc	2 %	2%	2%	2%

*The coat contained combinations of HPMC K100 and K4000M. The amount of HPMC K4000 was 12.5, 25, 37.5 or 50%.

3.5. Tabletting

Cores were tableted and compression coating undertaken using an instrumented Korsch EK-O single punch press (Erweka Apparatebau GmbH, Germany). The compression force was adjusted to 11 ± 1 kN. It was controlled by means of computer software (PuuMan Oy, Finland).

3.5.1. Cores

For tabletting the cores, drug, lactose and potassium carbonate were mixed in a Turbula mixer (W.A. Bachofen, Switzerland) for 15 minutes. Magnesium stearate and talc were added and mixed for an additional 2 minutes. Cores were compressed using concave punches (7 mm diameter).

3.5.2. Compression coating

Components of the coat were mixed for 10 minutes. Batches containing sodium alginate were moistened with a 10% water-ethanol solution of PVP. The mass was granulated by sieving through a 0.7 mm sieve. The granules formed were dried overnight at 35 °C. Fraction of 0.3 – 0.7 mm was used for compression coating. Magnesium stearate and talc were added to all batches, with subsequent mixing 2 minutes.

Die filling, core centralization and machine operation were undertaken using by a standardized manual process. Half of the powder mass for one tablet coat was weighed into a die (11 mm in diameter). A lower coating layer was consolidated and the core centred on an even bed. The remaining powder was then added to the die.

3.6. In vitro dissolution studies

Drug release from the press-coated tablets was determined using the USP 23 apparatus 2 paddle method. The dissolution media (USP 23) used were phosphate buffers, pH 7.2 and pH 5.8, and hydrochloric acid buffer, pH 1.2. In the case of ibuprofen only the pH 7.2 buffer was used (900 ml at 37 ± 0.5 °C) and the rotation speed was 50 min^{-1}. For pseudoephedrine hydrochloride tablets, the amount of medium was 500 ml at 37 ± 0.5 °C. Dissolution was studied at rotation speeds of 50, 100 or 150 min^{-1}. The dissolution apparatus (Sotax AT7, Sotax AG, Switzerland) was connected to a spectrophotometer and 2 mm (ibuprofen) or 10 mm (pseudoephedrine hydrochloride) cells (Ultrospec III, LKB Biochrom Ltd., U.K.) via a peristaltic pump (Watson-Marlow 202U, Smith and Nephew, U.K.). Dissolution of the drug was monitored for 20 hours. Measurement of absorbance from six parallel samples was controlled by means of tablet dissolution software (TDS™, LKB Biochrom Ltd., U.K.). The standard curves for the drugs were found to be linear over a concentration range of 5 to 120 mg/l ($r > 0.998$) for ibuprofen and a concentration range of 5 to 200 mg/l ($r > 0.998$) for pseudoephedrine hydrochloride. In vitro re-

lease data (10 to 90% of the cumulatively dissolved drug) was fitted to zero-order, first order and square-root of time equations using the least squares minimization procedure (Minsq™, Micromath Sciences Software, U.S.A.).

3.7. Bioavailability studies in man

Single-dose studies were carried out on healthy volunteers. A cross-over -technique was used. Between the administration of formulations there was a wash-out period of one week. There was a test-free period of at least three months between each study. The ages of the volunteers varied from 18 to 37 years and their weights from 43 to 87 kg. All were non-smokers. They were each subjected to a physical examination, routine laboratory tests and an ECG. The volunteers were informed of possible risks and side effects of the drugs, and written consent was obtained from each. Plasma samples were collected from a forearm vein into heparinized tubes. After collecting blood samples plasma was separated and stored at - 20 °C until analysed. Bioavailability studies were carried out in accordance with the recommendations of the Declaration of Helsinki (World Medical Assembly 1964) as revised in Tokyo in 1975. The study protocol had been approved by the Ethical Committee of the University Hospital of Tartu.

3.7.1. Overall experimental procedure with press-coated tablets

Groups of eight volunteers participated in bioavailability studies. Each formulation was administered with 200 ml of water following a fast of at least 10 hours, except in the study in which the effect of food intake was investigated. Venous blood samples were collected just prior to drug administration and 1, 2, 3, 4, 5, 6, 8, 10 and 12 (tablets containing sodium alginate, I) or 2, 4, 6, 8, 10, 12 and 24 h (tablets containing HPMC, I, II, IV) thereafter. A standard lunch was provided 3 hours after drug administration.

3.7.2. Experimental procedure in chronopharmacokinetic and food effect studies

A group of five healthy volunteers participated in three cross-over single-dose investigations. The dose was three press-coated tablets (total dose 300 mg). Hard gelatin capsule containing plain drug without adjuvants was used as a reference. The dose was two capsules (in all 300 mg of ibuprofen). Both formulations were administered at 08:00 or 22:00. Between morning and evening administration there was a washout period of at least one week. A 10 hour fast was maintained before daytime investigations. Lunch was provided 3 h after drug ingestion in the morning. In connection with the night-time investigations, dinner was served 5 h before drug administration and breakfast at 06:00 on the following morning.

In the next stage the press-coated tablets were administered 2 h after a light meal (1500 kJ, two slices of bread with cheese or ham, yoghurt and juice) or im-

mediately after meal at 22:00. The volunteers were told to avoid physical activity and to lie down and sleep (if possible) during the night. Blood samples were collected just prior to and 1, 1.5, 2, 3, 4, 6, 8 and 10 h after capsule administration and 2, 4, 6, 8, 10 and 12 h after tablet administration (III).

3.7.3. Determination of ibuprofen in plasma

Ibuprofen plasma concentrations were determined by means of high performance liquid chromatography (HPLC) using the method described for ibuprofen by Avgerinos and Hutt (1986) with slight modifications. The HPLC system was equipped with a Waters Model 501 piston pump, a Waters Model 700 Intelligent Sample Processor, a Waters Millennium Chromatography Manager Workstation and a Waters Model 486 Tunable Absorbance Detector (Waters, USA) operated at 222 nm. Sample separation was carried out on a 3.9×300 mm column packed with 10 μm reverse-phase silica (μBondapak C-18, Waters, USA). The isocratic mobile phase consisted of acetonitrile and 0.1 M sodium acetate (35:65), and the rate of flow was 2 ml min^{-1}. Two parallel samples were determined. The method was validated and accuracy and precision of the method investigated as recommended by Shah et al. (1992) by analysing six plasma samples containing known amounts of ibuprofen. The standard curve was linear ($r > 0.998$) over the used concentration range 0.5 - 40 mg l^{-1}. There were no interfering peaks in the plasma blanks.

3.7.4. Determination of pseudoephedrine in plasma

Plasma concentrations of pseudoephedrine were determined using HPLC and a method described by Dowse et al. (1983) with slight modifications. The HPLC system used was same as that used for ibuprofen HPLC-analysis. The detection wavelength was 220 nm. The isocratic mobile phase consisted of acetonitrile (220 ml), 0.005 M sodium acetate (780 ml) and 1 M HCl (2 ml). The flow rate trough the column was 1.3 ml min^{-1}. Three parallel samples were determined. The standard curve was found to be linear ($r^2 > 0.999$) over the concentration range of 35 - 800 ng ml^{-1} used. The method was validated as recommended by Shah et al. (1992) analysing six plasma samples containing known amounts of pseudoephedrine hydrochloride. No interfering peaks were detected in the plasma blanks.

3.7.5. Pharmacokinetic parameters

Maximum concentration (C_{max}) and time to peak concentration (t_{max}) were determined directly from individual time versus plasma concentration curves. Pharmacokinetic parameters calculated using the Siphar™ program (Simed, France) were apparent elimination half-life ($t_{½}$), lag time for absorption (t_{lag}), mean residence time (MRT) and area under the curve ($AUC_{0\text{-}12/24h}$). AUC values were calculated using the trapezoidal method. Rate of absorption was also evaluated by means of the ratio C_{max}/AUC. Statistical analyses were carried out using Student's paired t-test, the Mann-Whitney non-parametric U-test or Wilcoxon's matched-pairs rank test.

3.8. In vitro/in vivo correlations

Level C and level A correlations was used to study correlation between in vitro and in vivo data. Level C was chosen for an easy method to find rough an in vitro/in vivo correlation. Level A was selected because it takes account the whole plasma curve and is recommended for controlled release formulations.

Level C correlation was determined using the in vitro parameters time at which 50% of drug had dissolved ($t_{50\%}$) and amount dissolved in 6 hours (D_{6h}) and the in vivo parameters C_{max}, t_{max} and AUC. Each in vivo parameter was plotted against an in vitro parameter and linear regression was calculated.

Level A correlation was determined by transforming in vivo plasma data to fraction of drug absorbed, using the Wagner-Nelson equation (Wagner and Nelson, 1964) in the Siphar™ program. Elimination rate constants were calculated from a mean elimination half life of two hours for ibuprofen formulations and six hours for pseudoephedrine formulations. Fractions of drug absorbed were then plotted against fractions released in vitro at corresponding times. Linear regression was then calculated.

4. Results and discussion

4.1. Effects of different variables of press-coated tablets on drug dissolution and bioavailability

Numerous formulation variables are known to affect drug release from hydrophilic tablet matrices. Viscosity grade of polymer, amount of polymer, drug-polymer ratio and nature of the drug used in the tablet system are known to affect drug release from matrices containing HPMC (Alderman 1984, Ford et al. 1985a, Hogan 1989). Variables such compression force and particle size of drug do not significantly affect drug release (Ford et al. 1985a,b). Studies of a press-coated tablet system developed in our department have shown that drug release can be controlled mainly by the amount of polymer and the viscosity grade of the polymer in the coat. Drug release and absorption can also be affected by dividing the drug dose between the core and the coat (Sirkiä et al. 1992, 1994a,b,c). In the studies described here the formulation variables below were optimized to control drug absorption from the tablet system.

4.1.1. Polymer type

In the first stage of the studies two types of polymer were used in the coat (I). Sodium alginate and HPMC were chosen on the basis of results of studies of Sirkiä et al. (1992b, 1994c) to control drug release and absorption from the tablet system. These polymers were found to act suitably in a press-coated prolonged-release formulation.

Drug release in vitro was faster from press-coated tablets containing sodium alginate than from tablets containing HPMC (I). The difference between these formulations was, however, most marked in relation to pharmacokinetic parameters. Peak concentrations from HPMC tablets were not reached in a 12 hour study. In the case of sodium alginate tablets peak concentrations were reached in about 4 hours (I, table I). AUCs were several times greater for alginate tablets than for HPMC K4000 tablets.

The aim of achieving t_{max} values of 6 to 8 hours was not achieved with sodium alginate tablets containing 360 mg of sodium alginate. According to Murata et al. (1993) increasing amount of alginate in a tablet reduces drug release. In the studies reported here, however, tablet size restricted the amount of polymer that could be added to the tablet coat. The maximum amount that could be used was 360 mg. Sodium alginate was therefore not used in further studies.

4.1.2. Amount of hydroxypropylmethylcellulose

Amount of HPMC in the tablet coat had a notable effect on drug release and drug bioavailability (I, Fig. 1). Doubling the amount of HPMC K4000 from 180 mg to 360 mg decreased the amount of drug released during dissolution test about 20%.

With tablets containing 360 mg of HPMC, absorption was negligible (I, Fig. 6). When the amount was reduced to 180 mg t_{max} values of 12 to 13 hours were obtained i.e. the aim of having a t_{max} of 6 to 8 hours was not achieved (I, Table I). The amount of polymer could not have been reduced without reducing the core size and amounts of drug in the tablet. We therefore concentrated on modifying the viscosity of the coat to control drug release.

Effects of amounts of HPMC on drug release in vitro were also studied using three quantities of HPMC K4000 and K100 (II). Amounts of polymer in coats were 180 mg, 240 mg and 300 mg. There were no statistically significant differences between tablets containing HPMC K100. After a lag time, dissolution rates were similar with each amount of polymer. The amount of polymer seemed to affect lag time relating to drug diffusion through the gel layer around the tablet core, not the diffusion rate of the drug.

4.1.3. Viscosity grade of hydroxypropylmethylcellulose

Two grades of HPMC were selected for the study. The low viscosity grade HPMC K100 and high viscosity grade HPMC K4000 have been used in the press-coated formulations by Sirkiä et al. (1992, 1994a,b). HPMC K4000 forms a gel 40 times more viscous than that formed with K100, and decreases drug release from matrix tablets by 50% (Ford et al. 1985a). In our studies the viscosity grade had a marked effect on drug release rate and release profile from press-coated tablets (II, Fig. 3). Drug release in vitro from HPMC K100 tablets was biphasic. These findings are in accordance with those of Sirkiä et al. (1994a) with press-coated salbutamol sulphate tablets. Drug release from HPMC K4000 tablets obeyed zero order kinetics. Overall release from HPMC K4000 tablets was considerably slower than from HPMC K100 tablets. Variation between drug dissolution curves was high with HPMC K100 tablets. This indicates that dissolution from the formulations can not be controlled. HPMC K100 is obviously unsuitable for used as such in the kinds of formulation being investigated. It has been suggested that HPMC K100 does not swell homogeneously (Gao et al. 1996), and that lack of homogeneity of the HPMC K100 is responsible for the more rapid gel layer dissolution and higher drug release rates than with HPMC K4000. Drug diffusion and erosion of the gel is much more slower from the HPMC K4000 tablets.

Rate and extent of bioavailability was higher from tablets containing HPMC K100 compared to tablets containing HPMC K4000 (I, II). With ibuprofen tablets containing HPMC K100 t_{max} was 4.5 hours, with tablets containing HPMC K4000 t_{max} had not been reached by 12 hours. Ibuprofen tablets containing HPMC K4000 exhibited bimodal plasma curve when some drug was included in the coat. Corresponding HPMC K100 tablets exhibited no such pattern. C_{max} values were over twice as high with HPMC K100 tablets. When pseudoephedrine hydrochloride was used as model drug differences in t_{max} and C_{max} values between tablets containing HPMC K100 and K4000 were similar (IV). The objective of achieving a t_{max} of 6 to 8 hours was, however, not obtained with either of these viscosity grades of HPMC when they were used on their own.

4.1.4. Combinations of hydroxypropylmethylcellulose grades

The choice of viscosity grade of HPMC is an important consideration controlling drug release from hydrophilic matrices. Drug release rate can also be adjusted by combining HPMCs of different viscosity grades (Shah et al. 1989, Tahara et al. 1995). As mentioned above HPMC K4000 was found to be too viscous for t_{max} values of 6 to 8 to be obtained. Four combinations of HPMC K100 and K4000 in the tablet coat were therefore studied. Each tablet contained 180 mg of the polymer. Percentages of HPMC K4000 in the combinations were 12.5, 25, 37.5 and 50%. When mixtures of HPMC K100 and K4000 were used, drug release was inversially proportional to amount of HPMC K4000 (II, Fig. 1a). When the amount of HPMC K4000 was exceeded over 25% differences between release curves were not significant. A rank order correlation however existed. Release was least from the formulations containing HPMC K4000. Even a small percentage of HPMC K4000 (12.5%) in combination with HPMC K100 decreased release rate markedly. By combining HPMCs of low viscosity with higher viscosity grades, drug release rate can thus be adjusted. Gel layer obviously become more viscous and therefore less susceptible to erosion when HPMC K4000 is added to the coatings.

Three combinations of HPMC K100 and K4000 were used in the bioavailability study: Percentages of HPMC K4000 were 12.5, 25 and 50. Increasing amounts of HPMC K4000 had the effects expected from results of in vitro studies. Values for t_{max} were lowest (6 hours) when most of the coat consisted of HPMC K100 (II, Table II). The greater the amount of HPMC K4000 the greater the values of t_{max}. When the percentage of HPMC K4000 was 50, t_{max} values were 8 to 10 hours. The extent of bioavailability, assessed via C_{max} and AUC values, did not differ significantly between formulations containing different HPMC combinations. The results indicate that by choosing an appropriate combination of HPMC grades timing of the plasma peak can easily be controlled.

4.1.5. Proportion of model drug in coat

In studies on press-coated tablets it has been discovered that most of the drug (e.g. 2/3) should be in the core of the tablet if an increase in drug release rate is desirable (Sirkiä et al 1994a). We studied drug release and absorption using four ratios. Percentages of drug in the core were 50, 67, 80 or 100 (I). HPMC K4000 was used in coat to control drug release. Drug release was slowest from the tablets containing all of the drug in the core. A marked lag time, of about 4 hours, was evident in release curves (I, Fig. 1.). Lag time was also evident in all other dissolution studies of formulations containing all of the drug in the core, regardless of the polymer or amount of polymer used in the coat (II, IV).

In bioavailability studies on man two peaks in the plasma curves were noted when 50, 67 or 80% of the drug was in the core and the coat contained HPMC K4000 (I, Fig. 4), with only two exceptions, one in the 50% group, the other in 80% group. Bimodal characteristic of the absorption curves was most marked with formulations containing least drug in the core (50 and 67%). This was also seen in relation to tablets containing combinations of HPMC K4000 and K100 (II, Fig. 5 and Fig. 6). It would seem that if a coat contains some drug and a polymer in the coat is viscous enough (e.g. if it contains at least 25% of HPMC K4000) to affect

drug release a bimodal plasma curve will be obtained. Lag times were greatest for formulations containing the entire dose in the core (II, Table I and II; IV, Table 2).

Other sustained-release dosage forms of ibuprofen have also exhibited bimodal characteristics. It has been suggested that the second plasma peak reflects loss of integrity of the dosage form. Various matrix systems exhibited bimodal absorption profiles (Parr et al. 1997, Shah et al. 1989, Wilson et al. 1989). These systems are however monolithic formulations. In our studies we had cores surrounded by a gel layers. The first peak may have been caused by diffusion of drug in the coat from the gel layer. A gel layer might also be more subject to erosion if the drug is in the coat. The second peak could be caused by the erosion of the gel layer and release of drug from the core. If a drug is, like ibuprofen, absorbed from the colon second peak may occur 8 hours after administration. This was seen with tablets containing a polymer of high viscosity grade (HPMC K4000) in the coat. If maximum effect were required in the night-time a formulation in which the entire drug dose was situated in the core would be preferable. Formulations in which some drug was located in the coat might be best ones if a more even therapeutic effect were desirable.

4.1.6. Aqueous solubility of model drug

We investigated whether two different types of drug, ibuprofen and pseudoephedrine hydrochloride, were suitable for use with the drug delivery system described, for controlling t_{max} values. Drugs can be released from HPMC gels by diffusion via the gel layer or by erosion of the gel (Alderman 1984). Sirkiä et al. (1994b,c) found that addition of alkalazing agent is necessary for release and absorption of sparingly water soluble drugs from the press-coated tablet system studied. We added potassium carbonate to cores to ensure dissolution of ibuprofen. Diffusion of drug through the gel layer was therefore enhanced.

Time to peak concentrations did not depend on the drug used in the formulation (Table 2). In a study with ibuprofen tablets containing 80 mg of drug in the core and HPMC K4000 in the coat plasma curves were bimodal (I, Fig. 3.). In most subjects, the first peak occurred after four to six hours, the second after 10 to 12 hours. With pseudoephedrine tablets no bimodal plasma curves are detected (IV, Fig. 1.). Pseudoephedrine formulations exhibited just one peak, 8 to 12 hours after administration. Both drugs are known to be absorbed readily throughout the gastrointestinal tract. If ibuprofen were absorbed more readily than pseudoephedrine from certain parts of an intestine this could have resulted in the dissimilarity in absorption profiles.

Table 2. Time to peak concentrations of ibuprofen (3 × 100 mg) and pseudoephedrine (100 mg) from press-coated tablets, mean ± S.D.

Drug in core	80 mg	80 mg	100 mg	100 mg
Polymer in the coat	*K4000*	*K100*	*K4000*	*K100*
t_{max} for ibuprofen	13.5 ± 6.7	4.5 ± 1.4	12.3 ± 4.8	4.5 ± 0.9
t_{max} for pseudoephedrine	10.3 ± 1.7	5.0 ± 1.1	13.1 ± 7.6	4.8 ± 1.5

The amount of tablets ingested could be another explanation for bimodal plasma curves. In bioavailability studies on ibuprofen, three tablets (total amount of drug 300 mg) were administered. In the pseudoephedrine studies one tablet (100 mg) was given. Non-disintegrating solid particles are known to leave the stomach gradually during four hours in fasted state (Smith and Feldman 1986). Gradual emptying of ibuprofen tablets could have resulted in bimodal absorption. One or two tablets entering the intestine could have caused the first peak and the rest of the tablets could have caused the second peak, when they entered the intestine. This is obvious because the best site for absorption of acidic drugs is duodenum. This does not however explain why no bimodal curves were seen with ibuprofen tablets containing HPMC K100. These formulations obviously disintegrated readily in the stomach and then pass more easily into the intestine.

4.2. Chronopharmacokinetics of ibuprofen

Two formulations, a conventional hard gelatin capsule and a press-coated time-controlled release tablet, were administered in the morning and in the evening, to determine whether ibuprofen pharmacokinetics depended on time of administration (III). The capsule formulation (active ingredient in a hard gelatin capsule) allowed definition of the chronopharmacokinetic properties of the drug substance used in press-coated formulation. The composition of the press-coated tablet was selected on the basis of the results of study II. The formulation that exhibited least interindividual variation was used (II, Table II, Fig. 7). The tablets contained some drug in the coat (20 mg) and combination of HPMC K4000 (12.5%) and K100 (87.5%) in the coat.

There were no statistically significant differences in the pharmacokinetic parameters between evening and morning dosing of ibuprofen capsules, but a tendency towards a slower absorption after the evening dose was evident. In four subjects, times to peak concentration were shorter after dosing at 08:00 than after dosing at 22:00. Circadian rhythms in relation to the bioavailability of other lipophilic NSAIDs have been reported. C_{max} values for ketoprofen and indomethacin have been higher and the rate of absorption higher after administration in the morning than after administration at other times during day or evening (Ollangier et al. 1987, Clench et al. 1981). This phenomenon was also seen in the mean curves for ibuprofen capsule formulation in the studies reported here (III, Fig. 1).

The chronopharmacokinetic behaviour of the press-coated ibuprofen tablet administered under fasting conditions differed from that of the capsule formulation. After the evening dose, peak plasma level was obtained earlier than after the morning dose. Both the rate and extent of bioavailability were highest when the drug was administered in the evening. Interindividual variation in plasma curves was minimal after evening dosing of tablets.

The effects seen may be explained on the basis that the gel forming properties of HPMC depend on environmental pH. In aqueous solutions, a stable HPMC gel is formed over the pH range 3 to 11 (Alderman 1984). In this case, a lower pH leads to a less stable gel around the tablet and the formulation losses its integrity. Gastric acid secretion in man is highest and, consequently, the pH of the gastric contents lowest (pH 1 - 3), between 18:00 to 24:00 (Moore and Englert 1970). The

HPMC gel formed after the morning dose will therefore obviously be more stable than that formed after the evening dose. An in vitro study with pseudoephedrine (dissolution independent of pH) tablets contributes the conclusion of gelforming properties of HPMC in acidic milieu. Release rate was higher at pH 1.2 than at pH 5.8 and 7.2 with press coated tablets, especially with those containing HPMC K4000 (IV, Fig. 3). Similar findings had been reported earlier by Ford et al. (1985c). Release of promethazine hydrochloride from HPMC matrices gave higher rates at pH 1 and 3 than at pH 5, 7 or 9. This effect was apparent with all viscosity grades of HPMC, including K100 and K4000.

Peak plasma concentrations were obtained four hours after when press-coated formulation was administered in the evening, too short in view of the aim of this study. If drug dosing takes place at 22:00 maximal effect would be obtained too early in relation to the treatment of diseases displaying nocturnal symptoms at 04:00 to 06:00. A way of achieving this goal can be to increase the relative amount of HPMC K4000 in the tablet coat.

4.3. Effect of timing of food intake on drug absorption

If a drug dose is administered in the evening aimed for treatment of nocturnal symptoms a drug dose is unlikely to be taken more than 5 hours after the last meal of the day. We therefore studied the effect of time of food intake on bioavailability of the time-controlled release ibuprofen tablets. The formulation was the same as that used in the chronopharmacokinetic studies. The study was carried out with drug administration in the evening at 22:00 concomitantly and two hours before food ingestion.

The results show that eating a meal markedly lowered bioavailability. Statistically significant differences were seen in relation to absorption rate parameters, C_{max}/AUC and t_{max}. Extent of bioavailability in relation to AUC was also decreased (IV, Table 1). When drug was administered two hours after a meal it still had a slight effect on the extent of bioavailability. There was a difference between AUC values for tablets taken with the meal and tablets taken two hours after the meal. Interindividual variation was lowest when tablet was taken in the evening after a four hour fast. For all subjects t_{max} value was the same.

Concomitant intake of a light meal with the press-coated formulation in the evening resulted in peak plasma concentrations approximately 6 hours after dosing. Maximum therapeutic effect would appear at 04:00 to 06:00 if the drug were dosed at 22:00. This would be suitable for treatment of nocturnal symptoms of diseases.

The most marked effect of a meal was a decrease in rate of ibuprofen absorption, perhaps because of a general retarding effect of food on drug absorption. The gel forming properties of HPMC under acidic conditions could also explain the effect. Gastric pH is readily elevated by meals, up to pH 4 to 6 (McLaughlan et al. 1989). At pH 3 to11 the gelforming properties of HPMC are greatest as mentioned earlier (Alderman 1984). In fasted state gastric pH is about 1 to 2. Release of ibuprofen will obviously be relatively low through gel layer at higher pH. These conclusions are in accordance with those from our chronopharmacokinetic study. However, with food intake the situation is more complex. Food affects viscosity of

stomach contents. A relatively high viscosity may retard the gel formation in the tablet coat and drug release rate can be decreased. Both stomach pH and the viscosity of the stomach contents could therefore affect in drug absorption.

Different results have been obtained in previous studies of the effects of food on absorption of ibuprofen from sustained release formulations. Food ingestion has even been found to raise maximum concentrations, although it at the same time delays gastric emptying (Borin et al. 1990, Pargal et al. 1996). In the study of Borin et al. (1990) the tablet was a pH-independent erodible matrix. In our study, drug release from a core was controlled by a hydrophilic gel layer. It therefore can be concluded, that the effect of food seems likely to be highly dependent on the nature of the formulation concerned. The content of a meal has also been found to influence the pharmacokinetic profile of ibuprofen (Wilson et al. 1989). Because the caloric and protein contents of meals in these studies are different, it might explain the differences in effects of meals on ibuprofen absorption.

4.4. In vitro/in vivo correlations

4.4.1. Level C

Single-point level C correlations for ibuprofen formulations are shown in Table 3. The greatest degree of correlation was obtained when $t_{50\%}$ values were plotted against t_{max} values for tablets containing combinations of HPMCs, especially for the formulations containing 12.5% and 25% of HPMC K4000 in the coat. Overall, correlation of in vitro parameters with in vivo parameters was poor in the case of ibuprofen formulations. No linear correlation was found in relation to formulations containing 50 to 100 mg of ibuprofen in the cores. In contrast, with pseudoephedrine correlations between $t_{50\%}$ and t_{max} values were always good (IV, Table 3). The greatest degree of correlation was obtained at pH 7.2 with agitation at 50 min^{-1}. AUC and C_{max} values correlated poorly with both in vitro parameters. The results suggest that pH 7.2 and agitation at 50 min^{-1} are the best dissolution conditions for press-coated pseudoephedrine formulations containing HPMC. To allow study of level C correlation for ibuprofen more adequate dissolution conditions need to be established.

Table 3. Level C correlations for press-coated ibuprofen tablet formulations, determined using linear regression analysis. Tablets contained 50, 67, 80 or 100 mg of drug in the core, the rest of the drug (a total of 100 mg) in the coats. The coats contained combinations of HPMC K100 and K4000. The amount of HPMC K4000 was 0, 12.5, 25, 50 or 100%. In vitro parameter plotted against mean pharmacokinetic parameter.

Core	y =	50/67/80/100 mg*	80/100 mg**	80/100 mg**
HPMC K4000	kx + b	*100%*	*0 and 50%*	*12,5 and 25%*
D_{6h} vs C_{max}	k	-0.0071	0.0788	0.1075
	b	6.376	9.937	12.294
	R^2	0.0005	0.4816	0.121
D_{6h} vs t_{max}	k	-0.0803	-0.0998	-0.0459
	b	12.113	10.131	6.7751
	R^2	0.0259	0.8736	0.2389
D_{6h} vs AUC	k	1.36	-0.0607	-0.5256
	b	61.88	111.93	127.87
	R^2	0.1225	0.0493	0.0975
$t_{50\%}$ vs C_{max}	k	0.0217	-0.3945	-0.1315
	b	5.909	16.661	15.235
	R^2	0.0019	0.6445	0.0429
$t_{50\%}$ vs t_{max}	k	0.0991	0.3926	0.1891
	b	9.4654	3.1339	3.9682
	R^2	0.0172	0.8744	0.9600
$t_{50\%}$ vs AUC	k	-1.9322	0.1751	3.1551
	b	111.29	108.13	84.178
	R^2	0.1078	0.0219	0.8324

* Original in vitro dissolution and in vivo data obtained in study I

** Original in vitro dissolution and in vivo data obtained in study II

4.4.2. Level A

Degrees of level A in vitro/in vivo correlations were low for all ibuprofen formulations (Figs. 3 and 4). The greatest degree of correlation was obtained in the case of ibuprofen formulations containing different amounts of drug in the cores (Fig. 3). The data indicate that dissolution conditions for ibuprofen formulations need to be developed in order to improve degrees of level A in vitro/in vivo correlation. Because ibuprofen dissolved more slowly than the drug was absorbed (II, Fig. 8) the speed of agitation may need to be increased or surfactants (e.g. bile salts) could be added to dissolution media to enhance drug dissolution.

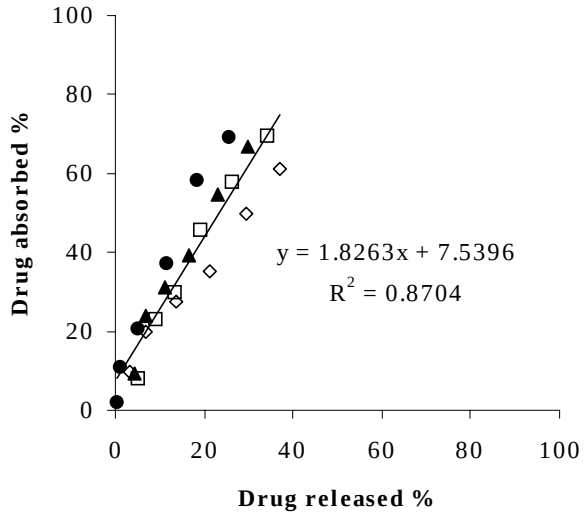

Figure 3. Level A in vitro/in vivo correlations for press-coated ibuprofen tablet formulations containing 50 mg (❑), 67 mg (▲), 80 mg (◊) and 100 mg (●) of the total amount of drug (100 mg) in the core. The amount of HPMC K4000 in the coat was 180 mg. Original data reported in study I.

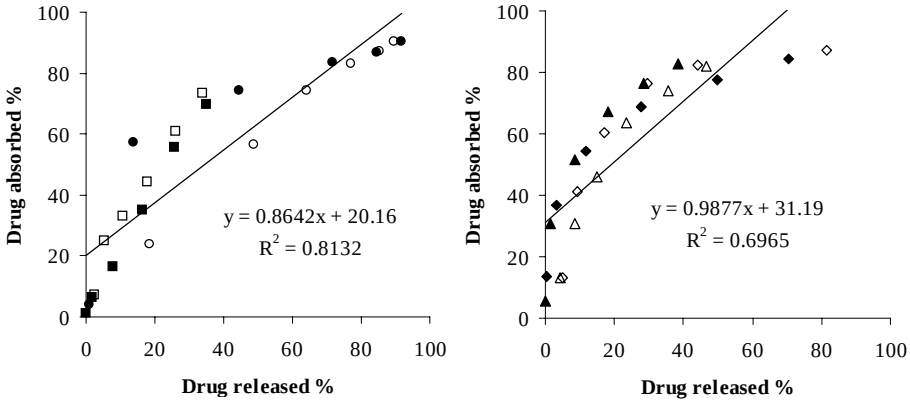

Figure 4. Level A in vitro/in vivo correlations for press-coated ibuprofen tablet formulations containing 0% (●) or 50% (■) and 12.5% (◆) or 25% (▲) of HPMC K4000 in the combinations of HPMC K100 and K4000 in the coat. The amount of drug in the core was 80 mg (open symbols) or 100 mg (closed symbols). Original data reported in study II.

Level A correlation was poor under all dissolution conditions in relation to all four pseudoephedrine formulations. The relationship between in vitro dissolution and in vivo performance in the case of the formulation containing all of the drug in the core and HPMC K4000 in the coat was different from the relationships for other formulations. This formulation had clearly the lowest release rate and data relating

to it was therefore excluded (Malinowski et al. 1996). The degree of correlation was greater in relation to the remaining data (IV, Fig. 5). Because of the lack of data points in the early stage of the absorption studies of formulations containing HPMC K100 degree of correlations were less satisfactory. For further development studies of the drug delivery system containing pseudoephedrine dissolution test method at pH 7.2, with a rotation speed of 150 min^{-1} can be recommended. If the viscosity grade of the polymer used in the coat is HPMC K4000 and the drug is in the core no direct conclusions regarding in vivo properties can be drawn from in vitro results.

5. Conclusions

The main objective of the studies described was to develop a time-controlled release formulation based on a press-coating technique. The intention is that the formulation should be administered in the evening at 22:00 in treating diseases in which symptoms are experienced in the early morning hours (from 04:00 to 06:00).

The following conclusions can be drawn on the basis of the results of the studies:

- HPMC grades are suitable for use in systems to achieve a time to peak concentration of 4 to 12 hours. Amounts and viscosity grade of the polymer are particularly important. By combining different HPMC viscosity grades it is possible to obtain a plasma peak 6 to 8 hours after administrating i.e. to achieve the main aim of the studies.

- If continuous drug plasma levels are desirable, e.g. overnight, by incorporating some drug (over 20%) in the core, the rest in the coat, a double plasma peak can be obtained.

- Both ibuprofen and pseudoephedrine hydrochloride behave similarly in the delivery system as regards time to peak concentrations. Absorption of both sparingly water-soluble drug and readily water-soluble drug can be controlled by changing the HPMC viscosity grade.

- The chronopharmacokinetic behaviour of press-coated formulation depends on the nature of the formulation, not only on the nature of the drug substance. The term of "chronobiopharmaceutics" could be used to describe the phenomenon where formulation variables are responsible for time dependent variations in pharmacokinetics. The evening meal should be eaten at least two hours before any evening dose of a time-controlled release formulation, to ensure that the food has minimal or no effect on drug absorption.

- In developing time-controlled release formulations for treatment of diseases having nocturnal symptoms bioavailability tests should be conducted not just in the daytime but also in the evening. Incorrect conclusions may be drawn from the results of absorption studies in which the drug is traditionally administered in the morning.

- Needs for bioavailability testing on healthy volunteers in developing of the present formulation would be reduced, if t_{max} values correlated with a dissolution parameter, e.g. $t_{50\%}$. Values for t_{max} are approximately predictable from dissolution parameter. To obtain a good degree of level A correlation for press-coated formulations, dissolution test methods need to be developed for each drug and polymer type used in the press-coated tablet.

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