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USE OF HARD GELATIN CAPSULES AND SODIUM ALGINATES IN PERORAL PROLONGED-RELEASE FORMULATIONS

PEEP VESKI

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ABSTRACT

USE OF HARD GELATIN CAPSULES AND SODIUM ALGINATES IN PERORAL PROLONGED-RELEASE FORMULATIONS

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During the last years much attention has been paid to research and development of prolonged-release formulations. Quite few studies have been published concerning the biopharmaceutical characteristics of hard gelatin capsules as single-unit systems containing a simple mixture of a drug and hydrophilic polymer. The main aim of the present study was to define the usability of sodium alginate to modify drug release from hard gelatin capsules and press-coated tablets recently developed in the Department of Pharmacy, University of Helsinki.

Sparingly water-soluble ibuprofen and highly water-soluble pseudoephedrine hydrochloride were used as model drugs. For simulation of the plug formation in dosator-type capsule filling machines a special equipment was also constructed. Altogether 14 different grades of sodium alginate by trade names of Manucol and Manugel were used.

In vitro release of ibuprofen was determined at pH 7.2 and that of pseudoephedrine hydrochloride at pH 1.2, 4.4. and 7.2. To study the mechanism by which sodium alginate control drug release the dissolution medium contained also 0.1% fuchsin. At predetermined times capsules were removed from the dissolution apparatus and cut in two. Penetration of the coloured solution was evaluated by visual inspection and photography. Single-dose cross-over bioavailability studies were carried out in young healthy volunteers. Drug plasma concentrations were determined by HPLC.

Using different grades of sodium alginate as diluents in hard gelatin capsules it was possible to prepare prolonged-release products from which drug absorption can be controlled over a fairly wide range without any fall in the amount of drug absorbed. This system was better suitable for the sparingly water-soluble drug, ibuprofen, than for the highly water-soluble drug, pseudoephedrine hydrochloride. At pH 1.2 from all grades of sodium alginate alginic acid precipitated and it formed a tight outermost layer, which acts as rate-limiting layer for diffusion of the drug. The second layer was gelatinous and smooth. At pH 7.2 the outermost layer consisted only of sodium alginate gel and its tightness depended on the viscosity grade and chemical character of the sodium alginate brand used. The plug formation had only a minimal effect on drug release from capsule formulations containing sodium alginates. Sodium alginates could also be utilized for controlling drug release from press-coated prolonged-release tablets, using different types and different amounts of sodium alginate in the coat of the tablet.

LIST OF ORIGINAL PUBLICATIONS

This study is based on the following papers:

I Veski, P. and Marvola, M., 1991. Design and use of equipment for simulation of plug formation in hard gelatin capsule filling machines. Acta Pharm.Fenn., 100, 19-25.

II Veski, P. and Marvola, M., 1993. Sodium alginates as diluents in hard gelatin capsules containing ibuprofen as a model drug. Pharmazie, 48, 757-760.

III Veski, P., Marvola, M., Klinge, E. and Jürjenson, H., 1994. Bioavailability of ibuprofen from hard gelatin capsules containing sodium alginates. Eur.J.Drug Metabol.Pharmacokin., Special Issue IV, in press.

IV Sirkiä, T., Salonen, H., Veski, P., Jürjenson, H., and Marvola, M., 1994. Biopharmaceutical evaluation of new prolonged-release press-coated ibuprofen tablets containing sodium alginate to adjust drug release. Int.J.Pharm., in press.

V Veski, P., Marvola, M., Smal, J., Heiskanen, I., and Jürjenson, H., 1994. Biopharmaceutical evaluation of pseudoephedrine hydrochloride capsules containing different grades of sodium alginate. Int.J.Pharm., accepted.

The papers are referred to in the text by the Roman numerals I - V.

1. INTRODUCTION

1.1. Prolonged-release drug preparations

In the last two decades much research and development work has been devoted to prolonged-release drug formulations because they have many advantages over conventional immediate-release formulations. For example, they allow less frequent drug administration, high peak-plasma concentrations resulting systemic side effects can be avoided, local high drug concentrations in the gastrointestinal tract resulting local side effects can be avoided, and the reduced degree of fluctuation in drug plasma concentrations improves therapeutic response. All of these advantages improve patient compliance (Notari 1980).

Prolonged-release dosage forms owe a subset of modified-release dosage forms. The nomenclature describing such formulations is confused. Words used to describe modification of release include controlled, sustained, slow, prolonged, retarded, extended, depot, timed, delayed and rate-controlled. Few years ago, American and European health authorities suggested standardization of nomenclature for such drug products. In the study reported here this suggestion has been adopted on the basis described below.

STANDARDIZED NOMENCLATURE OF
MODIFIED-RELEASE DOSAGE FORMS

1. Prolonged-release dosage forms
   1.1. Slow-release dosage forms
   1.2. Extended-release dosage forms
2. Delayed-release dosage forms

Categorization of a drug product in a subgroup is based on pharmacokinetic parameters determined in bioavailability tests. Reference must be made to parameters relating to an immediate-release formulation containing the same drug substance (Table 1).

Most prolonged-release drug products are intended for peroral administration. The main criteria for approval of a prolonged-release preparation are (1) that drug absorption must be predictable and consistent, (2) that fluctuations in drug plasma concentrations in the steady-state must be equal to but preferably, less than those following more frequent administration of an immediate-release formulation and (3) that the amounts of drug absorbed should be at least 75 - 80 % of amounts absorbed from an immediate-release formulation (Skelly 1989).

Table 1. Assignment of modified-release dosage forms to subgroups on the basis of pharmacokinetic parameters as compared with corresponding parameters for an immediate-release dosage form containing the same drug substance. t_{lag} = lag time until commencement of absorption, t_{max} = time to peak concentration, C_{max} = peak concentration, $t_{½}$ = half-life of elimination phase.

Type	t_{lag}	t_{max}	C_{max}	$t_{½}$
Slow release	=	>	<	=
Extended-release	=	>	<	>
Delayed-release	>	>	=	=

= equal to, < less than, > greater than corresponding parameter for immediate-release dosage form.

Many techniques for obtaining prolonged-release drug products have been described. They include use of drug derivatives of low solubility in water, leading to low dissolution rates. Salts, complexes or prodrugs may be less water-soluble than the parent drug. Dissolution rate can also be decreased by increasing particle size of a drug. Drug can also be bound to ion exchange resins (Sjögren 1985).

Use of such chemical and physical means of prolonging drug release are not common in preparing prolonged-release peroral dosage forms. It is commoner to devise special dosage forms or use additives. Peroral prolonged-release formulations are usually categorized in one or other of two groups, namely ,(1) single-unit preparations and (2) multiple-unit (multiparticulate) preparations (Beckett 1985). A single-unit preparation acts in its entirety as a drug releasing system. A multiple-unit preparation consists of numerous small drug delivery systems. The drug-release profile of the product as a whole is a sum of the drug-release profiles of the individual parts.

Peroral prolonged-release drug products can be prepared e.g. by mixing a drug with a resin insoluble in water. The resulting powder mass is granulated and the granules filled into hard gelatin capsules (multiple-unit system) or compressed into tablets (single-unit system). The resin forms an insoluble matrix from which the drug is released by diffusion through pores. Waxy materials can be used instead of resins. The mechanism of drug release is then erosion of the wax matrix.

Another way of preparing prolonged-release tablets is to coat the tablets with an insoluble semipermeable coat. Granules can be similarly coated with such of coat.

A multiparticulate product can be prepared accordingly (Lordi 1986).

In recent years use of hydrophilic polymers in prolonged-release peroral drug products has been intensively studied. The commonest type of preparation containing a hydrophilic polymer such as hydroxypropylcellulose, hydroxypropylmethylcellulose (HPMC) and sodium carboxymethylcellulose (NaCMC) is a single-unit tablet (Lordi 1986). Drug release from a hydrophilic matrix can take place by diffusion through a gel layer formed around the matrix or by gradual erosion of the gel matrix (Alderman 1984).

1.2. Hard gelatin capsules

The two-piece telescopic gelatin capsule, invented by James Murdock, was patented in the United Kingdom in 1865. It is a popular dosage form, especially in Central Europe and USA. Gelatin is prepared by hydrolytic treatment of animal collagen. Common sources of collagen are animal bones and pigskin. Hard gelatin capsules allow ready availability of any drug they contain, since few excipients and little pressure are required (van Hostetler 1986).

Hard gelatin capsules can also be used in preparing modified-release dosage forms. One simple way of producing multiple-unit products is to fill coated granules or matrix pellets into capsule shells (Lordi 1986). Prolonged-release single-unit systems can be made by using hydrophilic polymers as diluents in capsules. Liquid or semisolid hydrophobic materials can be used instead of hydrophilic powders in filling capsules (Hunter et al. 1982; Marvola et al. 1988; Bodmeier et al. 1990).

Although prolonged-release hydrophilic matrix tablets have been the subject of intensive research and development few reportes have been published on the biopharmaceutical characteristics of hard gelatin capsules containing simple mixtures of drug and hydrophilic polymer. Prolonged-release ibuprofen capsules have been prepared using NaCMC (Marvola et al. 1991; Ojantakanen et al. 1993a) and HPMC (Ojantakanen et al. 1993a) as diluents. Furosemide capsules containing HPMC have also been shown to behave as a prolonged-release product in dogs (Smal et al. 1994). Drug release rate from hard gelatin capsules containing HPMC as a diluent has been shown to be decreased (Jalil and Ferdous 1993).

Hard gelatin capsules have also been used to prepare prolonged-release products known as hydrodynamically balanced or buoyant capsules (Ingani et al. 1987; Oth et al. 1992). Such capsules contain sodium bicarbonate, which leads to formation of gas bubbles in the gel of the polymer (e.g. HPMC)in the stomach. Hydrophilic matrix capsules as modified-release drug delivery systems are easy to prepare on both bench and industrial scales.

On an industrial scale, hard gelatin capsules are most frequently filled by means of so-called dosator-type machines (Jones et al. 1988). These consist of a dosing tube inside which there is a spring-loaded piston. The tube is plunged, open end first, into a powder bed. Material rises up into the tube, as far as the piston, to form a plug of powder. This can be consolidated by applying a compressive force to the piston. The plug is then placed in a capsule. The compressive forces nowadays used in industrial-scale machines for plug formation range typically from 50 to 300 N, or 5 to 30 kg (Lerk et al. 1979; Botzolakis and Augsburger 1984; Shah et al. 1986; Augsburger 1988).

On a small scale, and in development phases and basic research, capsules are filled manually. Such filling does not involve the plug formation that occurs on an industrial scale. Plug formation can, however, change the disintegration and gel-forming properties of the capsule contents. It is important to know whether plug formation affects prolonged-release formulations. One aim of the study reported here was to develop simple equipment for simulating plug formation in connection with capsule filling.

1.3. Press-coated prolonged-release tablets

During the last five years, a press-coated prolonged-release tablet has been developed in the Division of Biopharmaceutics and Pharmacokinetics, Department of Pharmacy, University of Helsinki, (Sirkiä et al. 1992). The tablets consist of a core and a coat. Both the core and the coat would contain the drug but only the coat contains a polymer controlling release of the drug. Such a tablet can easily be prepared using the well-known compression-coating technique. An international patent application concerning this invention has been filed (patent application PCT/FI 92/242).

Drug release from such tablets can be modified to obtain zero-order kinetics or kinetics reflering a release rate increasing with time (Sirkiä et al. 1992). A drug release-rate increasing with time could be valuable in diseases having marked diurnal rhythms. In such diseases, therapeutic drug concentrations should vary during the day. Drug levels should be highest when symptoms are most severe. For example, in rheumatism, morning stiffness is common. In theory, maximum drug levels could be achieved in the morning if a formulation from which drug release increased with time were administered the previous evening.

Factors affecting release rates and release profiles from press-coated tablets are amounts and viscosity grades of polymers used in the coat, and ratios of drug dose in core and coat. Up to now, the only polymer that has been found to behave as predicted in the invention has been HPMC (Sirkiä et al. 1993). In the study

reported here, the behavion of sodium alginates in the new type of dosage form was therefore also examined.

1.4. Sodium alginates

Sodium alginates are hydrophilic polysaccharides produced from selected species of brown seaweeds. Structurally, they are linear copolymers containing two types of sugar residue: D-mannuronate (M) and L-guluronate (G). These occur in alginate molecules in three types of sequence: poly-M, poly-G and poly-MG (McDowell 1986). Sodium alginates have been used in the food industry for a long time. They have also been intensively studied as additives to solid and liquid drug products.

In 1978 Klaudianos published a report of his attempts to prepare prolonged-release alginate tablets. Sodium alginate has subsequently been used for preparation of calcium-induced alginate gel beads (matrices) by means of which prolonged drug release can be achieved (Badwan et al. 1985; Yotsuyanagi et al. 1987; Segi et al. 1989; Östberg and Graffner 1992; Murata et al. 1993; Tateshita et al. 1993; Östberg et al. 1993).

Use of sodium alginate as such, without formation of calcium alginate, has been unusual. Timmins et al. (1992) studied use of two grades of sodium alginate as a hydrophilic polymer in verapamil matrix tablets. Alginate-based prolonged-release theophylline tablets and suspensions have also been studied (Fu Lu et al. 1991; Zatz and Woodford 1987). Ojantakanen et al. (1993b) used sodium alginate in ibuprofen capsules but drug absorption from the resulting formulation in man was not prolonged. This could have been because sodium alginate of too low a viscosity grade was used. Sodium alginate has also been used with sodium bicarbonate in buoyant capsules (Stockwell et al. 1986).

It is common in scientific papers for the term sodium alginate to be used without further classification. However, there are many different types of sodium alginate on the market differing in chemical and physical characteristics such as molecular weight and particle size (McDowell 1986). In research work, attention must be paid to such properties.

1.5. Ibuprofen

Ibuprofen is a nonsteroidal anti-inflammatory drug that inhibits prostaglandin synthetase. Ibuprofen is used for relief of acute pain and for pain relief in chronic diseases such as rheumatoid arthritis and osteoarthritis (Kantor 1979). Chemically it is d,1-2-(4-isobutylphenyl)propionic acid a weak acid (pK_a 4.8) (Ritschel 1992).

It is practically insoluble in water. At pH 2.0 its solubility is 22 $mg \cdot l^{-1}$, at pH 7.0 2440 $mg \cdot l^{-1}$ (Herzfeldt and Kummel 1983).

Ibuprofen is rapidly and completely absorbed after peroral administration. It has been shown to be absorbed throughout the gastrointestinal tract, from the stomach to the rectum (Wilson et al. 1989). It is therefore a good candidate for formulation a prolonged-release product. In studies with solutions for oral administration, peak plasma concentrations were achieved 0.5 to 0.7 hours after administration (Gillespie et al. 1982; Lockwood et al. 1983; Marvola et al. 1991). For conventional tablets and capsules t_{max} values of 1.3 to 2.7 hours have been reported (Gillespie et al. 1982; Stead at al. 1983; Palva et al. 1985; Benvenuti et al. 1986; Regazzi et al. 1986; Dash et al. 1988; Karttunen et al. 1990; Vidgren et al. 1991).

Elimination half-life of ibuprofen has been found to range from 1.5 to 2 hours (Lockwood et al. 1983; Karttunen et al. 1990). A short elimination half-life results in wide fluctuations between steady state maximum and minimum concentrations (Ritschel 1992). In long-term therapy, fluctuations in the plasma concentration with high concentration peaks are common with drugs rapidly absorbed and eliminated. To avoid this, use of a prolonged-release product is appropriate.

Prolonged-release ibuprofen formulations have been prepared by filling coated pellets into hard gelatin capsules (Regazzi et al. 1986; Wilson et al. 1989). Marvola et al. (1991) prepared prolonged-release ibuprofen capsules using NaCMC, Ojantakanen et al. (1993a) used HPMC as a diluent. Shah et al. (1989; 1990) prepared bimodal release gel matrices and divisible tablets to extend the absorption of ibuprofen. Matrix formulations containing hydrophilic and hydrophobic polymers have also been prepared (Malamataris and Ganderton 1991).

1.6. Pseudoephedrine hydrochloride

Pseudoephedrine [(+)-(1S,2S)-2-methylamino-1-phenylpropan-1-ol] is a stereoisomer of ephedrine. It is a sympathomimetic, usually used as a decongestant but also employed as an antiasthma drug. Pseudoephedrine has fewer central nervous system effects than ephedrine. Pseudoephedrine is readily absorbed from the gastrointestinal tract. It is largely excreted unchanged in the urine, with an elimination half-life of 5 to 8 hours. An increase in urinary pH to 8 lengthens the elimination half-life up to 18 hours (Kuntzman et al. 1971; Yacobi et al. 1980; Lin et al. 1985; Martindale The Extra Pharmacopoeia 1989).

Pseudoephedrine has a pK_a value of 9.86 (Ritschel 1992) or 9.22 (Merck Index 1983). The hydrochloride salt is freely soluble in water. Pseudoephedrine hydrochloride is usually administered via conventional dosage forms as 60 mg

three or four times daily. Prolonged-release formulations containing 120 mg of pseudoephedrine hydrochloride have been marketed (Wecker et al. 1987; Bodmeier et al. 1991). Such formulations are administered twice daily. In commercial preparations, pseudoephedrine is often combined with codeine or an antihistamine.

2. AIMS OF STUDY

The main aim of the study reported here was to determine whether sodium alginate could be used to modify drug release in formulations for peroral administration. Hard gelatin capsule formulations were studied first because they are easy to prepare on a small scale and industrially. Use of sodium alginate in a new type prolonged-release press-coated tablet developed in the Division of Biopharmaceutics and Pharmacokinetics, Department of Pharmacy, University of Helsinki was also studied.

In detail, the aims of the study were:

- to determine the effects of the chemical and physical properties of different grades of sodium alginate on the pharmaceutical characteristics of products

- to determine the properties of formulations containing only a sparingly water-soluble drug (ibuprofen) of a highly water-soluble drug (pseudoephedrine hydrochloride)

- to determine the mechanism by which sodium alginate controls drug release from capsule formulations

- to establish whether there were any differences between capsules filled manually and capsules filled using equipment that simulates plug formation in capsule-filling machines

- to conduct bioavailability studies of selected formulations in man.

3. MATERIALS AND METHODS

3.1. Sodium alginates

The polymers used to modify drug release in the studies reported in papers II-V were sodium alginates. Fourteen grades of sodium alginate manufactured by Kelco Ltd, were used in the study reported in paper II. Particular, grades were then selected for further experiments (reported in papers III-V). The trade names and specifications (chemical structure, viscosity grade and particle size) of the 14 grades are reported in paper II. More detailed information about these substances can be found in the booklet by McDowell (1986).

3.2. Model drugs

In the studies reported in papers I-IV *ibuprofen* manufactured by Orion-Farmos Pharmaceutical was used as a model drug. It met the specifications of the European Pharmacopoeia and was used as supplied. It was regarded as representative of drugs that are only sparingly soluble in water.

Pseudoephedrine hydrochloride manufactured by Knoll AG was selected as representative of highly water soluble drugs (paper V). It met the specifications of the European Pharmacopoeia.

3.3. Additives

In the study reported in paper I the capsules contained, in addition to ibuprofen, microcrystalline cellulose (Emcocel 90M™, E. Mendell), methylcellulose (Methocel A4C, Dow Chemicals), lactose (De Melkindustrie Veghel), corn starch (Maydis amylum, Thibola DRM), and dicalcium phosphate dihydrate (Emcompress™, E. Mendell).

The press-coated tablets described in paper IV contained, in addition to ibuprofen and sodium alginate, potassium carbonate (Carlo Erba), directly compressible lactose (Pharmatose DCL), polyvinylpyrrolidone (PVP) (Kollidon K25, Fluka), magnesium stearate (EP) and talc (EP).

3.4. Preparation of capsule formulations

Size 0 hard gelatin capsules (Posilock™, Elanco) were used for all formulation. Amounts of drug required were weighed out in graduated cylinders and the other ingredients added to produce material sufficient for batches of 25 or 100 capsules. Powder were mixed in mortars and dispensed into capsule shells manually, using

a Feton apparatus.

The compositions (amounts of drugs and other ingredients) of each formulation are given in the original publications.

3.5. Plug formation

To simulate plug formation in dosator-type capsule filling machines special equipment was constructed (paper I, Fig. 1). A dosing tube from a mG2 filling machine was fixed to a plastic plate. The plate was placed on a digital balance. A piston from the same mG2 machine was fixed to a lever system that could move up and down with a static rod.

Plugs were made from the contents of capsules filled manually as described in section 3.4. The powder content of one capsule was poured into the dosing tube. The lever was steadily pulled down and the compression force towards the powder bed measured via the digital balance. After compression, the dosing tube was removed from the plastic plate and the plug was loaded into the capsule body.

The compression forces tested in the study reported in paper I were 10, 20 and 30 kg. For capsules containing sodium alginate compression force of 30 kg was used. Results are reported only in this summary.

With powder mixtures containing sodium alginate it was not possible to prepare firm plugs. Powder mixtures containing sodium alginate were therefore pregranulated. To prepare granules, powders were moistened with a 10% polyvinylpyrrolidone (Kollidon K25) solution. The solvent consisted of water and ethanol (1:1). The wetted powder was sieved through a 0.7 mm sieve and dried overnight at 35°C.

3.6. Preparation of press-coated tablets

Press-coated tablets each consisted of a core and a coat. Drug (100 mg of ibuprofen) was divided between core and coat in the ratio 2:1. Only the coat contained sodium alginate, intended to control drug release. Detailed compositions of all tablets studied are given in paper IV.

Cores containing ibuprofen, potassium carbonate, lactose, magnesium stearate and talc were compressed in a Korsch EK-0 (Erweka Apparatebau) single-punch machine, using concave 7-mm punches. The compression force used was 10-12 kN.

Compression coating was performed manually using the same Korsch single-punch machine equipped with 11-mm punches. Ibuprofen and sodium alginate were mixed in a mixer (Turbula AG) for 10 minutes. The powder mass was moistened with a 10% PVP-water-ethanol solution and sieved through a 0.7 mm sieve. The granules were dried overnight at 35°C. For tableting, the fraction 0.3-0.7 mm was used. Magnesium stearate and talc were added to the granules. Half of the granules for one tablet were weighed into the die and the core was placed on the granule bed. The rest of the granules were added to the die and the tablet was compressed manually, using a force of about 20 kN.

3.7. Dissolution tests

3.7.1. Dissolution of ibuprofen

Dissolution of ibuprofen was determined using the rotating basket method (capsules, papers I and II) or the paddle method (tablets, paper IV), as described for ibuprofen tablets in USP XXII. The dissolution medium was phosphate buffer, pH 7.2 (900 ml at 37°C). The speed of rotation was 150 min^{-1} for capsules and 50 min^{-1} for tablets.

The dissolution apparatus (Dissolutest 07, Prolabo) was connected to a flow-through spectrophotometer (Ultraspect II, LKB Biochrom Ltd) via a peristaltic pump (Watson-Marlow 503S, Smith and Nephew). Absorbances of dissolution medium in 2-mm flow-through cells at 221 nm were recorded automatically at regular intervals. The reference cell contained solvent saturated with the grade of sodium alginate used in the formulation concerned. Measurements were monitored using a computer running tablet-dissolution software (TDS™, LKB Biochrom Ltd). Release data relating to alginate-based ibuprofen capsules were fitted to zero-order kinetics curves (II).

3.7.2. Dissolution of pseudoephedrine hydrochloride

Dissolution of pseudoephedrine hydrochloride from capsules (V) was determined using the USP rotating basket method. Solvents of three pH values were used, namely (1) pH 1.2 (0.1 $mol \cdot l^{-1}$ hydrochloric acid), (2) pH 4.4 (phosphate buffer) and (3) pH 7.2 (phosphate buffer). The volume of dissolution medium was 900 ml and the temperature of the dissolution apparatus (Sotax AT 7) 37°C. The speed of rotation was 150 min^{-1}. Samples of 1 ml were taken manually at predetermined times.

Drug concentrations in the samples were determined using the high-performance liquid chromatography (HPLC) method described in section 3.10.2. Determination

of pseudoephedrine (Dowse et al. 1983). The volume of sample administered to the injector was 10 µl. No extraction of samples was needed. Goodness of fits of dissolution curves to first-order and square-root-of-time equations were tested using Minsq™ software (Mircomath).

3.8. Penetration of dissolution medium into capsules

Penetration of dissolution medium into capsules was studied with formulations containing pseudoephedrine hydrochloride (V). The test was analogous to the ordinary dissolution test but the dissolution medium contained 0.1% fuchsin (E. Merck), giving it a red colour. At predetermined times, capsules were removed from the dissolution apparatus and cut in two. Penetration of the coloured solution was evaluated by visual inspection and recorder by photography.

This summary includes results relating to penetration of dissolution medium into capsules not included in the original publications.

3.9. Bioavailability studies

All bioavailability studies were carried out in young, healthy volunteers (III-V) who participated in randomized, single-dose, cross-over studies carried out in accordance with the recommendations of the Declaration of Helsinki (World Medical Assembly 1964) as revised in Tokyo (1975). The study protocols were approved by the Ethical Committee of the University of Tartu.

One week before the study, participants underwent routine medical control. Volunteers were informed about possible risks and side-effects of the drug. Their written consent to participation in the study was obtained. All were non-smokers. None took any medicine during the study or one week before it.

Each drug product was administered with 200 ml of water following an overnight fast of at least 10 hours. The dose of ibuprofen was 400 mg, that of pseudoephedrine hydrochloride 100 mg. A standard lunch was provided 3 hours after drug administration. The washout period was at least one week. Blood samples (10 ml) were collected from a forearm vein into heparinized tubes at predetermined times. Plasma was separated by centrifugation approximately 30 minutes after collection, and stored at -20 °C until analysed.

3.10. Plasma assay

3.10.1. Determination of ibuprofen

Ibuprofen plasma concentrations were determined by means of HPLC, using a slightly modified version of the method described by Avgerinos and Hutt (1986). The system was equipped with a Waters Model 501 piston pump, a Waters Model 717 Intelligent Sample Processor, a Waters Model 486 tunable Absorbance Detector operating at 222 nm and a Waters Model 820 Maxima Workstation (Waters Ltd). Sample separation was carried out on a µBondapak C_{18} reverse-phase column (3.9 x 300 mm). The guard column was an RCSS µBondapak C_{18}. The mobile phase was acetonitrile and 0.1 M sodium acetate (35:65), the pH of which was adjusted to 6.2 with glacial acetic acid. All chemicals were of analytical or HPLC grades. The flow rate was 2 $ml \cdot min^{-1}$.

The standard curve was found to be linear over the concentration range 2-40 $mg \cdot l^{-1}$ ($r > 0.99$), and passed close to the origin. The accuracy and precision of the method were investigated as recommended by Shah et al. (1992) by analysing six plasma samples containing drug concentrations of 2.0 and 40.0 $mg \cdot l^{-1}$. Mean values were 2.33 $mg \cdot l^{-1}$ coefficient of variation (CV 3.8%) and 40.2 $mG \cdot l^{-1}$ (CV 5.8%), respectively. The limit of quantitation was 2 $mg \cdot l^{-1}$. No interfering peaks were observed in plasma blanks.

3.10.2. Determination of pseudoephedrine

Pseudoephedrine concentrations were determined by HPLC, using a version of the method of Dowse et al. (1983) modified in relation to handling of plasma samples. One millilitre of plasma, 50 µl of a saturated solution of sodium carbonate and 100 µl of 2 M sodium hydroxide solution were vortexed for 15 seconds. Four millilitres of diethyl ether were added and tube were vortexed for one minute and centrifuged for 5 minutes. Two millilitres of ether extract were transferred to a centrifuge tube containing 100 µl of 5% acetic acid. The mixture was vortexed for one minute and centrifuged for 5 minutes. The ether layer was reduced and the water layer transferred to a clean tube, from which 50 µl were taken for determination of drug levels. Each plasma sample was analysed in triplicate. Mean values were calculated.

HPLC equipment (Waters Ltd.) was as described in section 3.10.1. (Determination of ibuprofen). The UV detector was operating at 220 nm. The mobile phase was prepared by mixing acetonitrile (200 ml) with a 0.005 M solution of sodium-1-heptanesulfonate in water (800 ml) and adding 2 ml of 1 M hydrochloric acid. The flow rate was 1.3 $ml \cdot min^{-1}$.

The standard curve was found to be linear over the concentration range 50-1000 $ng \cdot ml^{-1}$ and passed close to the origin. The linear coefficient of determination was 0.993 or better. Accuracy and precision of the method were investigated by analysing six plasma samples of pseudoephedrine concentrations of 50 and 500 $ng \cdot ml^{-1}$. Mean values were 45.4 $ng \cdot ml^{-1}$ (C.V. 18.3%) and 484 $ng \cdot ml^{-1}$ (C.V. 2.7%). The limit of quantitation was estimated to be 50 $ng \cdot ml^{-1}$. No interfering peaks were observed in plasma blanks.

3.11. Pharmacokinetic parameters

The pharmacokinetic parameters assessed using the Siphar™ program (Simed) were maximum plasma concentration (C_{max}), time to peak concentration (t_{max}), area under concentration-time curve from time 0 to infinity (AUC), half-life of elimination phase ($t_{½}$) and mean residence time (MRT). C_{max} and t_{max} values were used as measured. AUC and MRT values were calculated by the trapezoidal method, without logarithmic transformation. The ratio C_{max}/AUC was also calculated and used to evaluate of the rate of the absorption phase (Shall and Luus 1992).

Statistical analyses were carried out using Student's t-test and Student's paired t-test. Values of t_{max} were analysed using the nonparametric tests of Wilcoxon and Mann-Whitney.

4. RESULTS AND DISCUSSION

4.1. Effects of different grade of sodium alginate on pharmaceutical properties of formulations

4.1.1. Sodium alginate as diluent in hard gelatin capsules (II)

Fourteen grades of sodium alginate were studied. Six were of the Manugel series (rich in guluronic acid), 8 of the Manucol series (rich in mannuronic acid). Viscosity grades in the Manugel series varied from 75 to 500 mPa·s, in the Manucol series from 4 to 300 mPa·s. Some differences existed in particle size between the grades (in paper II, Table 1). The drug studied was ibuprofen. Three drug:diluent ratios were investigated (II, Table 1-2).

Dissolution of ibuprofen from 42 formulations was studied at pH 7.2. Drug release from each formulation followed zero-order kinetics. Rate constants for Manugel-based capsules varied from 5.8 to 19.4 $\%\cdot h^{-1}$, for Manucol based capsules from 8.0 to 57.5% $\cdot h^{-1}$. It was therefore concluded that release rates of ibuprofen can be altered markedly through choice of a sodium alginate with appropriate chemical and physical properties. Additional adjustment is possible by varying the drug:diluent ratio. The relationship between release rate constant (k_0) and relative amount of sodium alginate in the capsule was approximately linear.

As a rule, release of ibuprofen from Manugel-based capsules was slower than that from capsules containing the equivalent viscosity grade of Manucol. This is in accordance with findings relating to tablets of verapamil hydrochloride based on Manugel and Manucol (Timmins et al. 1992). Manugels have been reported to form more rigid gels when hydrated than Manucols (McDowell 1986). More rigid gels may be less prone to erosion and constitute more effective barriers to release of drugs by diffusion.

Because the grades of Manugels and Manucols studied differed as regards viscosity grade, it was difficult to draw conclusions about effect of particle size alone. A tendency for drug release to be slower as particle size increased was evident with Manugel (II, Fig. 5). With Manucol, there was no correlation between drug release rate and particle size.

Use of various grades of HPMC as diluents in ibuprofen capsules resulted in square-root-of-time release kinetics. With many grades of NaCMC fairly good fits with zero-order kinetics were obtained (Ojantakanen 1992). The release rates of ibuprofen found in the studies forming the subject of this dissertation were similar to those with NaCMC-based ibuprofen capsules but higher than those with HPMC

based capsules. Release of ibuprofen, a weak acid, is no doubt faster from sodium-alginate- and NaCMC-based capsules because of the ionic natures of the polymers. Zero-order release of ibuprofen, desirable in prolonged-release drug products, would seem to be related to use of ionic, and sodium-containing polymers, e.g. sodium alginate and NaCMC.

4.1.2. Sodium alginate in coats of press-coated tablet (IV)

Sodium alginate was studied as an ingredient of press-coated prolonged-release tablets. Four grades of sodium alginate were investigated (Manugel GHB, Manugel DPB, Manucol LF and Manucol DM). Amounts of sodium alginate in coats were also varied. The model drug was ibuprofen. The pH of dissolution medium was 7.2.

In every case, the release profile was biphasic (IV, Fig. 1). In the initial phase, release rates increased with time. The second phase fitted best with zero-order kinetics (IV, Fig. 2). Release rates in the second phase were higher than in the initial phase. By selecting an appropriate grade of sodium alginate it was possible to delay commencement of the faster second phase by 2 to 7 hours. Such release profiles were in accordance with the goals set for the press-coated tablets.

A rank-order correlation existed between viscosity grade of sodium alginate and mean curves for cumulative amounts of ibuprofen released. The higher the viscosity grade, the lower the release rate (IV, Fig. 1). There were no marked differences between curves for tablets containing Manucol DM (viscosity 250 mPa·s) and tablets containing Manugel GHB (viscosity 75 mPa·s). Viscosity grade of sodium alginate is therefore not the only factor that affects drug release from the present kind of press-coated tablet. This finding is in agreement with findings relating to capsule formulations (section 4.1.1).

Amount of sodium alginate in coats affected the overall release rate but not release profile (IV, Fig. 3). However, amount of sodium alginate had a smaller effect than that of viscosity grade of sodium alginate.

It was concluded that drug release rate from press-coated tablets developed could be controlled by appropriate choise of grade of sodium alginate. In this respect, sodium alginate differed from NaCMC, which did not function as expected in the type of press-coated tablets studied (Sirkiä et al. 1993). However, using sodium alginate, it did not prove possible to prolong release of ibuprofen from the press-coated tablets as much as with HPMC (Sirkiä et al. 1992; Sirkiä et al. 1994).

4.1.3. Effects of dissolution pH on properties of sodium alginate capsules (V)

Effects of pH of dissolution medium were examined for capsule formulations containing pseudoephedrine hydrochloride, the aqueous solubility of which does not depend markedly on pH in the physiological range. The pH levels investigated were 1.2, 4.4 and 7.2. Sodium alginate grades studied were Manugel DPB, Manugel GHB, Manucol DM and Manucol LD.

At pH 1.2, similar to that in the stomach, there were no differences between the formulations. At higher pH values, differences between formulations were minimal, especially at pH 7.2 (V, Fig. 1). When the capsules contained Manucol DM, Manugel GHB or Manugel DPB, release rates of pseudoephedrine hydrochloride were highest at pH 1.2 and lowest at pH 4.4., except for Manugel DPB at pH 7.2 (V, Fig. 1). Capsules containing the alginate of lowest viscosity grade (Manucol LD) differed markedly in behaviour. Drug release was slowest at pH 1.2, highest at pH 7.2.

Timmins et al. (1992) found that release rates of verapamil hydrochloride from sodium alginate matrix tablets were only partially dependent on pH of the dissolution medium. If matrices had been prepared from sodium alginate rich in mannuronic acid (Manucol DMF) dissolution medium pH (1.2 or 7.4) had no marked effect on dissolution rate. In contrast, if the alginate used was rich in guluronic acid (Manugel DMP), reduction in pH significantly increased release rates of verapamil hydrochloride. In the studies reported here dissolution of pseudoephedrine hydrochloride depended on pH with all grades of sodium alginate. With Manugel DPB, Manugel GHB and Manucol DM, dissolution rates were highest at pH 1.2. With Manucol LD dissolution rate was lowest at pH 1.2.

Dissolution rates of pseudoephedrine, which is highly water soluable, were higher than those of ibuprofen, which is sparingly soluble in water, from similar capsules at pH 7.2 (II, V).

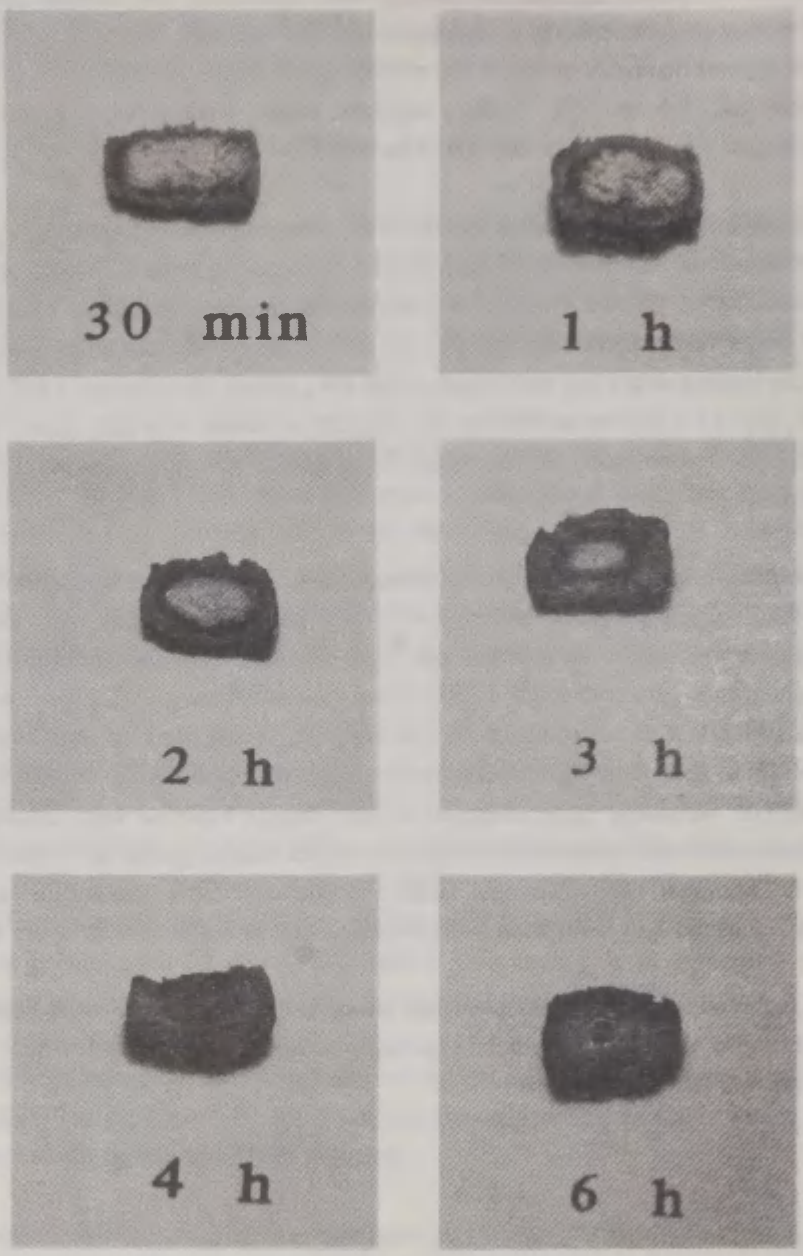

Fig. 1. Penetration of dye in solvent (pH 1.2) into pseudoephedrine hydrochloride capsules containing Manugel DPB as diluent.

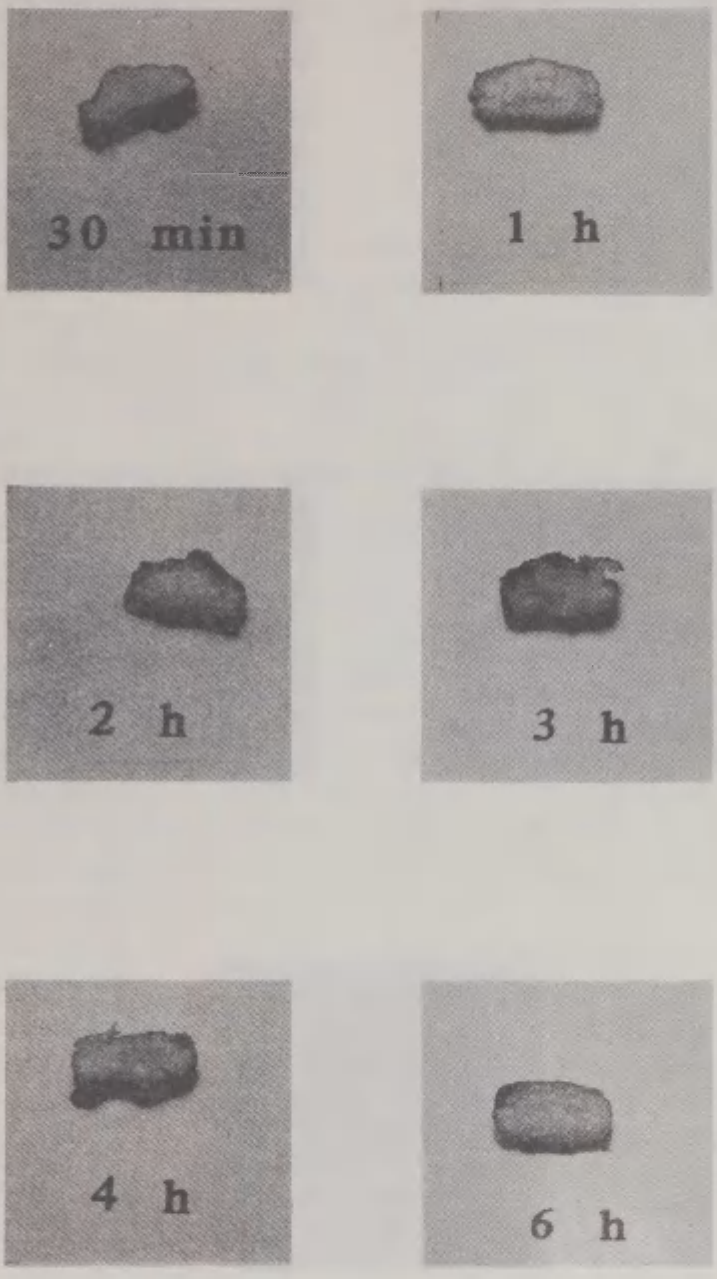

Fig. 2. Penetration of dye in solvent (pH 1.2) into ibuprofen capsules containing Manugel DPB as diluent.

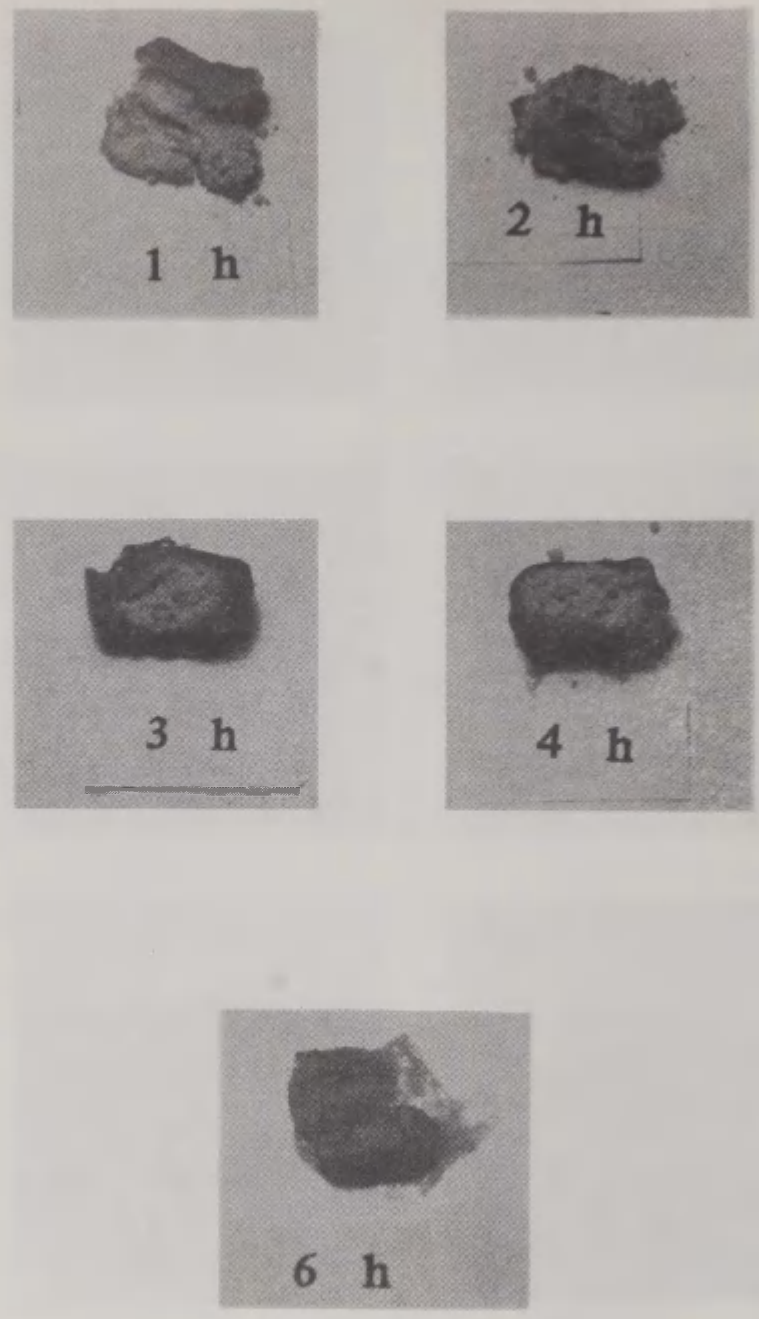

Fig. 3. Penetration of dye in solvent (pH 7.2) into pseudoephedrine hydrochloride capsules containing Manugel DPB as diluent.

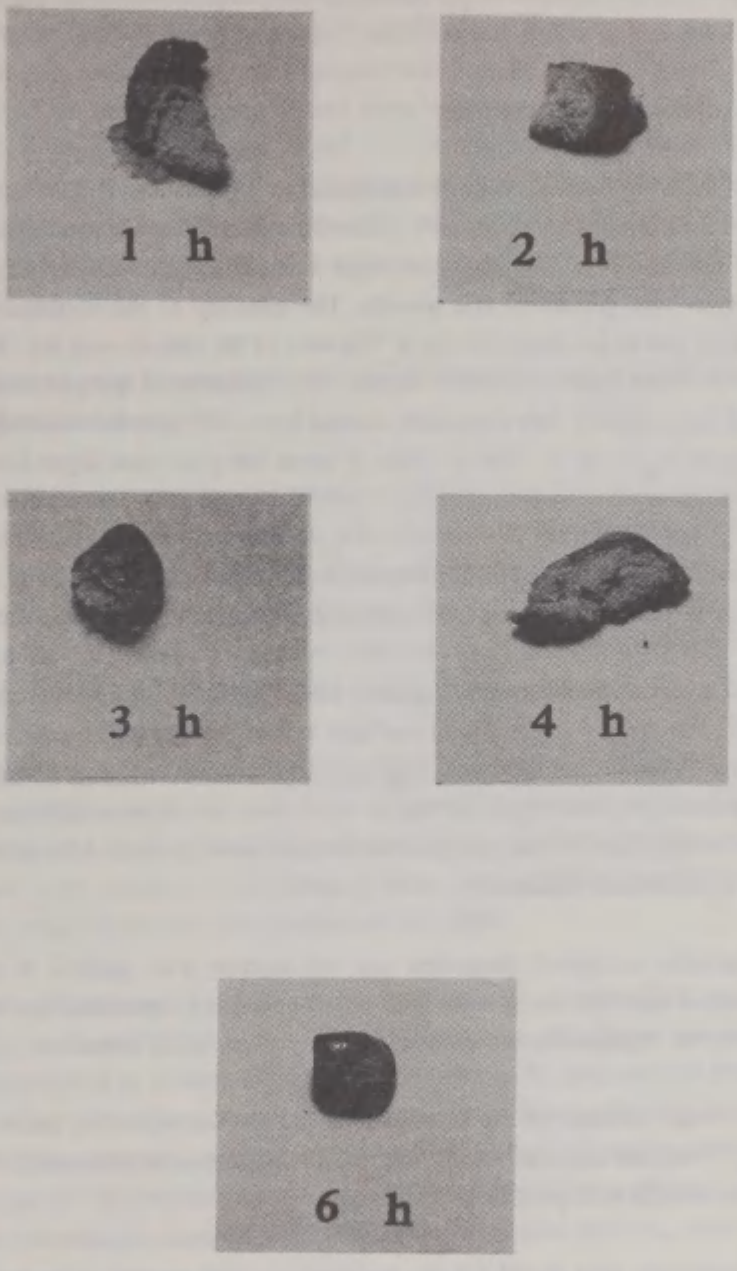

Fig. 4. Penetration of dye in solvent (pH 7.2) into ibuprofen capsules containing Manugel DPB as diluent.

4.2. Penetration of dissolution medium into capsules

To obtain more information on gel-formation and drug-release mechanisms, a dye (fuchsin) was added to dissolution media. Experiments were carried out at two pH levels (1.2 and 7.2) with Manugel-DPB-based formulations containing ibuprofen or pseudoephedrine hydrochloride.

Figure 1, showing findings with pseudoephedrine capsules at pH 1.2 is analogous to Figure 2 in original publication V. After 30 minutes three layers were visible, two wet and one dry. The outermost layer was thin, tight and fairly hard. The second layer was gelatinous and smooth. The intensity of red in this layer was greater than that in the outermost layer. The core of the capsule was dry. After one to 3 hours, three layers remained visible. The thickness of the outermost layer increased more rapidly than that of the second layer. Dry powder was only visible in photographs for up to 4 hours. After 6 hours the gelatinous layer had almost totally disappeared.

Under similar conditions (pH 1.2), ibuprofen capsules behaved similarly (Fig. 2). Three layers were visible but penetration of dye into the capsule was slower.

Only two layers were observed in capsules when dissolution tests were carried out at pH 7.2. For up to 6 hours dry or partially wetted powder was surrounded with a gel layer. Initially this layer was thin and brittle. After one to 2 hours the gel around pseudoephedrine capsules was so weak that it was impossible to cut the capsules in two (Fig. 3). The gel layer became thicker with time. After 6 hours the gel was of maximum thickness.

When capsules contained ibuprofen and dissolution was studied at pH 7.2, penetration of dye was slower than with pseudoephedrine capsules (Fig. 4). It was difficult to cut capsules in two without breaking them, at all times.

At pH 1.2 the volumes of the formulations did not increase, i.e. there was no swelling of sodium alginate. At pH 7.2. volumes of capsules increased. This was especially evident with pseudoephedrine capsules.

In the dissolution tests at pH 1.2 the hydrochloric acid reacted with the sodium alginate, and the outermost layer consisted of precipitated alginic acid. The gelatin shell could also have played a role in commencement of formation of an outermost layer (Carstensen and Rhodes 1993). As the dissolution medium penetrated the capsule, hydrogen ions would have been exchanged for sodium ions, and the dissolution medium would have declined in acidity. A second gelatinous layer would therefore have formed only when a slightly acidic, i.e. almost neutral

solution, moistened the sodium alginate. This would explain why there was no difference in dissolution curves between formulations at pH 1.2 (V, Fig. 1.). In all formulations, alginic acid precipitated and formed a tight outermost layer that acted as a rate-limiting layer in relation to diffusion of drug.

The differences between ibuprofen and pseudoephedrine hydrochloride capsules observed in penetration studies at pH 1.2 may be explicable on the basis of differences in aqueous solubility and chemical natures of the two model drugs. At pH 7.2 alginic acid cannot precipitate. The outer layer consists only of sodium alginate gel.Its tightness depends on the viscosity grade and chemical nature of the sodium alginate used.

4.3. Effect of plug formation on in vitro properties of pseudoephedrine hydrochloride capsules

In the study described in paper I, simple equipment simulating plug formation in dosator-type capsule filling machines was constructed. With this simulator it was possible to measure the compression force used in plug formation. Plug formation using the simulator corresponded to plug formation in a real capsule-filling machines. In this respect, it was better than the simulators designed by Lerk et al. (1979), Jolliffe et al. (1982) or Naidoo (1989).

The suitability of the simulator was tested by preparing ibuprofen capsules containing typical diluents. Various compression forces were used. Drug dissolution was studied. Dissolution characteristics of capsules filled using the simulator were similar to those obtained when corresponding formulations filled using on mG2 filling machine (Hannula et al. 1989).

With powder mixtures containing sodium alginate it was impossible to compress the plugs needed in dosator-type filling machines. A granulation was needed to allow preparation of sodium-alginate-based capsules. To determine of granulation affected drug release rate, capsules containing ungranulated and granulated powder mixtures were prepared, using pseudoephedrine as drug. There were no marked differences in drug-release curves between Manucol LD based capsules filled without compression force (Fig. 5). Differences in results at pH 1.2. and 7.2 were minimal.

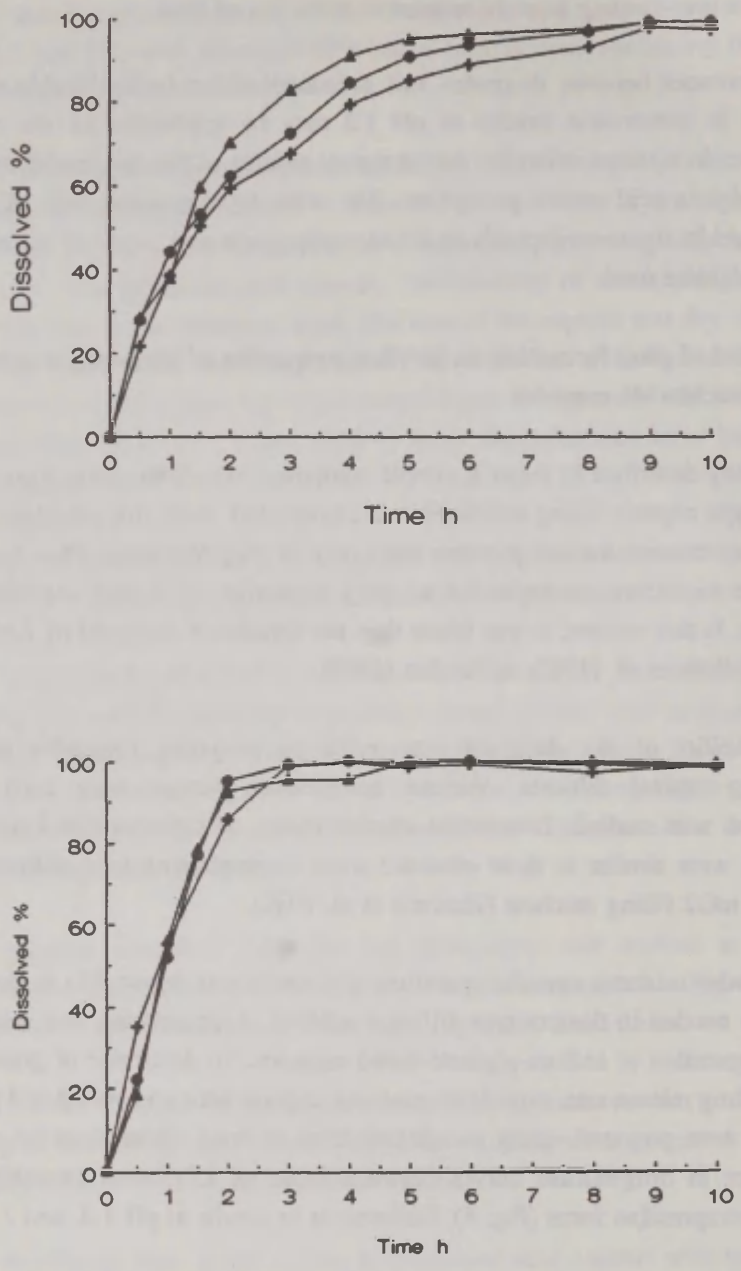

Fig. 5. Effects of granulation and compaction on dissolution of pseudoephedrine hydrochloride from Manucol LD based capsules at pH 1.2 (upper panel) and at pH 7.2 (lower panel). + = powder mixture, ▲ = granules, ● = granules with compression force of 30 kg.

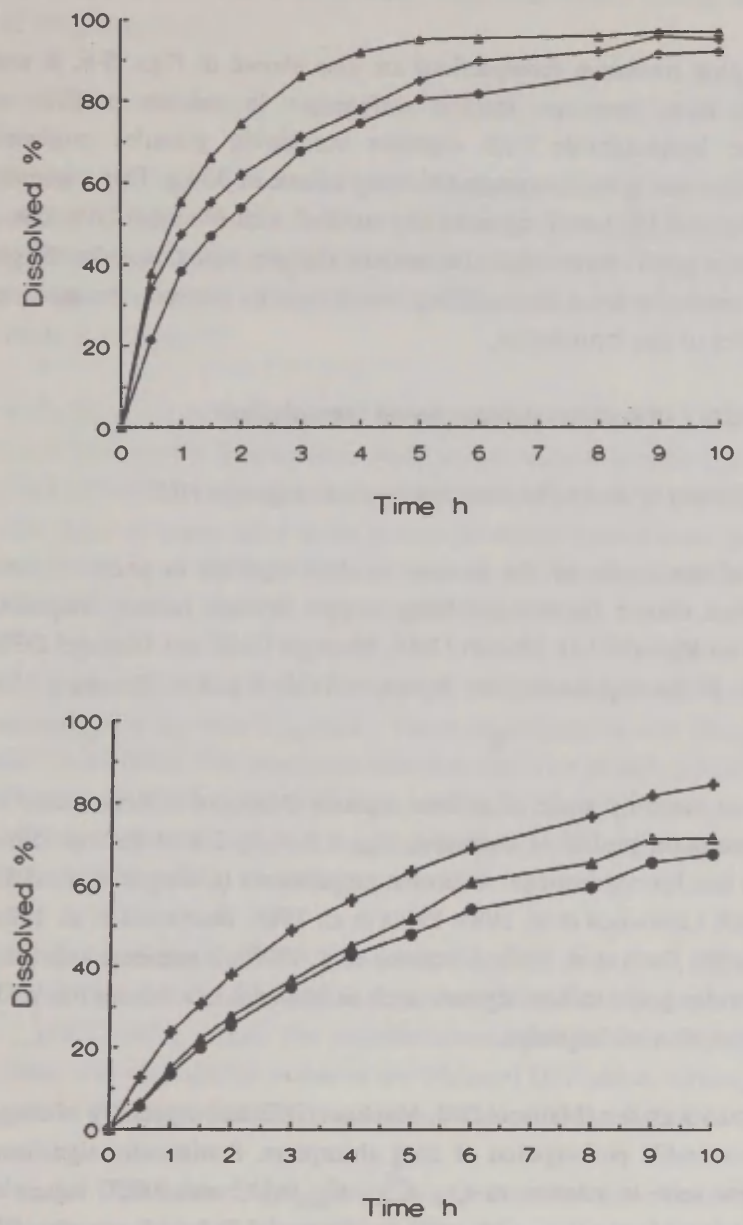

Fig. 6. Effects of granulation and compaction on dissolution of pseudoephedrine hydrochloride from Manugel DPB based capsules at pH 1.2 (upper panel) and at pH 7.2 (lower panel). + = powder mixture, ▲ = granules, ● = granules with compression force of 30 kg.

When Manugel DPB was used small differences were seen between the granulated and the ungranulated formulations (Fig. 6). At pH 1.2 granulation increased the dissolution rate of pseudoephedrine hydrochloride slightly. At pH 7.2 the effect was the reserve.

The effects of plug formation (compaction) are also shown in Figs. 5-6. It was concluded that there were no marked differences in release profiles of pseudoephedrine hydrochloride from capsules containing granules produced without compaction and granules compacted using a force of 30 kg. This was most evident with Manucol LD based capsules, less marked with Manugel DPB based capsules. This is a good characteristic for sodium alginate based capsules. Slight variations in compression force during filling would have no marked effects on the in vitro properties of the formulation.

4.4. Bioavailability of sodium alginate based formulations

4.4.1. Bioavailability of ibuprofen from hard gelatin capsules (III)

On the basis of the results of the in vitro studies reported in paper II, four formulations were chosen for bioavailability studies in man, namely ibuprofen capsules based on Manucol LD, Manucol DM, Manugel GHB and Manugel DPB. Detailed results of the experiments are shown in Table I and in Figures 1-3 on paper III.

When the lowest viscosity grade of sodium alginate (Manucol LD) was used as diluent, the absorption profile of ibuprofen (t_{max} 1.9 h, $t_{½}$ 2.5 h) did not differ markedly from that for conventional ibuprofen preparations (Gillespie et al. 1982; Stead et al. 1983; Lockwood et al. 1983; Palva et al. 1985; Benvenuti et al. 1986; Regazzi et al. 1986; Dash et al. 1988; Karttunen et al. 1990). It was concluded that a very low viscosity grade sodium alginate such as Manucol LD did not markedly prolong the absorption of ibuprofen.

The higher viscosity grades (Manucol DM, Manugel GHB and especially Manugel DPB) led to noticeable prolongation of drug absorption. Statistically significant differences were seen in relation to t_{max}, C_{max}, C_{max}/AUC and MRT values of capsules containing Manugels as compared to Manucol LD based capsules (III, Table II). The $t_{½}$ of Manugel DPB capsules also differed significantly from that of Manucol LD capsules. Accordingly, ibuprofen capsules based on Manucol DM or Manugel GHB was classified as slow-release products, and capsules containing Manugel DPB were categorized as an extended-release product.

The overall conclusion from the studies with ibuprofen capsules was that by using with different viscosity grades of sodium alginate it is possible to prepare capsules of a sparingly water-soluble drug such as ibuprofen the rate of absorption of which can be controlled over a fairly wide range without any decline in overall amount of drug absorbed.

4.4.2. Bioavailability of ibuprofen from press-coated tablets (IV)

In the next stage the suitability of sodium alginate was studied in press-coated modified-release tablets. The four grades of sodium alginate used were Manucol LF, Manucol DM, Manugel GHB and Manugel DPB. The sodium alginate was confined to the coat of the tablet. Detailed results are given in Figures 4-5 and Table 1 in paper IV.

As far as extent of bioavailability of ibuprofen was concerned, no differences were found between the formulations. AUC values were of similar magnitudes to those obtained with corresponding immediate-release products. These findings consistent with those of many other investigations in which formulations factors have been found to have no marked effects on amounts of ibuprofen absorbed (Regazzi et al. 1986; Marvola et al. 1991; Ojantakanen et al. 1993).

The parameter that appeared to distinguish the formulations from each other best seemed to be the ratio C_{max}/AUC. This is in accordance with the opinion of Shall and Luus (1992). The absorption rate characteristics of tablets containing Manucol LF were similar to those of immediate-release ibuprofen products (t_{max} 2.7 h and $t_{½}$ 2.3 h). Peak concentrations were seen in every volunteers. This finding is typical of immediate-release formulations.

Tablets containing Manucol DM were classified as a slow- release formulation. They differed statistically significantly from Manucol LF tablets in terms of C_{max}, C_{max}/AUC and $t_{½}$ values. The pharmacokinetic profile of the Manugel GHB based tablets was very similar to that of the Manucol DM tablets, although the viscosity grade of Manugel GHB is 75 mPa·s and that of Manucol DM 250 mPa·s.

Manugel DPB tablets were classed as an extended-release formulation, since the $t_{½}$ value was 4.3 hours, as compared with 1.6 hours for immediate-release products (Ojantakanen et al. 1993a).

The main conclusion drawn from this part of the study was that by using sodium alginates of different chemical structures or viscosity grades it is possible to prepare press-coated ibuprofen tablets from which the absorption rate can be controlled over a fairly wide range, from an immediate-release formulation via

slow-release formulations to an extended-release product. The pharmacokinetic parameters of the Manucol and Manugel based tablets described are similar to those for hard gelatin capsules containing the same viscosity grades of sodium alginate (III).

4.4.3. Bioavailability of pseudoephedrine hydrochloride from hard gelatin capsules (V)

Bioavailability studies of sodium alginate based hard gelatin capsules containing the highly water-soluble drug pseudoephedrine hydrochloride were also conducted. Three grades of sodium alginate were used, Manucol LD, Manucol DM and Manugel DPB. The fourth formulation studied contained the drug only.

When the lowest viscosity grade of sodium alginate (Manucol LD) was used, prolongation of absorption was relatively slight. The mean t_{max} value of the reference product was 2.9 hours. For the Manucol LD based product the corresponding value was 4.0 hours. There were no significant differences in relation to MRT on C_{max}/AUC values.

When Manucol DM and Manugel DPB were used, absorption of pseudoephedrine was more retarded: t_{max} for both formulations was 6.5 hours. MRT and C_{max}/AUC values also differed significantly from those for the reference product. Elimination half-lives ($t_{½}$) for the reference capsule and capsules containing sodium alginates were not significantly different. Manucol DM and Manugel DPB formulations were classified as slow-release preparations. In studies with ibuprofen, use of Manugel DPB led to extended-release formulations (III and IV).

The overall conclusion from this part of study was that prolonged-release formulations containing sodium alginate are better in relation to drugs sparingly soluble in water than in relation to highly water-soluble drugs. However, Manugel DPB based pseudoephedrine capsules are competitive, as far as biopharmaceutical characteristics are concerned with commercial prolonged-release pseudoephedrine tablets (Wecker et al. 1987).

4.5. Comparison of in vitro and in vivo results

With ibuprofen capsules, a fairly good correlation was found between in vitro and in vivo results. The best linear correlation was found between the ratio C_{max}/AUC and the zero-order rate constant k_0 (III, Fig. 4) (correlation coefficient 0.999). Between C_{max} and k_0 the correlation coefficient was 0.997). With the other rate parameters, t_{max} and MRT, not even a rank-order correlation was found.

A fairly good in vitro/in vivo correlation was found with the press-coated ibuprofen tablets (IV). A rank-order correlation existed between cumulative dissolution curves and pharmacokinetic rate parameters. The similarity between formulations containing Manucol DM and Manugel GHB was evident in both in vitro results (IV, Fig. 1) and absorption curves (IV, Fig. 5).

With the pseudoephedrine hydrochloride capsules drug release from sodium alginate capsules was studied of in solutions different pH levels (V). Results of in vitro studies in acid environments, e.g. at pH 1.2, are often said to allow optimum prediction of the in vivo fate of a drug product. In the study reported in paper V there were no differences between the four formulations at pH 1.2. However, in vivo differences between the formulations were fairly marked.

It is possible that the capsules remained for 0.5 to 2 hours in the stomachs of volunteers. During this time, an outer layer of precipitated alginic acid would have been formed. A similar layer was seen in in vitro studies (V, Fig. 2). The alginic acid layer, which is not hydrophilic, does not favour adherence of an formulation to the gastric mucosa for long periods. Under fasting conditions, the "housekeeper wave" appearing approximately every second hour (Minami and McCallum 1984), would have swept the capsule to the small intestine. The solution that would then have penetrated the capsule would no longer have been acid. The rest of the sodium alginate in the capsule would have formed a gel the tightness of which depended on the viscosity grade of the polymer. This may have been why the in vivo absorption rate correlated with the viscosity grade of the sodium alginate used although no differences were seen in dissolution studies at pH 1.2.

The results of the studies reported here confirm that although results of in vitro studies often allow prediction of in vivo behaviour of a drug product for oral administration there are cases where no in vitro/in vivo correlation exists. Biopharmaceutical evaluation of new formulations are therefore important from the onset.

5. CONCLUSIONS

On the basis of the present results reported the following conclusions can be drawn:

1. Using sodium alginate as a diluent in hard gelatin capsules prolonged-release drug profucts for oral administration can be prepared from which drug absorption can be controlled over a fairly wide range without any reduction in overall amount of drug absorbed. To adjust drug release rate and absorption rate, different viscosity grades of sodium alginate, different chemical types of sodium alginate and different drug/polymer ratios can be used.

2. Sodium alginate based capsules function adequately as a drug delivery system for highly water-soluble drugs (e.g. pseudoephedrine hydrochloride) and sparingly water-soluble drugs (e.g. ibuprofen). However, the system is better for sparingly soluble drugs such as ibuprofen.

3. Drug release from sodium alginate capsules is based both on drug diffusion though the gel layer formed around the capsule and on erosion of this gel layer. The durability and tightness of the gel depends on the viscosity grade and amount of sodium alginate used. At pH 1.2, however, alginic acid is precipitated with all grades of sodium alginate. This would explain why there were no differences in dissolution properties at pH 1.2 between formulations containing different grades of sodium alginate.

4. Plug formation, which is usually an essential part of capsule-filling procedures on an industrial scale, had only minimal effects on drug dissolution from sodium alginate based capsules. It may therefore be assumed that results obtained with capsules filled manually predict the characteristics of corresponding formulations filled by means of dosator-type filling machines.

5. Sodium alginate can be used to control drug release from a new type of press-coated prolonged-release tablet. By using different types and different amounts of sodium alginate in the coat of the tablet it is possible to adjust drug absorption rates without declines in overall amounts of drug absorbed.

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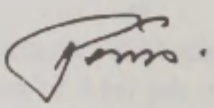

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I

Acta Pharmaceutica Fennica 1991; ***100,*** *19–25*

RESEARCH PAPERS

DESIGN AND USE OF EQUIPMENT FOR SIMULATION OF PLUG FORMATION IN HARD GELATIN CAPSULE FILLING MACHINES

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Key words: *Compression force, dissolution, hard gelatin capsules, ibuprofen plug formation*

Abstract

In the study reported, simple equipment was constructed to allow plug formation and compression force measurement, simulating dosator type capsule filling machines. A piston was removed from an industrial-scale filling machine and fixed to a lever system which could move up and down. A dosing tube was also removed and fixed to a plastic plate on a digital balance. The compression force during plug formation was recorded via the balance.

The equipment was used to prepare ibuprofen capsules containing typical diluents. Various compression forces were tested. Dissolution of ibuprofen from the formulation was tested using USP XXII the rotating disk method. The results showed that the dissolution properties of the formulations studied were similar to those previously demonstared for analogous capsule formulations. It was concluded that the equipment described may therefore be used in basic research on hard gelatin capsule formulations.

Tiivistelmä

Tässä työssä rakennettiin yksinkertainen laitteisto, jolla voitiin valmistaa samanlaisia puristeita, joita jauheseoksesta syntyy mäntäannostin-tyyppisessä kapselientäyttökoneessa, ja samalla pystyttiin mittaamaan myös puristeen muodostamisessa käytetty voima. Kaupallisesta kapselien täyttölaitteesta irroitettiin mäntä ja kiinnitettiin ylös ja alas liikkuvaan vivustoon. Myös annostussylinteri irroitettiin ja kiinnitettiin muovilevyyn, joka asetettiin ylätasovaa'alle. Puristava voima luettiin vaa'an asteikolta.

Konstruoidulla laitteella valmistettiin ibuprofeenia ja tyypillisiä täyteaineita sisältäviä kapseleja käyttäen eri suuria puristavia voimia. Ibuprofeenin liukeneminen valmisteista tutkittiin USP:n pyrivä kori -menetelmällä. Tulokset osoittivat, että nyt valmistettujen kapselien dissoluutio-ominaisuudet olivat samanlaiset kuin mitä aikaisemmin on kuvattu vastaaville koneellisesti täytetyille formulaatioille. Näin ollen nyt esitettyä laitetta voidaan käyttää kovien liivatekapselivalmisteiden perustutkimuksessa.

Introduction

Hard gelatin capsules are suitable for both manual and industrial-scale preparation of drug products. Typically, the only additive required is a diluent. For industrial-scale filling machines, a glidant or lubricant is also required. Nowadays, most commercially available capsules are filled by compressing a powder to a plug and loading it into the capsule body. The compression forces used typically range from 50 to 300 N (5 to 30 kg) (LERK *et al.* 1979, BOTZOLAKIS and AUGSBURGER 1984, SHAH *et al.* 1986, AUGSBURGER 1988).

Compression force can be measured during manufacture on industrial-scale machines if these are equipped with appropriate measuring instruments. Instrumented filling-machine simulators have also been designed (JOLLIFFE *et al.* 1982). Such equipments are, however, expensive, and not available in every laboratory.

On laboratory scale, instrumented single-punch tableting machines have been used to prepare plugs for capsule filling procedures (NAiDOO 1989). Special die and plunger assemblies, in which the plunger is connected to a load cell have been constructed for preparation of plugs (LERK *et al.* 1979). Plug formation in the above-mentioned equipment does not however correspond accurately to plug formation in capsulefilling machines.

The aim of the study reported here was to develop simple equipment for simulating plug formation in connection with capsule filling and measurement of compression force simply enough to allow it to be undertaken in basic research laboratories. The suitability of the assembly for its intended purpose was tested by preparing ibuprofen capsules containing typical diluents using different compression forces and studying the dissolution characteristics of the resulting formulations.

Material and Methods

Equipment for plug formation

The equipment constructed is shown in Fig. 1. A dosing tube from a mG2 dosator-type capsule filling machine was fixed to a plastic plate. The plate was placed on a digital balance (max. capacity 30 kg). A piston from the same mG2 capsule filling machine was fixed to a lever system which could move up and down a static rod.

Powder sufficient for one capsule was poured into the dosing tube. The lever was steadily pulled down and the compression force towards the powder bed was measured via the digital balance. After compression, the dosing tube was removed from the plastic plate and the plug was loaded into the capsule body.

Capsule formulations

Size 0 hard gelatin capsules (Posilock™, Elanco) were used in the formulations. As a model drug ibuprofen (Medipolar) was used. The diluents tested were microcrystalline cellulose (Emcocel 90 M™, E. Mendell), methylcellulose (Methocel A4C, Dow Chemicals), lactose (De Melkindustrie Veghel), corn starch (Maydis amylum, Thibola DRM), dicalcium phosphate dihydrate (Emcompress™, E. Mendell). The amounts of ibuprofen and the diluents in the formulations are shown in Table I.

The necessary amounts of drug substance were weighed out in a graduated cylinder and diluent was added in sufficient quantity material for a batch of 100 capsules (68 ml). The powder was mixed manually and the capsule shells were filled using a Feton apparatus. These capsules were regarded as having been prepared using a compression force of 0 kg. The required number of capsules from each batch were then opened and the contents poured into the dosing tube. Plugs were then compressed using forces of 10, 20 or 30 kg.

Dissolution test

Dissolution of ibuprofen was determined using the USP rotating basket method as described for dissolution of ibuprofen tablets in USP XXII (Dissolutest™, Prolabo). The dissolution medium was

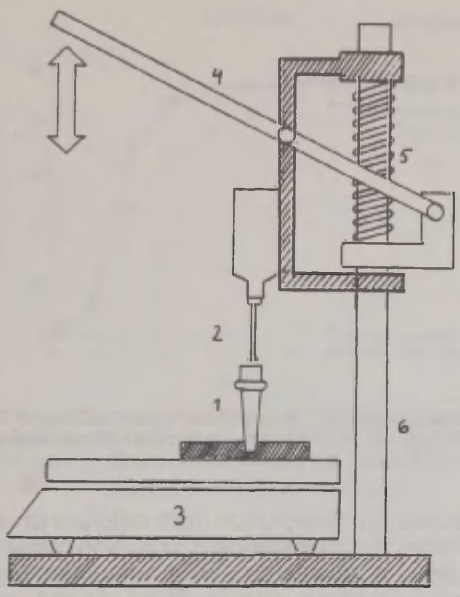

Fig. 1. *A schematic diagram of the equipment used for plug formation and measurement of compression force; 1. dosing tube, 2. piston, 3. balance, 4. lever, 5. spring, and 6. static rod.*

phosphate buffer pH 7.2 (900 ml at 37 °C) and the rotating speed 150 min^{-1}. The dissolution apparatus was connected via a peristaltic pump (Watson-Marlow 503S, Smith & Nephew) to a flow-through spectrophotometer (Ultrospec II, LKB Biochrom Ltd). The pump was operated at a delivery rate of 7 ml · min^{-1}. The absorbance of the dissolution medium in 2 mm flow-through cells was recorded at 221 nm, automatically, at regular intervals. Measurement was controlled by a computer running tablet-dissolution sofware (TDS™, LKB Biochrom Ltd).

Table I *Formulations studied.*

Diluent	Amount of diluent mg	Amount of ibuprofen mg
Microcrystalline cellulose	100	200
Microcrystalline cellusose	200	100
Microcrystalline cellulose	250	50
Methylcellulose	155	200
Methylcellulose	255	100
Methylcellulose	305	50
Calcium phosphate	300	200
Calcium phosphate	400	100
Calcium phopshate	450	50
Lactose	195	200
Lactose	380	100
Lactose	435	50
Corn starch	200	200

Results

The dissolution profiles of ibuprofen capsules (200 mg) filled manually without compression are shown in Fig. 2. The diluent had very little effect on the dissolution rate of the drug. Dissolution was most rapid from capsules containing calcium phosphate and slowest from capsules containing methylcellulose.

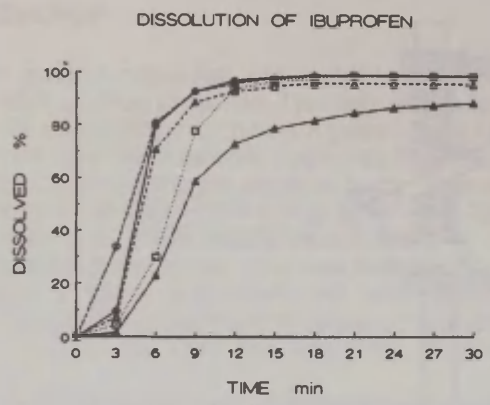

Fig. 2. Dissolution of ibuprofen from capsules containing various diluents and 200 mg of ibuprofen (no compression). Diluents: calcium phosphate (○), microcrystalline cellulose (●), lactose (△), corn starch (□), methylcellulose (▲); mean curves, n = 6.

The compression force used affected the dissolution from calcium phosphate based capsules most. The highest force (30 kg) retarded dissolution considerably (Fig. 3). Use of the various compression forces also retarded dissolution from corn starch based capsules (Fig. 4). When lactose was used as diluent, only the highest compression force had a retarding effect (Fig. 5). The capsules containing microcrystalline cellulose were most unaffected by the compression forces (Fig. 6).

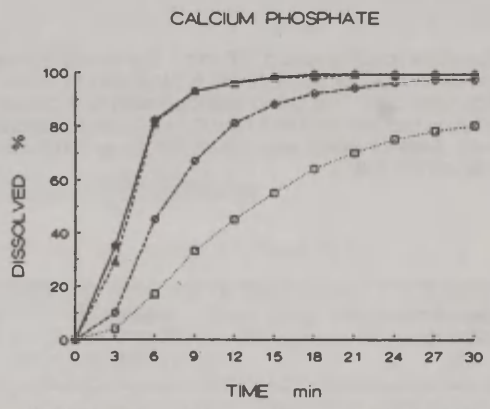

Fig. 3. Effect of compression on ibuprofen dissolution from capsules containing 200 mg of ibuprofen and 300 mg of calcium phosphate. Compession forces: 0 kg (●), 10 kg (△), 20 kg (○) or 30 kg (□); mean curves, n = 6.

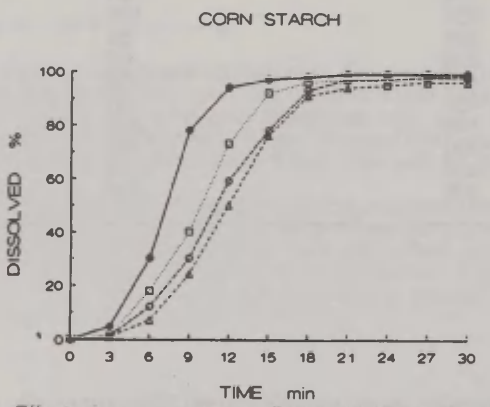

Fig. 4. Effect of compression on ibuprofen dissolution from capsules containing 200 mg of ibuprofen and 200 mg of corn starch. Compression forces: 0 kg (●), 10 kg (△), 20 kg (○) or 30 kg (□); mean curves, n= 6.

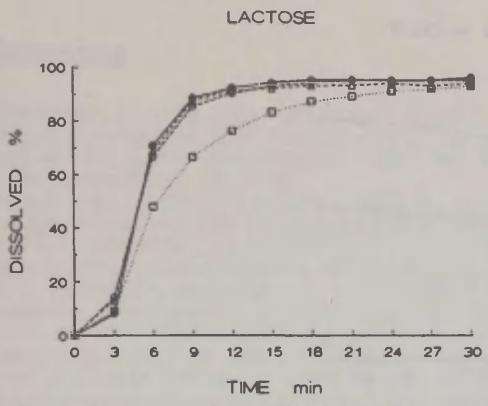

Fig. 5. *Effect of compression on ibuprofen dissolution from capsules containing 200 mg of ibuprofen and 195 mg of lactose. Compression forces: 0 kg (●), 10 kg (△), 20 kg (○) or 30 kg (□); mean curves, n= 6.*

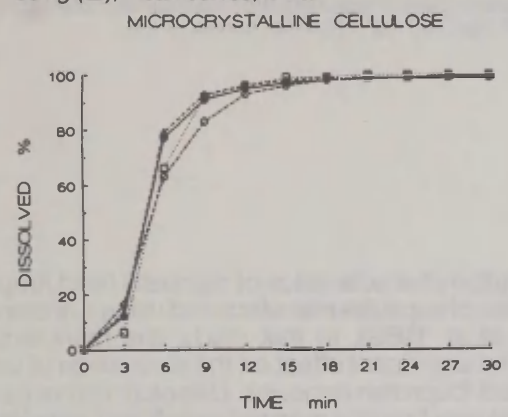

Fig. 6. *Effect of compression on ibuprofen dissolution from capsules containing 200 mg of ibuprofen and 10 mg of microcrystalline cellulose. Compression forces: 0 kg (●), 10 kg (△), 20 kg (○) or 30 kg (□); mean curves, N = 6.*

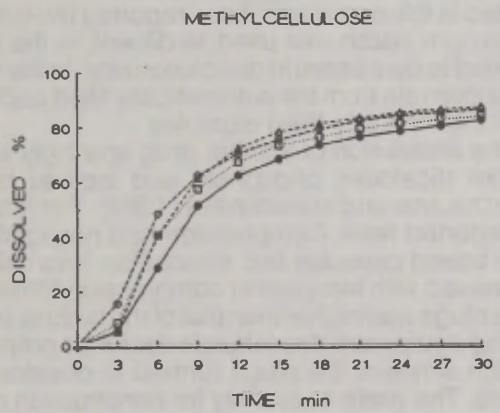

Fig. 7. *Effect of compression on ibuprofen dissolution from capsules containing 200 mg of ibuprofen and methylcellulose. Compression forces: 0 kg (●), 10 kg (△), 20 kg (○) or 30 kg (□); mean curves, n = 6.*

When plugs were compressed from powder mixtures containing methylcellulose, the dissolution rate was slightly enhanced (Fig. 7).

Changing the relative amounts of drug and diluent did not markedly alter the dissolution characteristics of the formulations studied, except in the case of methylcellulose (Fig. 8).

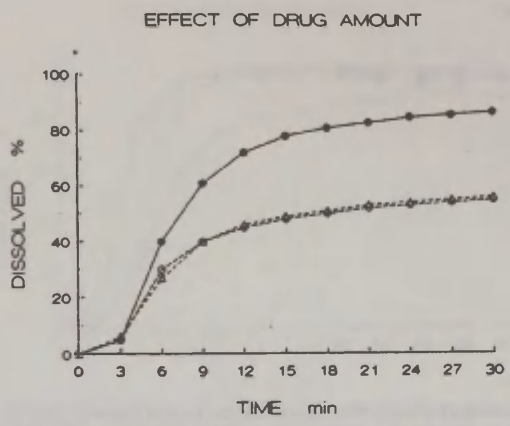

Fig. 8. *Effect of relative amounts of ibuprofen and methylcellulose on dissolution of the drug from hard gelatin capsules (compression force 10 kg). Amounts of substances: 200 mg / 155 mg (●), 100 mg / 255 mg (△) or 50 mg / 305 mg (○); mean curves, n = 6.*

Discussion

In a previous study, the dissolution characteristics of manually filled ibuprofen capsules were compared with those of capsules manufactured using a dosatortype filling machine mG2 (HANNULA *et al.* 1989). In that study, the manufacturing procedure (plug formation) had no significant effect on the dissolution of lactose or microcrystalline cellulose based ibuprofen capsules. Dissolution from calcium phosphate based capsules was slower from the automatically filled capsules than from the manually filled capsules. These findings are in good agreement with those reported here.

The results of the study described in this paper and those reported by HANNULA *et al.* (1989) differ, however, when corn starch was used as diluent. In the study reported here, compression force led to decreases in dissolution rate. In the study of HANNULA *et al.*, (1989) the dissolution rate from the automatically filled capsules was slightly higher than that from the manually filled capsules.

The effect of compression on the dissolution of another drug sparingly water-soluble, hydrochlorothiazide, from dicalcium phosphate and lactose based capsules has been studied by BOTZOLAKIS and AUGSBURGER (1983). The findings were in accordance with those reported here. Compression had no significant effect on dissolution from lactose based capsules but dissolution from calcium phosphate based capsules decreased with increase in compression force. The strength of the calcium phosphate plugs was higher than that of the lactose plugs.

According to our experiences the equipment described is useful for preparing plugs from powder mixtures which simulate the plugs formed in dosator-type automatic capsule-filling machines. The parts necessary for construction of the assemby can be found in many laboratories in universities and pharmaceutical development departments.

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II

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Sodium alginates as diluents in hard gelatin capsules containing ibuprofen as a model drug

P. VESKI and M. MARVOLA

The object of the study reported here was to investigate the effects of 14 grades of sodium alginate (Manugels® and Manucols®) on the dissolution of ibuprofen from hard gelatin capsules. Three drug: additive ratios were investigated. Dissolution rates of each formulation followed zero-order kinetics. The rate constants varied in the Manugel series from 5.8 to 19.4% · h^{-1} and in the Manucol series from 8.0 to 58.8% · h^{-1}. As a rule, the higher the viscosity grade of sodium alginate the lower the rate of release of ibuprofen. However, rank order correlation was not perfect. Particle size also seemed to have some effect: bigger particles gave less permeable gels.

Natriumalginate als Verdünnungsmittel in Ibuprofen-Hartgelatinekapsel

Das Ziel der hier dargestellten Untersuchungen war die systematische Analyse der Wirkungen von 14 Natriumalginat-Qualitäten (Manugels® und Manucols®) auf die Lösung von Ibuprofen aus harten Gelatinkapseln. Drei Medikament/Hilfsstoff-Relationen wurden untersucht. Für jede Zubereitungsform folgte die Lösungsgeschwindigkeit einer Kinetik nullter Ordnung. Die Geschwindigkeitskonstanten variierten in der Manugel-Reihe von 5,8 bis 19,4% · h^{-1} und in der Manucol-Reihe von 8,0 bis 58,8% · h^{-1}. Als Regel gilt, daß sich mit höherem Viskositätsgrad des Natriumalginats die Freisetzungsrate des Ibuprofens verringert. Die Rangordnungskorrelation war jedoch nicht vollkommen. Die Partikelgröße scheint ebenfalls einige Auswirkungen zu haben: größere Partikeln führten zu verringerten Geldurchlässigkeiten.

1. Introduction

Sodium alginates are hydrophilic polysaccharides produced from selected species of brown seaweeds. Structurally, they are linear copolymers containing two types of sugar residue: D-mannuronate (M) and L-guluronate (G) that occur in alginate molecules in three types of sequence: poly-M, poly-G and poly-MG [1]. Sodium alginates are widely used in the food industry. They have also been intensively studied as additives to solid and liquid drug products for peroral administration.

It is common in scientific papers for the term sodium alginate to be used without qualification. However, there are many different types of sodium alginate on the market. These differ from each other in chemical and physical characteristics. Well known among the many manufacturers of sodium alginates is Kelco, which markets two series of alginates under the trade names Manugel® and Manucol®. The Manugel alginates are rich in guluronic acid, the Manucol alginates rich in mannuronic acid. The various grades in the two series differ from each other in particle sizes and viscosity [1].

Ibuprofen is a nonsteroidal anti-inflammatory drug used for relief of acute pain but also in chronic diseases such as rheumatoid arthritis. Its elimination half-life is very short (about 2 h) [2]. There is therefore a need for sustained-release formulation of ibuprofen.

Sodium alginate, mostly no more precisely specified, has been studied as an additive in peroral sustained-release formulations. For example, Timmins et al. [3] studied two grades of sodium alginate for use as a hydrophilic polymer in manufacturing verapamil matrix tablets. Alginate-based prolonged-release theophylline tablets [4] and suspensions [5] have also been studied. In addition, sodium alginate has been used in microencapsulation, to achieve prolongation of drug release [6–9]. Stockwell et al. [10] prepared buoyant capsules containing sodium bicarbonate and sodium alginate as additives.

The object of the study reported here was to investigate the effects of 14 grades of sodium alginate (Manugels or Manucols) on dissolution of an acidic model drug (ibuprofen) from hard gelatin capsules. If prolonged drug release were obtained, the formulations studied would be a simple way to produce sustained-release drug products.

2. Investigations, results and discussion

Tables 1 and 2 contain the properties of the alginates and the compositions of the capsules studied.

Table 1 Properties of Manugels as stated by the manufacturer and compositions of the capsules studied

Designation of Manugel	Viscosity (1% sol.) [mPa · s]	Particle size [μm]	Amount of ibuprofen [mg]	Amount of Manugel [mg]	Relative amount of Manugel
DPB	500	355	100	345	0.78
			200	143	0.42
			250	103	0.29
DMB	300	150	100	358	0.78
			200	171	0.46
			250	49	0.16
DJX	200	75	100	257	0.72
			200	115	0.37
			250	64	0.20
GMB	180	355	100	340	0.77
			200	151	0.43
			250	81	0.24
DJB	110	150	100	339	0.77
			200	165	0.45
			250	69	0.22
GHB	75	355	100	363	0.78
			200	153	0.43
			250	78	0.24

2.1. Weight uniformity

Table 3 shows the results relating to formulations containing Manugels as diluent. Table 4 shows the results relating to Manucol-based capsules. All formulations met the weight-uniformity specifications of the European Pharmacopoeia. The relative standard deviations varied from 1.4% to 4.2%, i.e. weight uniformity for most formulations was good.

Table 2 Properties of Manucols as stated by the manufacturer and compositions of the capsules studied

Designation of Manucol	Viscosity (1% sol.) [mPa · s]	Particle size [µm]	Amount of ibuprofen [mg]	Amount of Manucol [mg]	Relative amount of Manucol
DMF	300	150	100	367	0.79
			200	125	0.38
			250	97	0.28
DM	250	35	100	398	0.80
			200	155	0.44
			250	67	0.21
SS/LL	215	355	100	372	0.79
			200	118	0.37
			250	83	0.25
LKX	150	63	100	343	0.77
			200	134	0.40
			250	74	0.23
LHF	60	150	100	313	0.76
			200	209	0.51
			250	113	0.31
LF	25	355	100	486	0.83
			200	223	0.53
			250	130	0.34
LD	9	355	100	419	0.81
			200	186	0.48
			250	102	0.29
LB	4	355	100	391	0.80
			200	179	0.47
			250	150	0.38

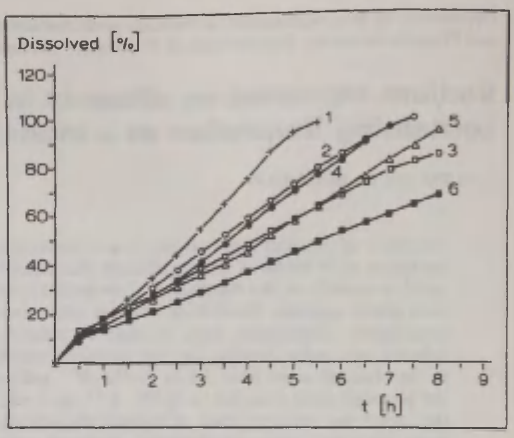

Fig. 1. Dissolution of ibuprofen (200 mg) from hard gelatin capsules containing Manugel as diluent (means of 6 parallel tests). 1: GHB, 2: DJB, 3: GMB, 4: DJX, 5: DMB, 6: DPB

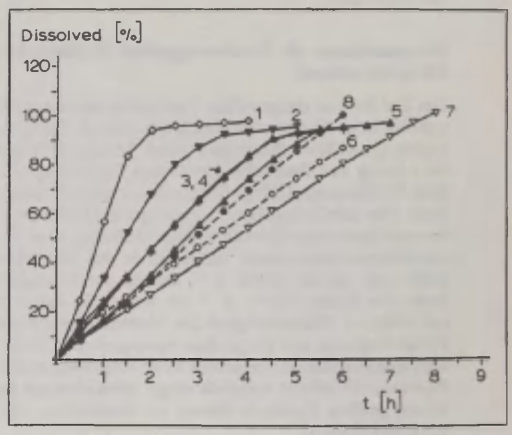

Fig. 2. Dissolution of ibuprofen (200 mg) from hard gelatin capsules containing Manucol as diluent (means of 6 parallel tests). 1: LB, 2: LD, 3: LF, 4: LHF, 5: LKX, 6: SS/LL, 7: DM, 8: DMF

2.2. Dissolution rate and profile

Figures 1 and 2 illustrate drug dissolution from capsules each containing 200 mg of ibuprofen. Dissolution kinetics are zero-order for each composition. Release also followed zero-order kinetics for formulations containing 100 mg or 250 mg of ibuprofen. Rate constants, relative standard deviations and $T_{80\%}$ values for Manugel-based capsules are shown in Table 3. The corresponding values for Manucol-based capsules are shown in Table 4. Its is evident that release rates of ibuprofen can be varied markedly through appropriate choice of chemical and physical properties of sodium alginate.

Table 3 Weight uniformity of 25 capsules and dissolution of ibuprofen from 6 to 12 capsules containing Manugels as diluent

Designation of Manugel	Amount of ibuprofen	Capsule weight		Rate constant, k_0		$T_{80\%}$
		mean [mg]	S_{rel} [%]	mean [% · h^{-1}]	S_{rel} [%]	[h]
DPB	100	545	2.6	5.82	5.3	13.7
	200	443	2.5	8.27	3.5	9.7
	250	453	2.5	8.42	15.9	9.5
DMB	100	558	2.5	6.24	14.9	12.8
	200	471	3.0	11.24	12.8	7.1
	250	399	2.2	16.89	8.8	4.7
DJX	100	457	1.4	11.28	7.7	7.1
	200	415	1.5	13.94	17.8	5.7
	250	414	2.7	19.42	14.8	4.1
GMB	100	540	3.0	7.64	9.4	10.5
	200	451	2.3	9.71	25.6	8.2
	250	431	2.5	12.04	22.3	6.6
DJB	100	539	2.7	10.17	5.4	7.9
	200	465	1.9	14.01	11.1	5.7
	250	419	1.8	18.71	10.6	4.3
GHB	100	563	3.3	11.11	4.5	7.2
	200	453	2.3	16.48	23.3	4.8
	250	428	2.7	19.40	20.7	4.1

k_0 = zero-order rate constant for dissolution of ibuprofen, $T_{80\%}$ = time for 80% of ibuprofen to be dissolved

Table 4 Weight uniformity of 25 capsules and dissolution of ibuprofen from 6 to 12 capsules containing Manucols as diluent

Designation of Manucol	Amount of ibuprofen	Capsule weight		Rate constant, k_0		$T_{80\%}$
		mean [mg]	S_{rel} [%]	mean [% · h^{-1}]	S_{rel} [%]	[h]
DMF	100	567	3.0	10.04	8.7	8.0
	200	425	2.2	18.21	8.5	4.4
	250	447	3.4	18.95	10.0	4.2
DM	100	598	3.1	8.44	11.9	9.5
	200	455	2.8	13.15	10.2	6.1
	250	417	2.5	17.67	11.2	4.5
SS/LL	100	572	2.8	8.02	18.2	10.0
	200	418	2.2	14.74	17.9	5.4
	250	433	4.3	18.91	6.9	4.2
LKX	100	543	1.6	12.90	14.0	6.2
	200	434	1.8	21.07	17.7	3.8
	250	424	2.4	23.83	6.4	3.4
LHF	100	513	1.7	20.46	8.5	3.9
	200	509	2.8	20.26	14.1	4.0
	250	463	2.5	19.14	6.1	4.2
LF	100	686	2.3	18.60	11.9	4.3
	200	523	3.3	21.17	17.0	3.8
	250	480	2.0	27.00	16.4	3.0
LD	100	619	4.2	27.86	15.3	2.9
	200	486	3.2	33.77	15.9	2.4
	250	452	2.3	47.42	7.2	1.7
LB	100	591	3.6	35.35	16.5	2.3
	200	479	3.7	58.79	16.1	1.4
	250	500	1.4	57.45	13.1	1.4

k_0 = zero-order rate constant for dissolution of ibuprofen, $T_{80\%}$ = time for 80% of ibuprofen to be dissolved

Dissolution of ibuprofen from hard gelatine capsules containing hydrophilic polymers as diluents has previously been studied. Use of different grades of hydroxypropylmethylcellulose (HPMC) resulted in square-root-of-time release kinetics. With many grades of sodium carboxymethylcellulose (NaCMC) fairly good fits to zero-order kinetics were obtained [11]. Release of chlorpheniramine hydrochloride from buoyant capsules containing different amounts of Manugel DMB obeyed square-root-of-time kinetics [10]. The present finding about zero-order release kinetics is desirable just for sustained-release drug products.

$T_{80\%}$ values for dissolution of ibuprofen from the sodium alginate based capsules showed here were similar to $T_{80\%}$ values for analogous NaCMC-based capsules but markedly lower than those for HPMC-based capsules (for which $T_{80\%}$ is more that 20 h) [11]. It is evident that release of ibuprofen, a weak acid, is faster from sodium alginate and NaCMC based capsules simply because of the anionic nature of the polymers. In contrast HPMCs are non-ionic polymers, and their use results in markedly slower release rates of acidic drugs. Zero-order release of ibuprofen seems to be related to use of anionic and sodium-containing polymers. Dissolution profiles from HPMC based capsules have followed best square-root-of-time kinetics [11].

2.3. Differences between Manugels and Manucols

As a rule, release of ibuprofen from Manugel based capsules was slower than that from capsules containing the equivalent viscosity grade of Manucol. This is in accordance with findings with Manugel DMB and Manucol DMF based tablets of verapamil hydrochloride [3]. Manugels are rich in guluronic acid. This has been said to form more rigid gels when hydrated than Manucols, which are rich in mannuronic acid [1]. Such more rigid gels may be less prone to erosion and constitute a more effective barrier to release of a drug by diffusion. Dissolution of verapamil hydrochloride from Manugel DMB based matrix tablets has been observed to be pH-dependent, the lower the pH the faster the dissolution rate [3]. In analogous studies with tablets containing Manucol DMF pH (1.2 or 7.4) of the solvent had no effect on rate of dissolution. In the study reported here, the pH was 7.2, much higher than gastric pH. The effect of pH on the dissolution rate of ibuprofen could not be investigated because of the solubility of the drug in acidic media is very low. Ultimate assessment of the value of Manugel-based capsules as a sustained-release dosage form for ibuprofen must therefore await availability of results of *in vivo* tests.

2.4. Effect of drug: diluent ratio

The correlation between the release rate constant (k_0) and the relative amount of sodium alginate in the capsule was approximately linear (see Table 3). Through appropriate choice of drug : diluent ratio the drug release-rate constant can be adjusted, e.g. with Manugel DMB from 6.2 to 16.9% · h^{-1}.

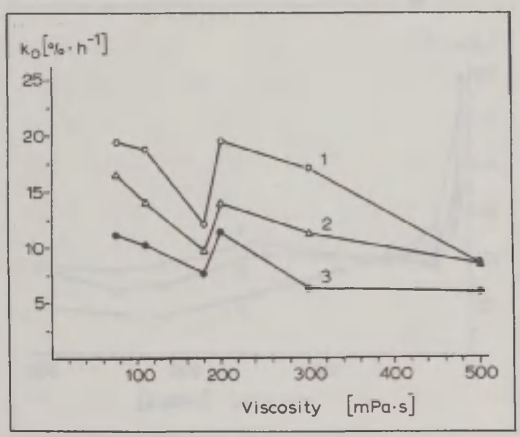

Fig. 3. Correlation between release rate constants (k_0) and viscosity grades of Manugel. 100 mg (1), 200 mg (2), 250 mg (3) of ibuprofen

This finding is in accordance with findings concerning drug release from buoyant capsules containing sodium bicarbonate and various amounts of Manugel DMB [10]. In that study, however, the correlation between the release rate constant and the reciprocal of the amount of alginate was most linear.

2.5. Effect of viscosity grade

In Figs. 3 and 4, the release rate constants are plotted against viscosity grades of Manugels and Manucols. Correlation was only slight. Both curves are biphasic. The greatest deviation from linearity was evident in the case of Manugel DJX. Release rate constants from capsules containing this were markedly lower than those expected on the basis of the viscosity grade. Viscosity grade alone is therefore an inappropriate parameter for use in selecting alternative sources of sodium alginate for inclusion in sustained-release hard gelatin capsule formulations. This conclusion is in accordance with findings relating to matrix tablets of containing three grades of sodium alginate [3].

2.6. Effect of particle size

Because the grades of Manugels and Manucols studied all differed from each other as regards viscosity grade, it is difficult to draw conclusions about the effect of particle size alone. An tendency to slower drug release with grades of bigger particle size was evident in the Manugel series (Fig. 5). The abnormal behaviour seen with Manugel DJX may be related to its very small mean particle size (75 µm). In the Manucol series, there was no correlation between drug release rate and particle size (Tables 2 and 4).

2.7. Conclusions

Dissolution of ibuprofen from all formulations studied, containing various grades of sodium alginate, closely followed zero-order kinetics. Such release is desirable in sustained-release drug products. Release rates could be adjusted over a very wide range by choice of sodium alginates with different chemical and physical properties. In addition, altering of the drug : diluent ratio was an additional means of adjusting drug release rate. Manufacturing of the formulations studied, both small and large scale, is simple.

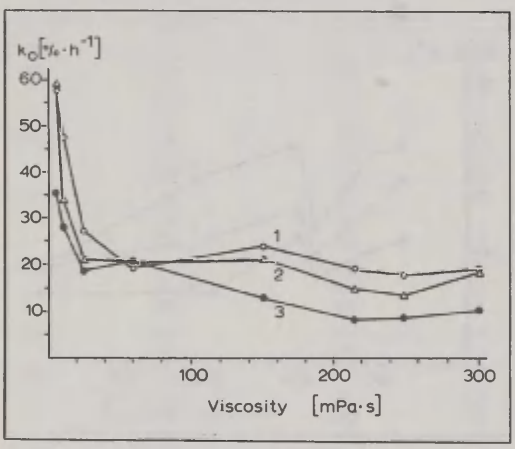

Fig. 4. Correlation between release rate constants (k_0) and viscosity grades of Manucol. Symbols as in Fig. 3

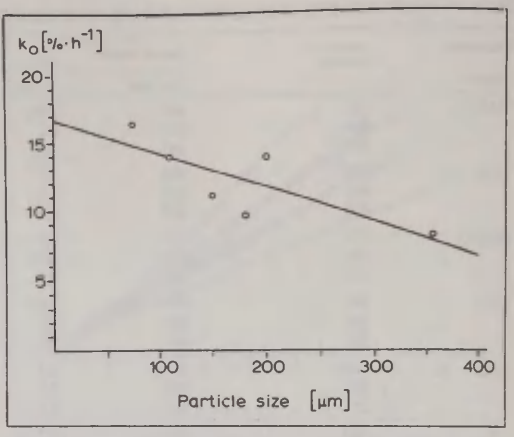

Fig 5. Correlation betwen release rate constants (k_0) and mean particle sizes of Manugels

3. Experimental

Size 0 hard gelatin capsules (Posilock®, Elanco, USA) were used for all formulations. Amounts of ibuprofen (Medipolar, Finland) required were weighed in a graduated cylinder and the diluent was added to produce sufficient material for batches of 25 capsules (17 ml). The powder was mixed and dispensed into capsula shells manually. Sodium alginates sold under the trade names of Manugel and Manucol (Kelco Ltd, U.K.) were used. The compositions of the formulations studied and the viscosity grades and particle sizes of the sodium alginates used are shown in Tables 1 and 2. Weight uniformity of filled capsules was determined using 25 capsules, according to the European Pharmacopoeia. Dissolution of ibuprofen from the capsules was determined using the USP rotating basket method as described for ibuprofen tablets in USP XXII (Prolabo, France). The solvent was phosphate buffer pH 7.2 (900 ml at 37 °C). The speed of rotation was 150 min^{-1}. The dissolution apparatus was connected *via* a peristaltic pump (Watson-Marlow 503S, Smith & Nephew, U.K.) to a flow-through spectrophotometer (Ultrospect II, LKB Biochrom Ltd., U.K.). The pump was operated at a delivery rate of 7 ml · min^{-1}. The absorbances of drug solutions in 2 mm flow-through cells at 221 nm were recorded automatically at regular intervals. The reference cell contained solvent saturated with the grade of sodium alginate used as diluent in the formulation concerned. Measurements were monitored using a computer running tablet dissolution software (TDS®, LKB Biochrom Ltd., U.K.). Release data were fitted to zero-order kinetics curves using MINSQ software (Micromath, USA).

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Bioavailability of ibuprofen from hard gelatin capsules containing sodium alginates

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Key words: Bioavailability, ibuprofen, extended release, slow release, sodium alginate, gelatin capsules

SUMMARY

The paper deals with bioavailability studies of hard gelatin capsules containing ibuprofen as drug and different viscosity grades of sodium alginate as diluent. Tests were carried out on healthy volunteers. It was concluded that with different viscosity grades of sodium alginate it is possible to prepare ibuprofen capsules from which the absorption rate of the drug can be controlled over a fairly wide range without any fall in the amount of drug absorbed. The correlation between the in vitro release rate constant k_0 and the in vivo absorption rate parameter C_{max}/AUC was excellent. The procedure is a simple and inexpensive way to produce a prolonged-release drug product. In addition, it is possible that sodium alginate may protect the gastric mucosa from the irritating action of anti-inflammatory analgesics. This would be an extra advantage for the formulations described here.

INTRODUCTION

Ibuprofen [d,l-2-(4-isobutylphenyl)propionic acid] is a nonsteroidal anti-inflammatory drug used for relief of acute pain but also for pain relief in chronic diseases such as rheumatoid arthritis and osteoarthritis. Ibuprofen is rapidly and completely absorbed after peroral administration. In studies with peroral solutions, peak plasma concentrations have been achieved at 0.5-0.7 h (1-3). For conventional tablets t_{max} values of 1.3 to 2.7 h have been reported (1, 4-9).

For relief of acute pain, rapid drug absorption is usually desirable. When anti-inflammatory analgesics are used in chronic disease rapid drug absorption is frequently avoided because it may result in systemic side effects due to high peak levels of the drug. Most important in this situation is a high degree of absorption, not a high absorption rate. Prolonged-release ibuprofen formulations have been prepared dispensing coated pellets into hard gelatin capsules (7, 10). In our previous studies we have developed ways of preparing prolonged-release ibuprofen capsules using different hydrophilic polymers or other gel-forming agents as a diluent (3, 11, 12).

Nonsteroidal analgesics like ibuprofen may also irritate the gastric mucosa. In theory, this kind of side effect can be avoided by protecting the mucosa with a gel-forming drug like sodium alginate (13). Sodium alginate has also been widely used as an additive in solid or liquid peroral drug products. Prolonged-release matrix tablets containing sodium alginate have been prepared from verapamil hydrochloride (14) and theophylline (15).

Although there are many different types of sodium alginate on the market, many scientific papers use the term sodium alginate without being more specific. In our previous paper we studied the effect of 14 specified grades of sodium alginate on the dissolution of ibuprofen from hard gelatin capsules (16). It was noted that the release of ibuprofen obeyed zero-order kinetics and was, as a rule, dependent on the viscosity grade of the sodium alginate. The rate constant k_0 varied from 5.8 to 57.5 $\% \cdot h^{-1}$.

The aim of the study reported here was to investigate whether it is possible to prepare, using four different grades of sodium alginate as diluent, ibuprofen capsules which provide prolonged release of the drug in vivo. A further aim was to determine whether the previous in vitro results correlate with the present results from bioavailability tests in man.

MATERIAL AND METHODS

Capsule formulations

Size 0 hard gelatin capsules (Posilock™, Elanco, USA) were used for all formulations. The amount of ibuprofen (Medipolar, Finland) per capsule was 200 mg. Four different viscosity grades of sodium alginate (Kelco Ltd, U.K.) were used a diluent. The trade names and the viscosities of 1% aqueous solutions of these sodium alginates were: Manugel DPB (500 mPa·s), Manugel GHB (75 mPa·s), Manucol DM (250 mPa·s), and Manucol LD (9 mPa·s). The particle size of all sodium alginates were the same (mean 355 μm).

The necessary amount of drug was weighed in a graduated cylinder and the diluent was added to produce sufficient material for a batch of 25 capsules (17 ml). The amounts of sodium alginate per capsule were: Manugel DPB 143 mg, Manugel GHB 153 mg, Manucol DM 155 mg and Manucol LD 186 mg. The powder was mixed manually and the capsules were filled using a Feton apparatus.

Bioavailability study

Two groups of eight volunteers (five women and three men in group I, four women and four men in group II) participated in two randomized cross-over single dose studies, which were carried out in accordance with the recommendations of the Declaration of Helsinki (World Medical Assembly 1975) as revised in Tokyo. The ages of the volunteers varied from 19 to 25 years and the weights from 45 to 84 kg. All were non-smokers and did not take any drug during the study or one week before it. One week prior to the study the participants underwent a physical examination, routine laboratory tests and an ECG. The study protocol was approved by the ethical committee of the University of Tartu.

Each formulation (two 200 mg capsules) was administered with 200 ml of water following an overnight fast. A standard lunch was provided 3 h after drug administration. Group I was administered capsules containing Manugels and group II capsules containing Manucols. The wash-out period between the formulations was one week.

Blood samples of 10 ml were collected via a forearm vein into heparinized tubes just prior to drug administration and 0.5, 1, 1.5, 2, 3, 4, 6, 8 and 10 h after drug ingestion. Plasma was separated approximately 30 min after collection by centrifugation (3000 g for 10 min), and frozen at -20°C until analyzed.

Plasma assay

Ibuprofen plasma concentrations were determined by means of high performance liquid chromatography (HPLC), using a slightly modified version of the method of

Avgerinos and Hutt (17). Each plasma sample was analyzed in duplicate and the mean value was used. The system was equipped with a Waters Model 510 piston pump, a Waters Intelligent Sample Processor Model 700, a Waters Model 484 Tunable Absorbance Detector operating at 222 nm, a Waters Model 820 Maxima Workstation (Waters Ltd, USA) and a Hibar column packed with Lichrosorb (10 µm, C_{18} reversed phase 240-4, E.Merck, Germany). The mobile phase was acetonitrile and 0.1 M sodium acetate (35:65), adjusted to pH 6.2 with glacial acetic acid. All chemicals were analytical or HPLC grade. The flow rate was 2 $ml \cdot min^{-1}$.

A series of standard plasma ibuprofen curves was prepared over the concentration range 2.0-80.0 $mg \cdot l^{-1}$. All standard curves were linear over the range examined ($r > 0.99$) and passed close to the origin. The accuracy and precision were tested by analyzing seven samples of blank plasma spiked with 32.0 $mg \cdot l^{-1}$ of ibuprofen. The inaccuracy was 1.4% and the imprecision 3.0%. The quantitation limit was 2.0 $mg \cdot l^{-1}$ (C.V. for precision less than 20%, $n = 5$). No interfering peaks were observed in the plasma blanks.

Pharmacokinetic parameters

The following pharmacokinetic parameters were assessed using the Siphar™ program (Simed, France): maximum plasma concentration (C_{max}), time to peak concentration (t_{max}), area under the concentration-time curve from time 0 to infinity (AUG), elimination half-life ($t_{½}$) and mean residence time (MRT). The ratio C_{max}/AUC was also calculated. Statistical analyses were carried out using Student's t-test or Student's paired t-test. t_{max} values were analyzed using Wilcoxon's test.

RESULTS

Individual plasma levels of ibuprofen after ingestion of the four different formulations studied are shown in Fig. 1. The corresponding mean curves are presented in Figs. 2 and 3. The results of the pharmacokinetic calculations are given in Table I. Table II contains the results of the statistical evaluations. The extent of bioavailability of ibuprofen evaluated on the basis of the AUC values was the same from each formulation. In contrast, statistically significant differences were observed many times in the parameters reflecting the rate of bioavailability (t_{max}, C_{max}, MRT and C_{max}/AUC).

In our previous study (16) the dissolution rate of ibuprofen from the formulations, which were the same as those studied here, was shown to obey zero-order kinetics. The rate constants (k_0) were: 8.27 $\% \cdot h^{-1}$ (Manugel DPB), 13.15 $\% \cdot h^{-1}$ (Manucol DM), 16.48 $\% \cdot h1^{-1}$ (Manugel GHB) and 33.77 $\% \cdot h^{-1}$ (Manucol

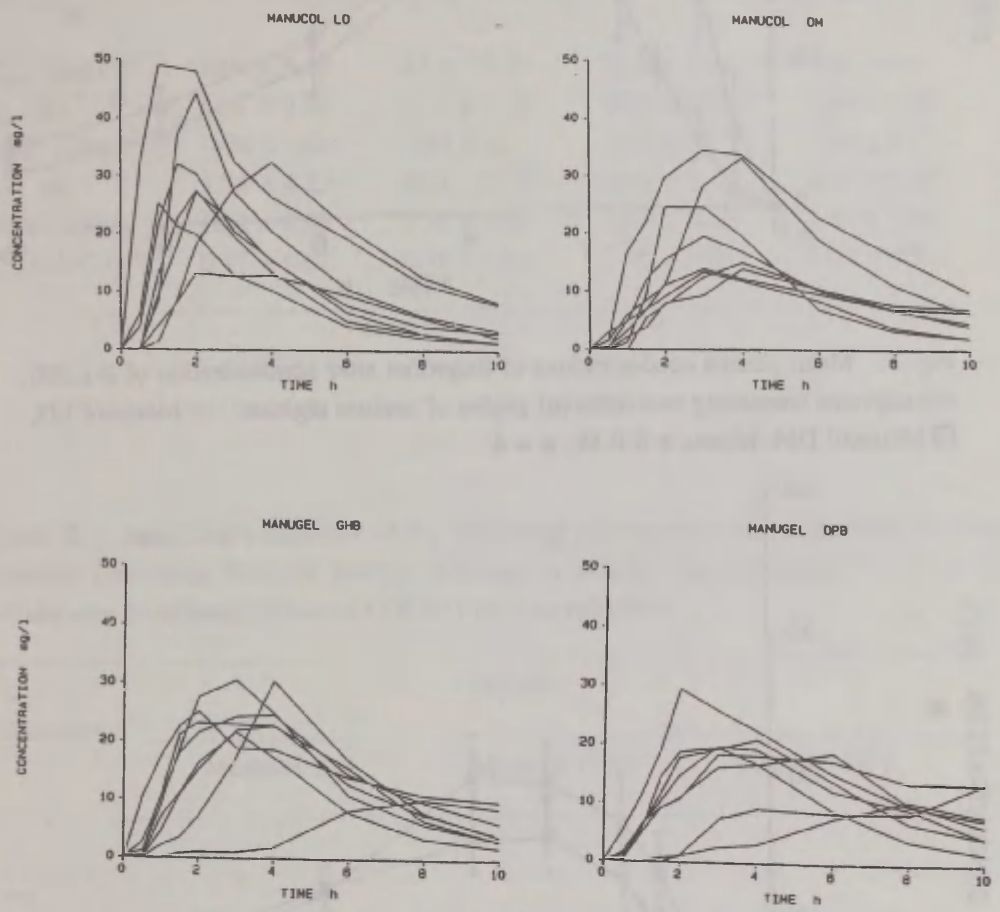

Fig. 1: Individual plasma concentrations of ibuprofen after administration of 400 mg in different capsule formulations.

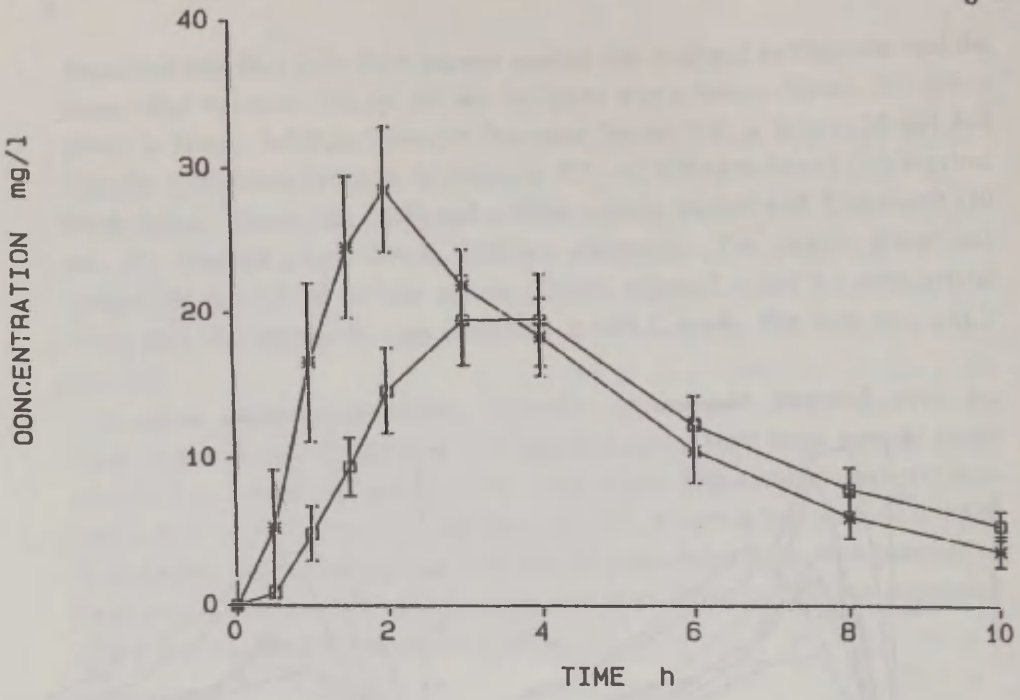

Fig. 2: Mean plasma concentrations of ibuprofen after administration of 2 x 200 mg capsules containing two different grades of sodium alginate: * Manucol LD, □ Manucol DM. Means ± S.E.M., n = 8.

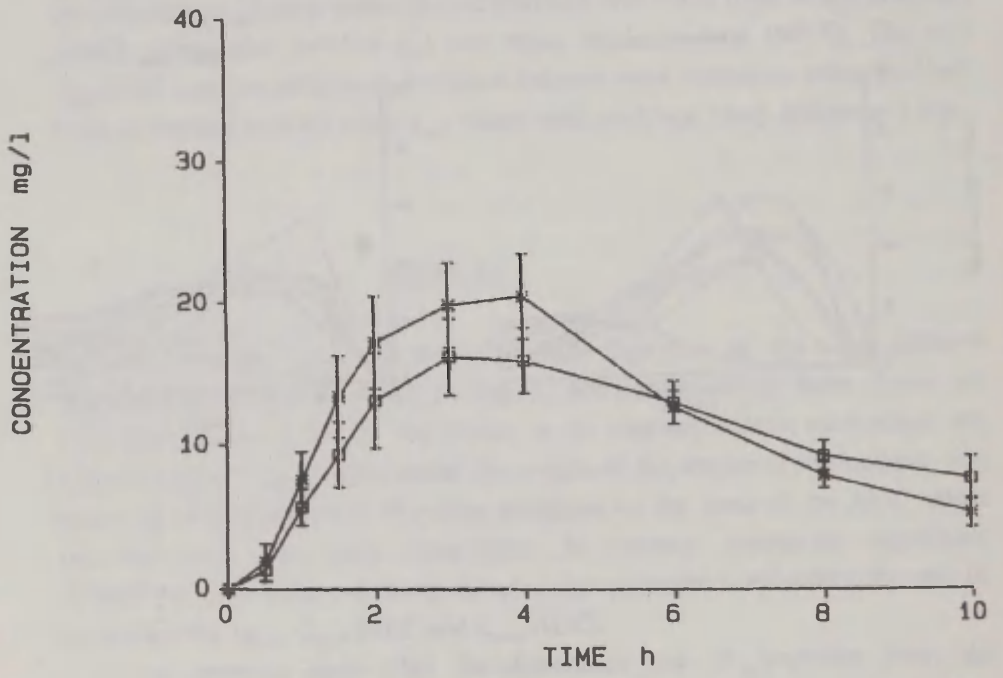

Fig. 3: Mean plasma concentrations of ibuprofen after administration of 2 x 200 mg capsules containing two different grades of sodium alginate: * Manugel GHB, □ Manugel DPB. Means ± S.E.M., n = 8.

Table I: Pharmacokinetic parameters of ibuprofen from hard gelatin capsules containing different sodium alginates as diluent. Single dose of two capsules (total 400 mg), mean ± S.D., n = 8.

Parameter	Diluent			
	Manugel DPB	Manugel GHB	Manucol DM	Manucol LD
C_{max} ($mg \cdot l^{-1}$)	19.0 ± 5.48	23.6 ± 6.27	21.0 ± 8.76	31.4 ± 11.1
t_{max} (h)	4.88 ± 2.83	3.75 ± 1.90	3.25 ± 0.70	1.94 ± 0.93
AUC ($mg \cdot l^{-1} \cdot h$)	194 ± 105	158 ± 42	145 ± 59	146 ± 67
$t_{½}$ (h)	5.75 ± 4.23	3.81 ± 2.46	3.66 ± 1.37	2.45 ± 0.56
MRT (h)	10.8 ± 6.83	7.50 ± 4.41	7.13 ± 2.18	4.68 ± 1.09
C_{max}/AUC (h^{-1})	0.17 ± 0.02	0.19 ± 0.03	0.18 ± 0.03	0.24 ± 0.05

Table II: Statistical evaluation of the calculated pharmacokinetic parameters for ibuprofen capsules containing different sodium alginates as diluent. The formulation with the highest release rate (containing Manucol LD) was used as reference.

Parameter	Diluent		
	Manucol DM	Manugel GHB	Manugel DPB
C_{max}	*	*	**
t_{max}	**	**	**
AUC	NS	NS	NS
$t_{½}$	NS	NS	*
MRT	NS	*	**
C_{max}/AUC	*	*	*

* = $p<0.05$, ** = $p<0.01$, NS = not significant

LD). The correlation of this in vitro parameter to the pharmacokinetic parameters calculated here was tested by means of the linear correlation test. The best linear correlation was found between the ratio C_{max}/AUC and k_0 (Fig. 4). The equation was y = 0.15 +.0.0028x and the correlation coefficient 0.999. Almost the same correlation was found between C_{max} and k_0 (r = 0.997). With the other rate parameters (T_{max} and MRT) the correlation was poorer. Not even a rank-order correlation was found, as can be seen from the values in Table I.

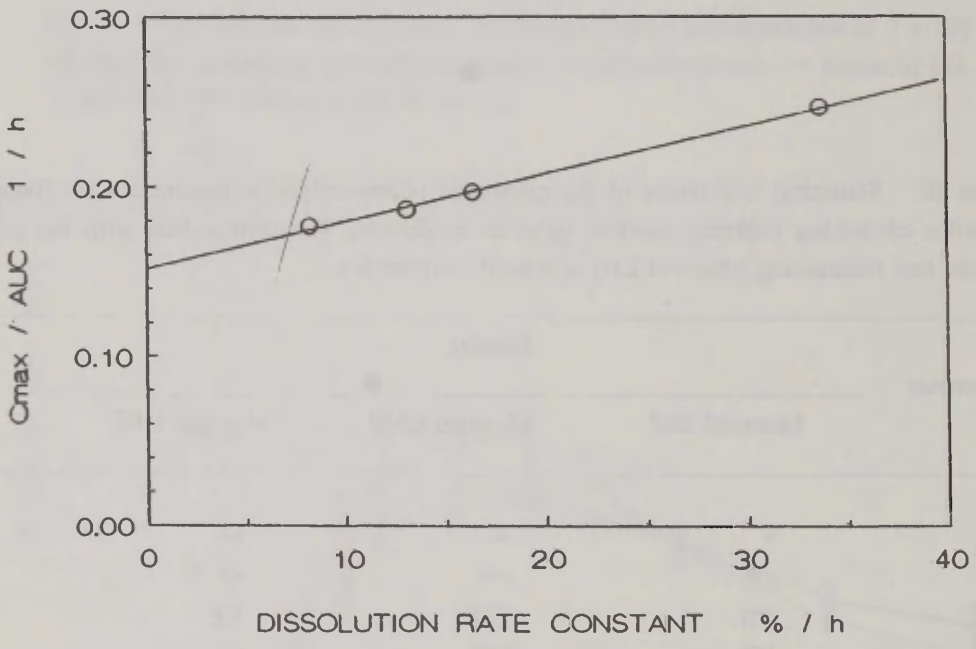

Fig. 4: In vitro/in vivo correlation between dissolution rate constant k_0 and absorption rate parameter C_{max}/AUC of the four ibuprofen capsule formulations studied.

DISCUSSION

When the lowest viscosity grade of sodium alginate (Manucol LD) were used as diluent, the absorption profile of ibuprofen did not differ markedly from that achieved for conventional ibuprofen tablets or capsules (1, 4-9). The mean t_{max} values have been 1.3 to 2.7 h and the C_{max} values 23.3 to 31.4 $mg \cdot l^{-1}$ as compared with 1.94 h and 31.4 $mg \cdot l^{-1}$ for Manucol LD capsules in the present study. The elimination half-life of ibuprofen from immediate release formulations has been reported to be 1.5 to 2 h (2, 9, 12). For Manucol LD capsules $t_{½}$ was 2.45 h. The conclusion is that Manucol LD, although slightly lowing the in vitro release rate of ibuprofen, does not markedly prolong the absorption of the drug.

The higher viscosity grades of sodium alginate (Manucol DM, Manugel GHB and especially Manugel DPB) led to a noticeable prolongation of drug absorption. Statistically significant differences were seen in t_{max}, C_{max}, C_{max}/AUC and MRT values of capsules containing Manugels (Table II). The $t_{½}$ of Manugel DPB capsules also differed significantly ($P<0.05$) from that of Manucol LD capsules. Thus, ibuprofen capsules containing Manucol DM or Manugel GHB can be classified as slow-release products, but capsules containing Manugel DPB as an extended-release product.

The difference between the four formulations can also be seen from the mean curves in Figs. 2 and 3. The individual plasma curves in Fig. 1 show a substantial interindividual variation. It is typical that one or two individuals differ from the rest. This is not a desirable characteristic for a prolonged-release product. The variations in pharmacokinetic parameters given as standard deviations in Table I are greater than those for ibuprofen capsules containing different viscosity grades of hydroxypropylmethylcellulose as diluent (12). However, the present distribution of individual plasma curves is not extraordinary in comparison with many other prolonged-release formulations.

Of the many pharmacokinetic parameters reflecting the absorption rate, one of the newest is the ratio C_{max}/AUC. It is said to be especially applicable when modified-release products are examined (18). As seen in Fig. 4, the correlation of this parameter to the in vitro parameter k_0 is excellent.

It can be concluded that with different viscosity grades of sodium alginate it is possible to prepare ibuprofen capsules from which the absorption rate can be controlled over a fairly wide range without any fall in the amount of drug absorbed. This is a simple and inexpensive way to produce prolonged-release drug products. In addition, sodium alginate may protect the gastric mucosa from the irritating action of anti-inflammatory analgesics, which would be an extra advantage for the formulations described here.

ACKNOWLEDGEMENT

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IV

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Biopharmaceutical evaluation of new prolonged-release press-coated ibuprofen tablets containing sodium alginate to adjust drug release

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Abstract

The aim of the study described here was to develop prolonged-release press-coated tablets containing ibuprofen. The drug dose was divided between the core and the coat in the ratio 2:1. Different chemical types, viscosity grades and amounts of sodium alginate were used in the coat to control drug release. Each of the variables studied affected the drug release rate. The in vitro release profiles were biphasic. The initial release rate was slow and in most cases increased with time. The terminal phase obeyed zero-order kinetics. The in vivo absorption profiles were also biphasic but both the initial and the terminal phases were markedly more rapid than in the in vitro dissolution studies. It was concluded that with different sodium alginates it is possible to prepare press-coated tablets from which the absorption rate can be controlled over a fairly wide range from an immediate release formulation via slow release formulations even to an extended-release formulation.

Key words: Bioavailability; Compression coating; Ibuprofen; Prolonged release; Sodium alginate

1. Introduction

In the development of prolonged-release drug products, it is common to attempt to achieve constant drug levels in the blood for as long as possible, on the assumption that the therapeutic effects will consequently be optimal. However, many diseases have marked diurnal rhythms. In such diseases, therapeutic drug concentrations should vary during the day. Drug levels should be highest when the symptoms are most severe. For example, in rheumatism, early morning stiffness is common. In theory, maximum drug levels can be achieved early in the morning if a formulation from which drug release increases with time is administered the previous evening.

Our previous studies (Sirkiä et al., 1992, 1993a) have shown that it is possible to prepare pro-

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longed-release furosemide and salbutamol tablets using a compression-coating technique from which the in vitro drug release rate increases with time. The total amount of drug in each tablet was divided between the core and the coat in the ratio 2:1. Drug release rate could be controlled principally by variation of the amount of polymer in the coat. In the first two studies the polymer used was hydrophilic hydroxypropylmethylcellulose (HPMC). The next study (Sirkiä et al., 1993b) used other hydrophilic polymers (sodium carboxymethylcellulose (NaCMC) and Carpobol 934P) but they did not control drug release as expected.

In the study described here, the polymer used to control drug release was sodium alginate. In previous investigations different viscosity grades of sodium alginate were successfully used as additives in the preparation of prolonged-release hard gelatin capsules of ibuprofen (Veski and Marvola, 1993; Veski et al., 1993). Alginates are anionic polysaccharides produced from selected species of brown seaweed. They are linear block copolymers containing two types of sugar residue, namely D-mannuronate (M) and L-guluronate (G). Three types of sugar residue sequence occur in the alginate molecules poly-M, poly-G and poly-MG. In this study we used two different types of sodium alginate sold under the trade names Manugel™ or Manucol™. Manugels contain a relatively high proportion of poly-G sequences and Manucols a low proportion of poly-G sequences (McDowell, 1986).

In the present study ibuprofen was used as a model drug. It is a nonsteroidal anti-inflammatory drug (NSAID) used for relief of acute pain and also in chronic diseases such as rheumatoid arthritis. Ibuprofen is readily absorbed throughout the gastrointestinal tract (Wilson et al., 1989) and its elimination half-life is only about 2 h (Ritschel, 1986).

The aim of this study was to investigate the suitability of sodium alginate for the press-coated tablet system developed, and to study by means of in vitro dissolution tests how the amount and the viscosity grade of sodium alginate affect drug release. The release rate of the drug from the tablet system prepared should ideally increase to a maximum at about 6 h. Finally, the bioavailabilities of the formulations judged to be the best were studied in man.

2. Materials and methods

2.1. Materials

Four different viscosity grades of sodium alginate – Manugel GHB (75 mPa s), Manugel DPB (500 mPa s), Manucol LF (25 mPa s) and Manucol DM (250 mPa s) – manufactured by Kelco Ltd, U.K. were used to control drug release. The values in parentheses are the viscosities of 1% aqueous solutions of each alginate at 20°C. The mean particle size of each grade of alginate was 355 μm. The model drug was ibuprofen (Orion-Farmos Pharmaceutical, Finland). To ensure reasonable dissolution of ibuprofen, which is sparingly water-soluble, the core contained potassium carbonate (Carlo Erba, Italy). Other excipients were polyvinylpyrrolidone (PVP, K25 Fluka, Switzerland), directly compressible lactose (Pharmatose DCL 21, The Netherlands), magnesium stearate (EP) and talc (EP).

2.2. Compositions

The tablets, each consisting of a core and a coat, were prepared using the compression coating technique. The drug was divided between the core and the coat in the ratio 2:1. The total amount of ibuprofen was always 100 mg. Only the coat contained polymer (Manugel™ or Manucol™) to control drug release. The compositions were:

Core		Coat	
Ibuprofen	67 mg	Ibuprofen	33 mg
Potassium carbonate	20 mg	Sodium alginate	300/340/360 mg
Lactose	40 mg	PVP-water-ethanol	10% q.s.
Magnesium stearate	1%	Magnesium stearate	1%
Talc	2%	Talc	2%

2.3. Preparation of tablets

To prepare the core ibuprofen, potassium carbonate and lactose were mixed in a mixer (Turbula AG, Switzerland) for 10 min. Magnesium stearate and talc were then added and mixing was continued for another 2 min. The cores were compressed in a Korsch EK-0 (Erweka Apparatebau, Germany) single-punch machine, using concave 7-mm punches. The compression force used was 10–12 kN.

Compression coating was performed manually using a Korsch EK-0 (Erweka Apparatebau, Germany) single-punch machine equipped with 11-mm punches. Ibuprofen and polymer were mixed in a mixer (Turbula AG, Switzerland) for 10 min. The powder mass was moistened with 10% PVP-water-ethanol solution and then sieved through a 0.7 mm sieve. The granules were dried overnight at 35°C. For tabletting, the fraction 0.3–0.7 mm was used. Magnesium stearate and talc were mixed with the granules in the same mixer for 2 min. Half of the granules for one tablet were weighed into the die and the core was placed on the granule bed. The rest (50%) of the granules were added to the die and the tablet was compressed manually using a force of about 20 kN.

2.4. Dissolution studies

The dissolution of ibuprofen was studied using the USP paddle method, as described for ibuprofen tablets in USP XXII (Dissolutest 07, Prolab, France). The dissolution medium was phosphate buffer, pH 7.2 (900 ml at 37 ± 0.5°C) and the speed of rotation was 50 min^{-1}. The dissolution apparatus was connected to a flow-through spectrophotometer (Ultraspect II, LKB Biochrom Ltd, U.K.) via a peristaltic pump (Watson-Marlow 503S, Smith and Nephew, U.K.). The absorbance of the dissolution medium in 2-mm flow-through cells at 221 nm was recorded automatically at regular intervals. Both absorbance measurements and pump were controlled by a computer running tablet dissolution software (TDS™, LKB Biochrom Ltd, U.K.). The release rates in 1-h periods were shown graphically. The amount of ibuprofen released was measured from six parallel samples.

2.5. Bioavailability study

Two groups of seven healthy volunteers participated in randomized cross-over single-dose studies, which were carried out in accordance with the recommendations of the Declaration of Helsinki (World Medical Assembly, 1975) as revised in Tokyo. The ages of the volunteers varied from 19 to 25 years and the weights from 45 to 84 kg. All were non-smokers and none took any drug during the study or 1 week before it. 1 week prior to the study the participiants underwent a physical examination, routine laboratory tests and an ECG. The volunteers were informed of the possible risks and side effects of the drug, and their written consent was obtained. The study protocol was approved by the ethical committee of the University of Tartu.

Each formulation (4×100 mg tablets) was administered with 200 ml of water following an overnight fast for at least 10 h. The washout period was at least 1 week. A standard lunch was provided 3 h after drug administration. Blood samples of 10 ml were collected from a forearm vein into heparinized tubes just prior to drug administration and 0.5, 1, 2, 3, 4, 6, 8, 10 and 12 h thereafter. Plasma was separated approx. 0.5 h after collection and stored at −20°C until analysis.

2.6. Plasma assay

Ibuprofen plasma concentrations were determined by means of HPLC using the method described by Avgerinos and Hutt (1986), with slight modifications. The system was equipped with a Waters Model 501 piston pump, a Waters Model 717 Intelligent Sample Processor, a Waters Model 486 Tunable Absorbance Detector operated at 222 nm, and a Waters Model 820 Maxima Workstation. Sample separation was carried out on a μBondapak C_{18} reverse-phase 125 Å column (3.9×300 mm). The guard column used was an RCSS μBondapak C_{18}. The isocratic mobile phase was acetonitrile and 0.1 M sodium

acetate (35 : 65), the pH of which was adjusted to 6.2 with glacial acetic acid. The flow rate was 2 ml min^{-1}.

The standard curve was found to be linear over the concentration range 2–40 mg l^{-1}. The linear coefficient of determination was 0.998. The accuracy and precision of the method were investigated as recommended (Shah et al., 1992) by analysing six plasma samples spiked with ibuprofen concentrations of 2 and 40 mg l^{-1}. The mean values were 2.33 mg l^{-1} (CV% 3.8) and 40.2 mg l^{-1} (CV% 5.8), respectively. The limit of quantitation was estimated to be 2 mg l^{-1}. No interfering peaks were observed in the plasma blanks.

2.7. Pharmacokinetic parameters

The pharmacokinetic parameters, assessed using a Siphar™ program (Simed, France), were maximum concentration (C_{max}), time to peak concentration (t_{max}), area under concentration time curve from 0 to infinity ($AUC_{0-\infty}$), apparent elimination half-life ($t_{1/2}$) and mean residence time (MRT). C_{max} and t_{max} values were used as measured. AUC and MRT values were calculated according to the trapezoidal method without logarithmic transformation. The rate of the absorption phase was also evaluated by means of the ratio $C_{max}/AUC_{0-\infty}$. Stastistical analyses were carried out using the Wilcoxon matched-pairs rank test and the Mann-Whitney U-test.

3. Results and discussion

The present formulation consists of two parts. The inner part, the core, is a conventional tablet containing most of the drug dose and thus acts as a drug reservoir. The outer part, the coat, contains a small amount of the dose and a hydrophilic polymer which forms a gel layer around the tablet both in vitro and in vivo. In theory, drug release from the system can occur via two mechanisms: as a consequence of erosion of the gel layer or by means of diffusion through the gel layer (Alderman, 1984). Ibuprofen is a sparingly water-soluble drug and, according to Alderman, should be liberated mainly from the gel formed via erosion. On the other hand, the core also contains potassium carbonate an alkaline compound that enhances the aqueous solubility of ibuprofen. Thus, diffusion of the dissolved drug through the gel layer is also a potential mechanism for drug release.

3.1. Effect of the chemical type and viscosity grade of sodium alginate on drug release

The first variables studied were the effects of the chemical type and viscosity grade of sodium alginate. As seen in Fig. 1 a rank order correlation existed between the viscosity grade of sodium alginate and the mean curves of the cumulative amounts of ibuprofen released; the higher the viscosity grade the lower the release rate. However, there was no marked difference between curves of tablets containing Manucol DM (viscosity 250 mPa s) and tablets containing Manugel GHB (viscosity 75 mPa s).

The conclusion is that the viscosity grade of sodium alginate is not the only parameter which predicts the release rate of ibuprofen from the present kind of formulation: the chemical structure of sodium alginate also has an effect. Manugels, which are composed of a relatively high proportion of polyguluronate sequences, slowed down drug release more than Manucols,

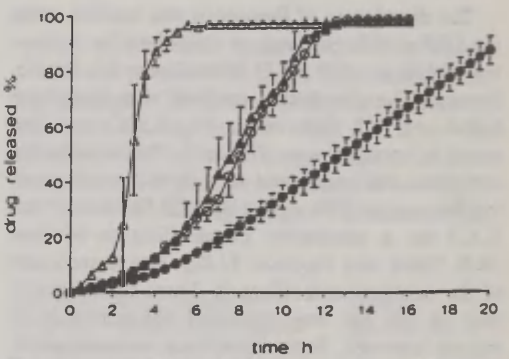

Fig. 1. Release of ibuprofen from press-coated tablets containing different viscosity grades of sodium alginate: (△) Manucol LF, (○) Manucol DM, (▲) Manugel GHB and (●) Manugel DPB. The amount of sodium alginate in the coat was always 360 mg. Each point is the mean ± SD, $n = 6$.

which are rich in polymannuronate sequences. The same phenomenon has been noted in hard gelatin capsules containing different viscosity grades of Manucols and Manugels as diluents (Veski and Marvola, 1993). In addition, Murata et al. (1993) in their studies concerning the release of brilliant blue (BB) from alginate beads concluded that the release of BB was slightly faster from the M-rich gel than from the G-rich gel, despite the similarity in the molecular weights of the polymers used.

The changes in drug release profiles are best seen in Fig. 2, where release rate is plotted as a function of time. As far as Manucol LF tablets are concerned (Fig. 2, upper panel) it is evident that during the first 2 h the release rate was slow and constant, indicating drug release via erosion of the gel layer. Thereafter, at 3–4 h the release rate was very fast, indicating disintegration of the whole tablet. Although this is the kind of release profile sought in this study, the burst in drug release happened too early.

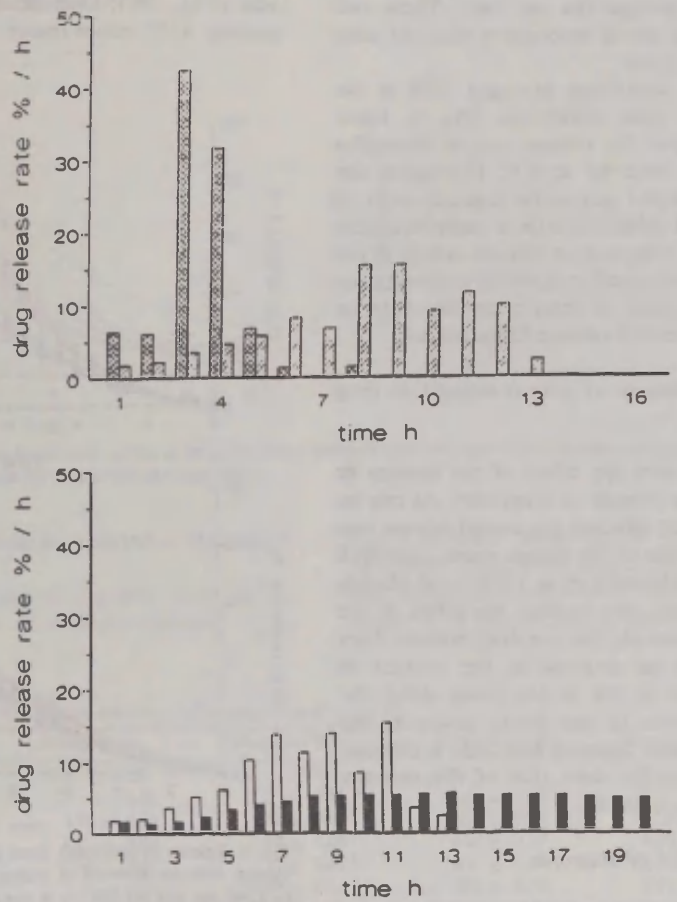

Fig. 2. Rate of drug release (per cent dissolved/h) vs time. (Upper panel) Manucols (cross-hatched bars) LF and (diagonally hatched bars) DM; (lower panel) Manugels (empty bars) GHB and (filled bars) DPB.

With Manucol DM and Manugel GHB tablets, the changes in the release profile of ibuprofen were identical. In both cases the release rate increased as a function of time up to 7 or 8 h (Fig. 2, upper and lower panels). The same phenomenon was observed in the cumulative amounts released in Fig. 1, where the drug release rates increase exponentially up to 7–8 h. The drug release rates from 8 to 12 h were constant or showed only a slight decrease (Manucol DM) from 7 to 11 h (Manugel GHB). It is obvious that the gel layer remained intact throughout and that the majority of the ibuprofen dose was released via diffusion through the gel layer. These two release profiles are in accordance with the aims of the present study.

The tablets containing Manugel DPB in the coat behaved quite differently (Fig. 2, lower panel). This time the release rate of ibuprofen increased with time up to 9 h. Thereafter, the release rate obeyed zero-order kinetics up to 20 h. This kind of release profile is understandable if after 9 h the drug release consists mainly of the diffusion of a saturated drug solution through the gel layer. This kind of release profile might be suitable for extended-release formulations.

3.2. Effect of amount of sodium alginate on drug release

Fig. 3 illustrates the effect of the amount of polymer on the release of ibuprofen. As can be seen, the amount affected the overall release rate but not the profile of the release curve. Stockwell et al. (1986), Takamura et al. (1992) and Murata et al. (1993) have also studied the effect of the amount of sodium alginate on drug release. They concluded that an increase in the amount of sodium alginate in the matrix slows down the drug release rate. In our study, however, the amount of sodium alginate had only a minimal effect, much smaller than that of the viscosity grade of sodium alginate.

3.3. Bioavailability of ibuprofen

Individual concentration/time curves for all four formulations are depicted in Fig. 4. The corresponding mean curves are given in Fig. 5 and the calculated pharmacokinetic parameters in Table 1. The interindividual variation in concentration/time curves was reasonable for each formulation, which is a desirable property for a modified-release preparation. Variation was lowest in the Manucol DM tablet.

As far as the extent of bioavailability of ibuprofen is concerned, no differences were found between the formulations. This is consistent with many other studies in which formulation factors have had no marked effect on the amount of ibuprofen absorbed (Regazzi et al., 1986; Marvola et al., 1991; Ojantakanen et al., 1993). The present AUC values (mean 117–151 mg l^{-1}) are

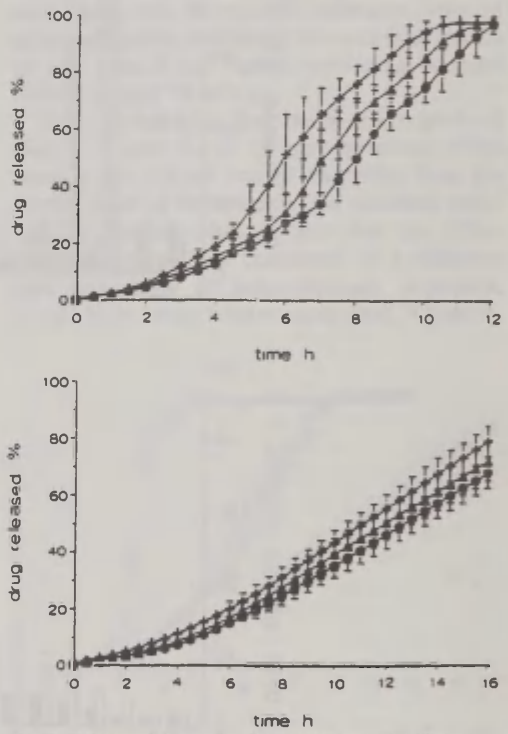

Fig. 3. Release of ibuprofen from press-coated tablets containing different amounts of sodium alginate: (+) 300 mg, (▲) 340 mg and (●) 360 mg in the coats. Each point is the mean ± SD. $n = 6$. The polymers used were Manucol DM (upper panel) and Manugel DPB (lower panel).

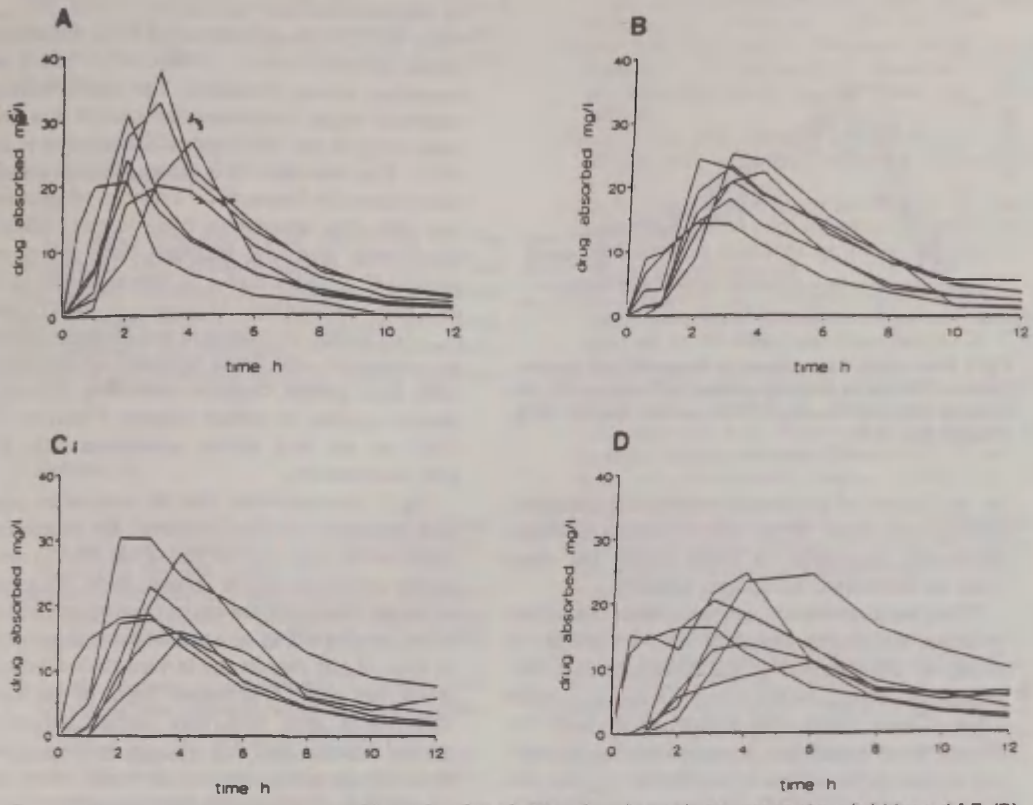

Fig. 4. Individual blood concentration curves of ibuprofen after administration of dose via test preparations: (A) Manucol LF, (B) Manucol DM, (C) Manugel GHB and (D) Manugel DPB.

of the same magnitude as reported in the papers mentioned above.

The absorption rate of ibuprofen from different preparations can be evaluated using the t_{max}, C_{max} and MRT values or the ratio C_{max}/AUC. As seen in Table 1, the highest statistically significant differences were noted in the C_{max}/AUC values. This ratio is said to be a good parameter

Table 1
Pharmacokinetic parameters for the test preparations (means ± SD, $n = 7$)

Parameter	Manucol LF	Manucol DM	Manugel GHB	Manugel DPB
AUC ($mg\,l^{-1}\,h$)	117 ± 32.2	128 ± 26.6	130 ± 54.1	151 ± 44.9
C_{max} ($mg\,l^{-1}$)	27.6 ± 6.58	21.2 ± 3.82 [a]	21.3 ± 6.00	18.28 ± 5.20 [d]
t_{max} (h)	2.71 ± 0.76	2.86 ± 0.69	3.29 ± 0.76	4.29 ± 1.25 [d]
MRT (h)	4.72 ± 0.83	5.88 ± 1.03	6.24 ± 1.19	8.97 ± 3.32 [e]
$C_{max}/AUC_{0-\infty}$ (h^{-1})	0.24 ± 0.04	0.17 ± 0.01 [b]	0.17 ± 0.04	0.12 ± 0.04 [b,f]
$t_{1/2}$ (h)	2.31 ± 0.31	2.87 ± 0.61 [a]	2.97 ± 0.73	4.71 ± 1.78 [a,c]

Wilcoxon matched-pairs rank test: [a] $p < 0.05$, [b] $p < 0.01$ and [c] $p < 0.001$, Manucol LF vs DM or Manugel GHB vs DPB. Mann-Whitney non-parametric U-test: [d] $p < 0.05$, [e] $p < 0.001$ and [f] $p < 0.001$, Manucol LF vs Manugel DPB.

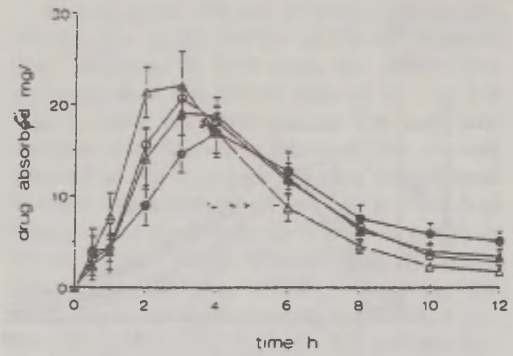

Fig. 5. Mean blood concentrations of ibuprofen after administration of 400 mg via test preparations: (△) Manucol LF, (○) Manucol DM, (▲) Manugel GHB and (●) Manugel DPB (means ± SE, $n = 7$).

for evaluation of prolonged-release formulations (Schall and Luus, 1992). MRT is also a useful parameter, especially in cases where the drug (such as ibuprofen) eliminates rapidly.

The pharmacokinetic characteristics of the formulation containing Manucol LF were similar to those of conventional or immediate release formulations. Its t_{max} value was 2.7 h and $t_{1/2}$ value 2.3 h. These differ only slightly from those reported for commercial or experimental immediate release formulations of ibuprofen: t_{max} 1.6–2.3 h or $t_{1/2}$ 1.5–2 h (Gillespie et al., 1982; Lockwood et al., 1983; Karttunen et al., 1990; Saano et al., 1991; Ojantakanen et al., 1993). The clear peak concentrations seen in every volunteer in Fig. 4A are typical of immediate release preparations.

The tablet containing Manucol DM can be classified as a slow release formulation. It differed statistically significantly from the Manucol LF tablet in terms of its C_{max}, C_{max}/AUC and $t_{1/2}$ values (Table 1). The pharmacokinetic profile of the Manugel GHB tablet is very similar to that of the Manucol DM tablet (Fig. 5) although the viscosity grade of the former is 75 mPa s and that of the latter 250 mPa s. Thus, the similarity between these two formulations in the dissolution tests (Fig. 1) could also be seen in the in vivo studies.

The Manugel DPB tablet can be classified as an extended-release formulation, since its t_{max} value was 4.3 h (compared to 2.2 h for immediate release products) and $t_{1/2}$ value 4.3 h (1.6 h for immediate release products). The aforementioned reference values have been determined in a previous study in our laboratory (Ojantakanen et al., 1993). The Manugel DPB tablet differed significantly from the Manucol LF tablet in all parameters reflecting absorption rate. It also differed significantly from the Manugel GHB tablet regarding C_{max}/AUC and $t_{1/2}$ values (Table 1). If the rate parameters (t_{max}, C_{max}, MRT and C_{max}/AUC) for the Manugel and Manucol tablets are compared with those achieved for ibuprofen from hard gelatin capsules containing the same viscosity grades of sodium alginate (Veski et al., 1993) we see very similar absorption rates for both formulations.

Fig. 5 demonstrates that the absorption profiles are slightly biphasic, however, the initial slow phase lasted only for 1 h. This is too short in view of the initial aim of the present study. Although in the in vitro tests the initial slow release phase lasted for 7–8 h (Fig. 1) it was dramatically shorter in vivo. In this respect the in vitro/in vivo correlation was poor. One reason might be the fact that the in vitro tests were carried out in a neutral solution (pH 7.2) whereas in the in vivo situation the tablets were in the acidic milieu of the stomach. For example, the dissolution of verapamil from Manugel DMP based matrix tablets has been observed to be pH-dependent: the lower the pH the faster the dissolution rate (Timmins et al., 1992). In their studies concerning theophylline alginate tablets, Fu Lu et al. (1991) concluded that the dissolution rate of drug was faster in acidic media.

With the Manugel DPB tablets, peak concentrations of ibuprofen ($t_{1/2}$ 1.5–2 h) were obtained at 3–6 h (mean 4.3 h). It can therefore be assumed that another drug with a much longer elimination half-life would give C_{max} values later on, e.g., at about 6 h, which was the main objective of our study.

It can be concluded that, with sodium alginates of different chemical structures or viscosity grades, it is possible to prepare press-coated ibuprofen tablets from which the absorption rate

can be controlled over a fairly wide range from a nearly immediate release formulation via slow release formulations to an extended-release formulation.

4. Acknowledgements

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Biopharmaceutical evaluation of pseudoephedrine hydrochloride capsules containing different grades of sodium alginate

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Key words: Bioavailability; Hard gelatin capsule; Prolonged-release; Pseudoephedrine; Sodium alginate

SUMMARY

In the study described here hard gelatin capsules containing pseudoephedrine hydrochloride and different grades of sodium alginate were prepared to obtain prolonged-release formulations. Evaluation was carried out by means of dissolution studies at three pH levels, 1.2, 4.4 and 7.2. Penetration of the dissolution medium into the capsule was followed by means of photographs. Bioavailabilities of the products were tested in man. At pH 1.2 there was no difference between the formulations. At pH 7.2 release rates correlated with viscosity grade of sodium alginate. The drug release mechanism could be explained on the basis of the photographs. The bioavailability tests confirmed that capsules containing high viscosity grades of alginate led to slow release formulations (t_{max} at 6.5 h) without any loss of amount of drug absorbed. It was concluded that the pseudoephedrine formulations, which are very simple to make, may be worth consideration in drug therapy.

Introduction

Sodium alginates are polysaccharides. They are structurally linear copolymers that contain two types of sugar residue: D-mannuronate (M) and L-guluronate (G). They occur in alginate molecules in three types of sequence: poly-M, poly-G and poly-MG (McDowell, 1986). Sodium alginates are nontoxic. They are widely used in the food industry. They have also been extensively studied as additives to solid and liquid drug products for peroral administration (Stockwell et al., 1986; Zatz and Woodford, 1987; Fu Lu et al., 1991; Timmins et al., 1992; Ojantakanen et al., 1993).

Among the many manufacturers of sodium alginates Kelco Ltd is well known. It markets two series of alginates under the trade names Manugel™, which is rich in guluronic acid, and Manucol™, which is rich in mannuronic acid. We have studied the effects of 14 grades of sodium alginate on dissolution rates of ibuprofen from hard gelatin capsules (Veski and Marvola, 1993). At pH 7.2, dissolution rates of each formulation containing sodium alginate as a diluent followed at pH 7.2 zero-order kinetics and varied from 5.8 to 58.8% $\cdot h^{-1}$, depending mainly on relative amounts and the viscosity grade of alginate used.

Results of bioavailability studies in man correlated well with in vitro results, and showed that it is possible using different grades of sodium alginate to prepare ibuprofen capsules from which absorption rates can be controlled over a fairly wide range, from slow release to extended-release formulations, without any decline in amount of drug absorbed (Veski et al., 1993). In this study the terms "slow release" and "extended-release" have been used to discriminate prolonged-release products to two subgroups as recommended by EC health authorities. Slow release products have higher t_{max} and lower C_{max} values than the corresponding immediate-release product, but in half-lives of the elimination phase there is no difference. Between extended-release products and immediate-release products it is a marked difference also in the elimination half-life. It is longer for an extended-release preparation. The model drug used in these studies was only sparingly water-soluble. With a drug that is highly soluble in water, it is possible that hard gelatin capsules containing sodium alginate as a diluent would behave differently. The effect of low pH on drug release rate could also not be evaluated using formulations containing a weak acid as the model drug.

In the study reported here, the model drug was pseudoephedrine hydrochloride. It is highly water-soluble and its aqueous solubility does not depend markedly on pH level in the physiological range. Pseudoephedrine is a stereoisomer of ephedrine but has fewer central nervous system effects. It is used as a decongestant. It is readily absorbed from the gastrointestinal tract. It is largely excreted unchanged in the urine, with an elimination half-life of 5 to 8 h (Kuntzman et al., 1971; Yacobi et al., 1980; Lin et al., 1985).

The primary aim of the study reported here was to study the effect of pH of the

dissolution medium on release rate of pseudoephedrine hydrochloride from hard gelatin capsule formulations containing four grades of sodium alginate. Secondarily penetration of the dissolution medium into the capsule was studied and an attempt was made to discover the mechanism by which the formulation acts as a modified-release preparation. Finally the bioavailabilities of the formulations in healthy volunteers were evaluated.

Materials and Methods

Capsule formulations

Size 0 hard gelatin capsules (Posiloc™, Elanco) were used for all formulations. The amount of pseudoephedrine hydrochloride (Knoll AG) per capsule was 100 mg. Four grades of sodium alginate (Kelco Ltd) were used as diluent. The trade names and viscosities (at 25°C) of 1% (w/w) aqueous solutions of these sodium alginates were: Manugel DPB (500 mPa·s), Manugel GHB (75 mPa·s), Manucol DM (250 mPa·s) and Manucol LD (9 mPa·s). The particle size of all of the sodium alginates was as given by the manufacturer <355 µm.

The amounts of drug needed were weighed in graduated cylinders and diluent added to produce sufficient material for 25 capsules (17 ml). Amounts of sodium alginate per capsule were: Manugel DPB 431 mg, Manugel GHB 489 mg, Manucol DM 513 mg and Manucol LD 513 mg. The powders were mixed manually, and capsules were filled using a Feton apparatus. The reference capsule in the bioavailability study contained 100 mg of pseudoephedrine hydrochloride without additive.

Drug dissolution

Dissolution of pseudoephedrine hydrochloride from capsules was determined using the USP rotating basket method. Solvents with three pH values were used, namely (1) pH 1.2 (0.1 mol/l hydrochloric acid), (2) pH 4.4 (phosphate buffer containing 6.81 g of KH_2PO_4 in one litre of water) and (3) pH 7.2 (phosphate buffer containing 6.81 g of KH_2PO_4 and 1.39 g of NaOH in one litre of water). The volume of dissolution medium was 900 ml and temperature 37 °C. The speed of rotation was 150 min^{-1}. Samples were taken manually. Drug concentrations were determined using the HPLC method described in "Plasma assay" (Dowse et al. 1983). The volume of sample administered to the injector was 10 µl. No extraction of samples was needed. Goodness of fit of dissolution curves to first-order and square-root-of-time equations were tested using Minsq™ software (Micromath).

Penetration of dissolution medium into capsules

The test was analogous to the ordinary dissolution test but the dissolution medium contained 0.1% fuchsin (E. Merck), which gave the solution a red colour.

At predetermined times, capsules were removed from the dissolution apparatus and cut in two. Penetration of the coloured solution was evaluated by visual inspection and photography.

Bioavailability study

Two groups of eight healthy volunteers (four women and four men in both groups) participated in randomized crossover single-dose studies. These were carried out in accordance with the recommendations of the Declaration of Helsinki (World Medical Assembly 1975) as revised in Tokyo. The ages of the volunteers ranged from 19 to 24 years, their weights from 45 to 84 kg. All were nonsmokers. None took any drug during the study or one week before it. One week prior to the study, participants underwent physical examination, routine laboratory tests and ECG examination. The study protocol had been approved by the Ethical Committee of the University of Tartu.

One capsule containing 100 mg of pseudoephedrine hydrochloride was administered with 200 ml of water following overnight fasting for at least 10 hours. A standard lunch was provided four hours after drug administration. The first group received reference capsules and capsules containing Manugel DPB, the second group capsules containing Manucols. The wash-out period between formulations was one week.

Blood samples of 10 ml were collected from a forearm vein into heparinized tubes just prior to drug administration, and 1, 2, 3, 4, 6, 8, 10, 12 and 24 hours thereafter. Plasma was separated approximately 30 min after collection by centrifugation (3000 g for 10 min), and frozen at -20 °C until analyzed.

Plasma assay

Pseudoephedrine plasma concentrations were determined by high-performance liquid chromatography (HPLC), using a modified version of the method of Dowse et al. (1983). One millilitre of plasma, 50 µl of a saturated solution of sodium carbonate and 100 µl of 2 M sodium hydroxide solution were vortexed for 15 s. Four millilitres of diethylether were added and the tube was vortexed for 1 min and centrifuged for 5 min. Two millilitres of ether extract were transferred to a centrifuge tube containing 100 µl of 5% acetic acid. The mixture was vortexed for 1 min and centrifuged for 5 min. The ether layer was reduced and the water layer transferred to a clean tube, from which 50 µl were taken for determination of drug levels. Each plasma sample was analyzed in triplicate. Mean values were used.

The system was equipped with a Waters Model 501 piston pump, a Waters Model 717 Intelligent Sample Processor, a Waters Model 486 Turnable Absorbance Detector operating at 220 nm and a Waters Model 820 Maxima Workstation. Sample separation was carried out on a µBondapak C_{18} reverse-phase column (3.9 x 300 mm). The guard column used was a µBondapak C_{18}.

The mobile phase was prepared by mixing acetonitrile (200 ml) with 0.005 M

solution of sodium-1-heptanesulfonate in water (800 ml) and adding 2 ml of 1 M hydrochloric acid. The flow rate was 1.3 ml·min^{-1}. All chemicals were analytical or HPLC grade.

The standard curve was found to be linear over the concentration range 50-1000 ng·ml^{-1} and passed close to the origin. The linear coefficient of determination was 0.993 or better. Accuracy and precision of the method were investigated as recommended by Shah et al. (1992), by analyzing six plasma samples of pseudoephedrine concentrations of 50 and 500 ng·ml^{-1}. Mean values were 45.4 ng·ml^{-1} (CV 18.3%) and 484 ng·ml^{-1} (CV 2.7%). The limit of quantitation was estimated to be 50 ng·ml^{-1}. No interfering peaks were observed in the plasma blanks.

Pharmacokinetic parameters

The pharmacokinetic parameters assessed using the Siphar™ program (Simed) were: maximum plasma concentration (C_{max}), time to peak concentration (t_{max}), area under the concentration-time curve from time 0 to infinity (AUC), elimination half-life ($t_{½}$) and mean residence time (MRT). C_{max} and t_{max} values were used as measured. AUC and MRT values were calculated by the trapezoidal method, without logarithmic transformation. The ratio C_{max}/AUC was also calculated. Statistical analyses were carried out using Student's t-test or Student's paired t-test. Values of t_{max} were analyzed using the nonparametric tests of Wilcoxon and Mann-Whitney.

Results and Discussion

Dissolution studies

When the hard gelatin capsule contained only 100 mg of pseudoephedrine hydrochloride dissolution of the drug was complete in 15 min, regardless of the pH of the dissolution medium. Fig. 1 shows the effect of pH on dissolution of pseudoephedrine hydrochloride from the four formulations that also contained sodium alginate. At pH 1.2, which should mimic in vivo conditions in the stomach, there were no differences between the four formulations. At higher pH values, the capsule containing the lowest viscosity grade alginate, Manucol LD, differed markedly from the others. The differences between the other three alginates were minimal, especially at pH 7.2.

When the capsules contained Manucol DM, Manugel GHB or Manugel DPB, release rate of pseudoephedrine hydrochloride was highest at pH 1.2 and lowest at pH 4.4, except for Manugel DPB at pH 7.2. Capsules containing the lowest viscosity grade alginate (Manucol LD) differed markedly in their behaviour. Slowest drug release was obtained at pH 1.2 and highest at pH 7.2.

In most cases, the release profiles of pseudoephedrine hydrochloride (Fig. 1) best

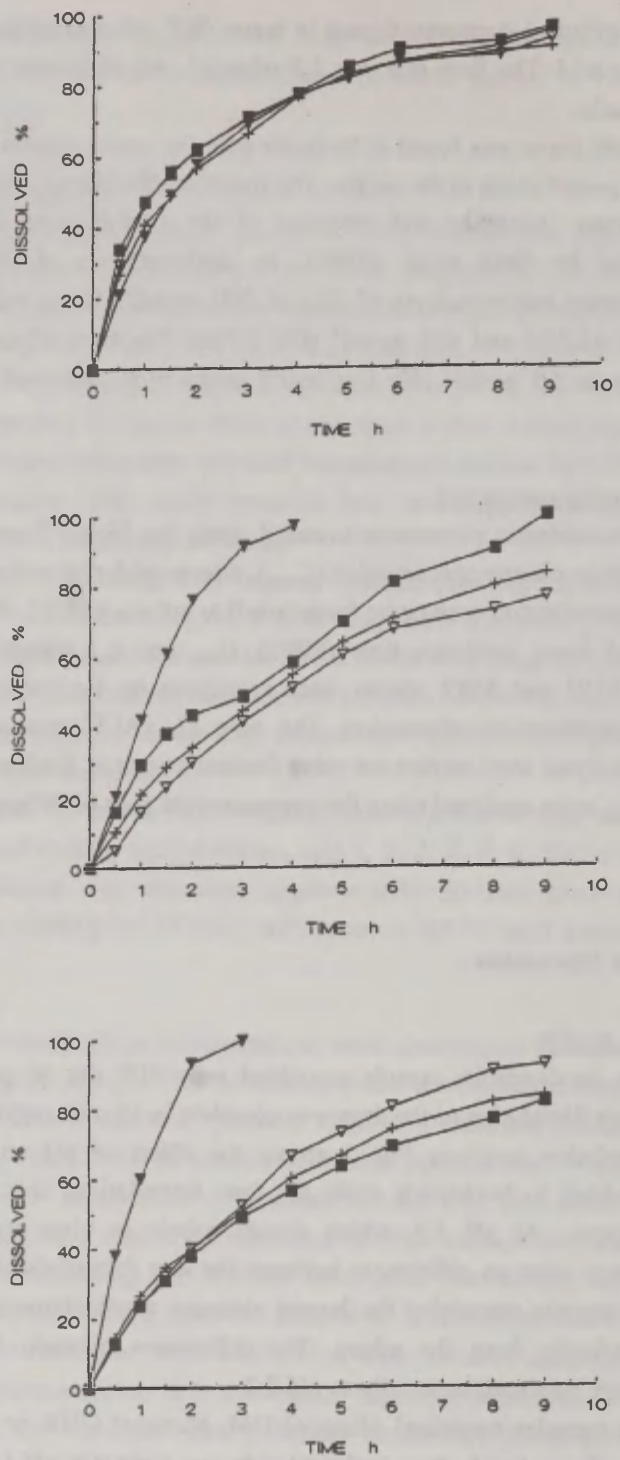

Fig. 1. Dissolution of pseudoephedrine hydrochloride from hard gelatin capsules containing different grades of sodium alginate as diluent: ▼ = Manucol LD, ▽ = Manucol DM, + = Manugel GHB, ■ = Manugel DPB. pH of dissolution medium was 1,2 (top), 4.4 (middle) or 7.2 (bottom), means of six parallel tests.

fitted first-order kinetics. The only exceptions were Manucol LD capsules at pH 4.4 and 7.2., where the best model was square-root-of-time kinetics. In this respect, the results in this study differ from our previous results with ibuprofen as model drug (Veski and Marvola 1993). In our earlier study the only dissolution pH used was 7.2, because of the solubility of the drug. In that study the drug-release profile followed zero-order kinetic, regardless of the grade of sodium alginate used in the capsules. The difference in kinetic profiles can be explained on the basis of aqueous solubility of the drugs. Overall release rates for ibuprofen were lower than those obtained for pseudoephedrine hydrochloride. In addition, release rate of ibuprofen was more readily controllable using different grades of sodium alginate.

The results reported here only partially correspond to those reported in the literature. Stockwell et al. (1986) reported that a cationic drug (chlorpheniramine maleate) had a slower release rate from alginate matrices than an anionic drug (sodium salicylate). In our study, an anionic drug (ibuprofen) was used as such, not as a water-soluble salt. In addition, unlike the matrix capsules of Stockwell et al., our capsule formulations did not contain calcium phosphate or sodium bicarbonate. These affect the gelation properties of alginate and the pH of the matrix. As far as in vitro results are concerned, the conclusion from our experience is that a simple capsule formulation, containing only the drug and sodium alginate, is better with drugs that are only sparingly soluble in water, e.g. weak acids, than with highly water-soluble drugs, e.g. hydrochloride salts of basic drugs.

Timmins et al. (1992) prepared sodium alginate matrix tablets containing verapamil hydrochloride. They found that release rates were partially independent of the pH of the dissolution medium. If matrices were prepared from sodium alginate rich in mannuronic acid (e.g. Manucol DMF) dissolution pH (1.2 or 7.4), had no marked effect on dissolution rate. In contrast, if the alginate used was rich in guluronic acid (e.g. Manugel DMP) reduction in pH led to a significantly higher release rates for verapamil hydrochloride. Our results indicate pH-dependent dissolution of pseudoephedrine hydrochloride for all four grades of sodium alginate studied. With Manucol DM, Manugel GHB and Manugel DPB, the dissolution rate was highest at pH 1.2. With Manucol LD it was lowest at the same pH.

Penetration studies

To obtained more information on the formulation, a dye (fuchsin) was added to dissolution media. At various times a capsule was removed, cut in two, and photographed (Fig. 2). The pH of the solution was 1.2 and the capsules contained Manugel DPB as additive.

At 30 min three layers were visible. The outer layer was tight and fairly hard. The second layer was gelatinous and smooth. The intensity of red colour in this layer was stronger than that in the outer layer. The core of the capsule was dry. At 1 to 3 hours all three layers were clearly evident. The thickness of the outer layer increased more rapidly than that of the second layer. The photograph at 4 h was

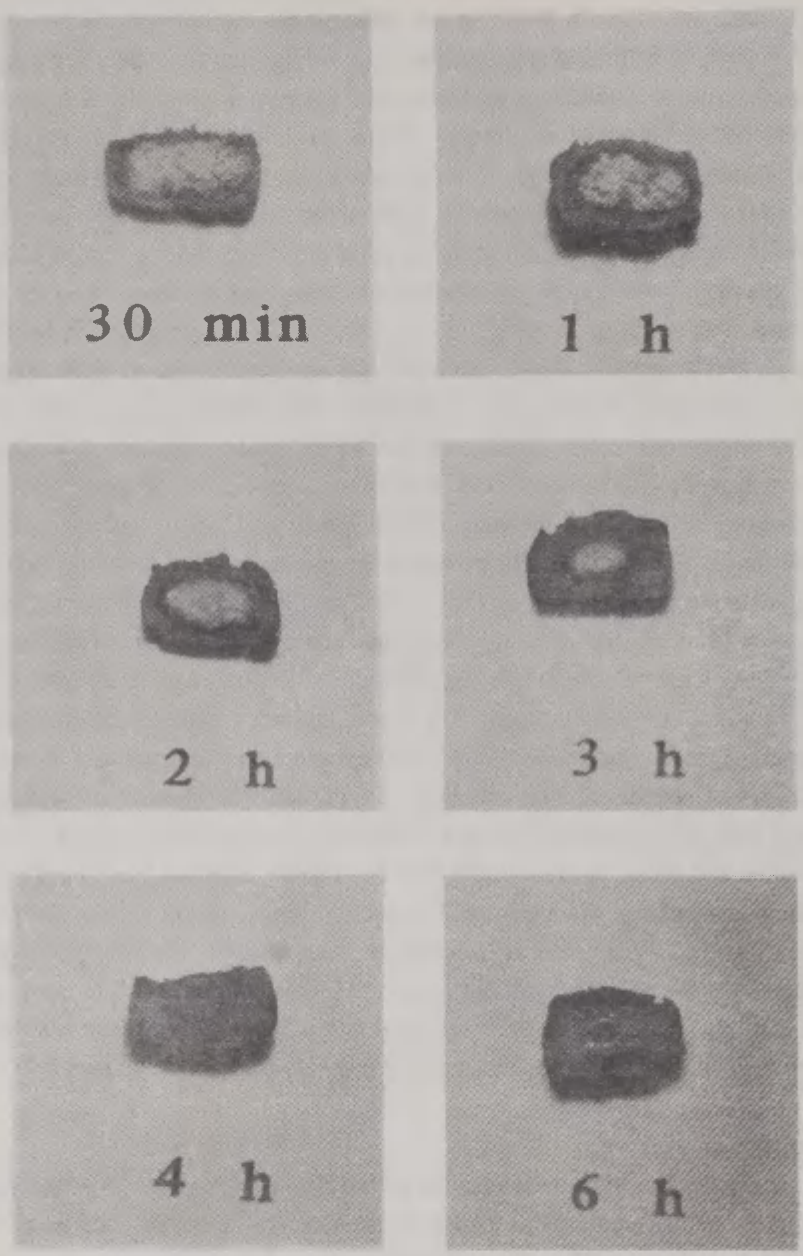

Fig. 2. Photographs showing penetration of the coloured dissolution medium into pseudoephedrine hydrochloride capsules containing Manugel DPB as diluent. The figures show the times when the capsules were removed from the dissolution equipment.

the last in which dry powder was visible in the core. At 6 h the gelatinous part had almost totally disappeared. The total volume of the formulation did not increase, i.e., there was no marked swelling of sodium alginate.

It is obvious that hydrochloric acid reacts with sodium alginate, and that an outer layer is formed when colloidal alginic acid precipitates. It is possible that the gelatin shell also plays a role in the commencement of formation of an outer layer. When dissolution medium penetrates the capsule, hydrogen ions are exchanged for sodium ions, and the dissolution medium declines in acidity. The second gelatinous layer is therefore formed when only slightly acidic or almost neutral solution moistens the sodium alginate. This explains why there was no difference in dissolution curves between formulations at pH 1.2 (Fig.1). In all formulations, alginic acid precipitated and formed the tight outer layer that acted as a rate-limiting layer in relation to diffusion of pseudoephedrine hydrochloride.

As the pH of the dissolution medium increased (4.4 or 7.2) no precipitation of alginic acid happened. The outer layer consisted only of sodium alginate gel and its tightness depended on viscosity grade and chemical nature of the sodium alginate used.

Why did Manucol LD behave differently from the other three grades of sodium alginate? The viscosity grade of Manucol LD is very low (9 mPa·s). The gel formed from it at pH 4.4 or 7.2 creates only a very weak barrier to diffusion of the drug. When a dissolution test is carried out at pH 1.2, colloidal alginic acid creates a tight outer layer that forms a better barrier than the low-viscosity sodium alginate gels formed at the higher pH's.

Bioavailability studies

Fig. 3 and 4 show mean curves for the two bioavailability studies. The corresponding individual curves are shown in Fig. 5. Table 1 shows calculated pharmacokinetic parameters for each formulation. Results of statistical analyses are given in Table 2. There were no statistically significant ($p > 0.05$) differences in the extent of bioavailability (AUC values) between the four formulations. When the capsules containing sodium alginate were compared with the reference capsule, significant differences were found in the pharmacokinetic parameters describing the rate of bioavailability (t_{max}, MRT and C_{max}/AUC).

When the lowest viscosity grade alginate (Manucol LD) was used, prolongation of the absorption phase was relative low, e.g. a change in mean t_{max} value from 2.88 h (reference) to 4.00 h. There were no significant differences in MRT and C_{max}/AUC values (Table 1). When Manucol DM or Manugel DPB was used, absorption of pseudoephedrine was more obviously retarded: t_{max} for both formulations was 6.5 h. MRT and C_{max}/AUC values also differed statistically significantly from those for the reference capsule (Table 2). As far as apparent elimination half-lives ($t_{½}$) were concerned, there were no differences between the reference capsule and the capsules containing sodium alginates. The conclusion

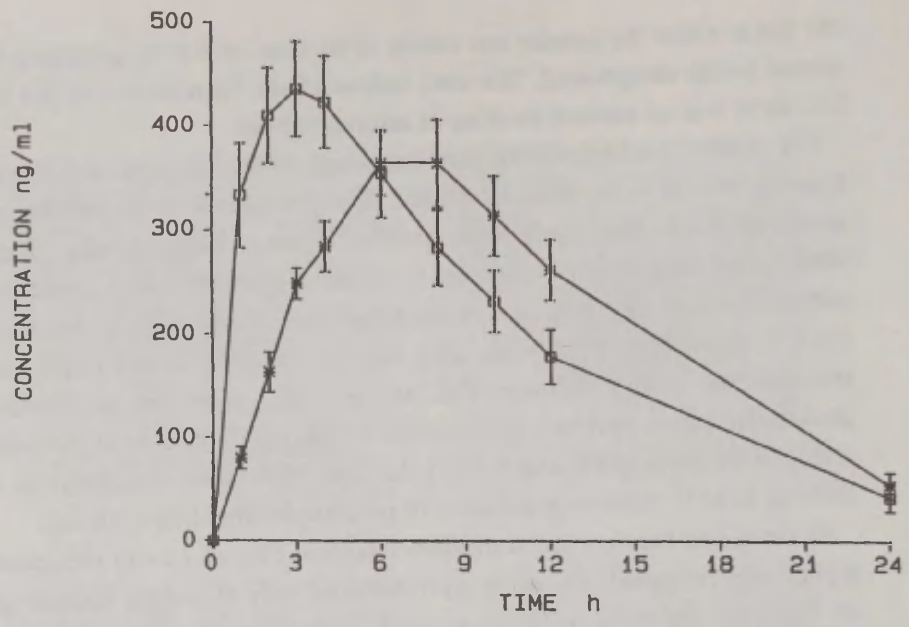

Fig. 3. Mean plasma concentration curves of pseudoephedrine after administration of 100 mg of pseudoephedrine hydrochloride in capsules containing the drug alone (□) or in capsules containing Manugel DPB as diluent (*), means ± S.E.M, n = 8.

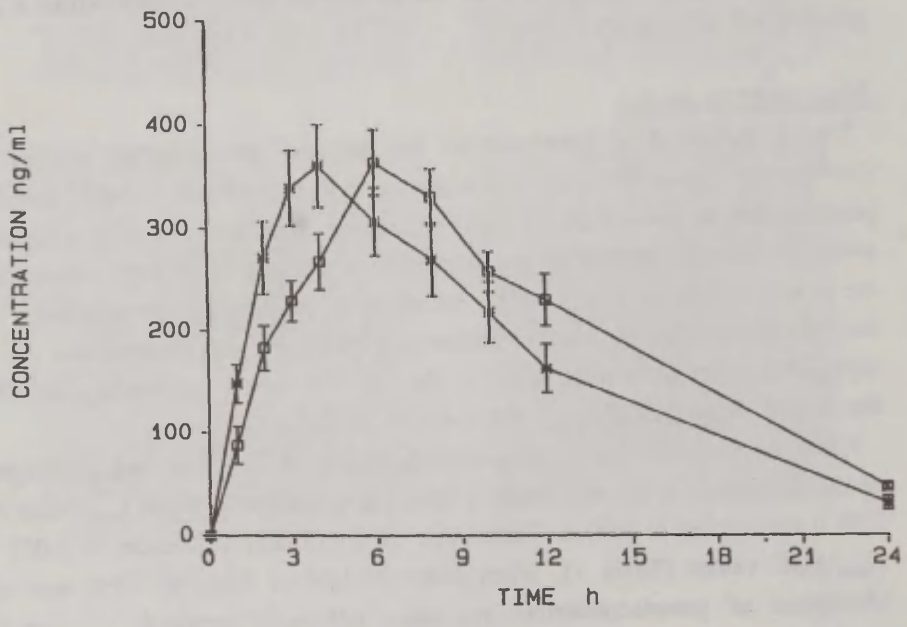

Fig. 4. Mean plasma concentration curves of pseudoephedrine after administration of 100 mg of pseudoephedrine hydrochloride in capsules containing Manucol LD (*) or Manucol DM (□) as diluent, means ± S.E.M., n = 8.

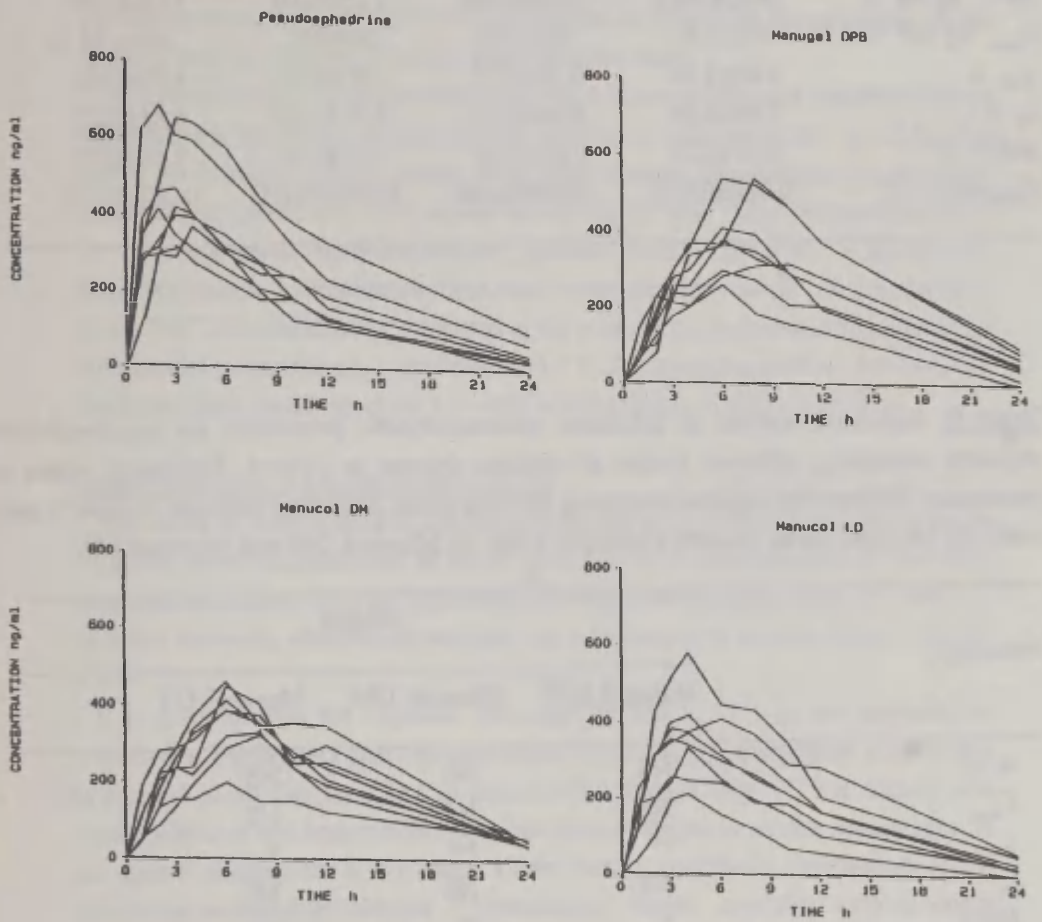

Fig. 5. Individual plasma concentrations of pseudoephedrine after administration of 100 mg of pseudoephedrine hydrochloride in different capsule formulations. Formulations: A = capsule containing drug alone, B = capsule containing Manugel DPB as diluent, C = capsule containing Manucol DM as diluent, and D = capsule containing Manucol LD as diluent.

Table I. Pharmacokinetic parameters of pseudoephedrine in hard gelatin capsules containing different grades of sodium alginate as diluent. Reference capsules contained only the drug. Single peroral dose: 100 mg of pseudoephedrine hydrochloride (means ± S.D, n = 8).

Parameter	Reference	Diluent		
		Manugel DPB	Manucol DM	Manucol LD
AUC $ng \cdot ml^{-1} \cdot h$	5465±2082	5742±1668	5121±810	4428±1607
C_{max} $ng \cdot ml^{-1}$	466±131	392±104	369±85	368±112
t_{max} h	2.88±0.64	6.50±1.77	6.50±0.93	4.00±0.93
$t_{½}$ h	5.98±0.94	6.04±1.11	6.31±1.83	4.81±0.57
MRT h	9.56±1.27	11.8±1.41	11.7±2.45	9.18±0.79
C_{max}/AUC h^{-1}	0.088±0.013	0.069±0.010	0.072±0.011	0.087±0.016

Table II. Statistical analysis of calculated pharmacokinetic parameters for pseudoephedrine capsules containing different grades of sodium alginate as diluent. Reference values are parameters obtained for capsules containing the drug alone. Statistical methods: Student's paired t-test for Manugel DPB, Student's unpaired t-test for Manucol DM and Manucol LD.

Parameter	Diluent		
	Manugel DPB	Manucol DM	Manucol LD
AUC	NS	NS	NS
C_{max}	NS	NS	NS
t_{max}	**	**	*
$t_{½}$	NS	NS	NS
MRT	*	*	NS
C_{max}/AUC	*	*	NS

* = $p<0.05$, ** = $p<0.01$, NS = not significant

from the results of in vivo studies is therefore that formulations containing Manucol DM or Manugel DPB can be classified as slow release preparations.

When the bioavailabilities of similar capsules containing ibuprofen instead of pseudoephedrine hydrochloride were studied the conclusion was that formulations containing Manucol DM or Manugel GHB could be classified as slow release preparation but formulation containing Manugel DPB as extended-release preparation (Veski and Marvola, 1993). The results of in vivo studies therefore confirmed the conclusion from results of in vitro tests that capsule formulations containing sodium alginate are better in relation to drugs that are sparingly soluble in water than in relation to highly water-soluble drugs.

The interindividual variation evident in Fig. 5 is normal for such modified-release formulations, especially if variation in weights of volunteers (45 to 84 kg) are taken into account. AUC values with slow release formulations in the study reported here (5742 and 5121 $ng \cdot ml^{-1} \cdot h$) are higher than the corresponding value for a commercial modified-release product (4483 $ng \cdot ml^{-1} \cdot h$), although the pseudoephedrine hydrochloride dose was lower: 100 mg versus 120 mg (Wecker et al., 1987). In addition, t_{max} occurred at 6.5 h in the study reported here. With the commercial preparation t_{max} occurred at 4.5 h. The pseudoephedrine formulations described here could therefore be worth considering in clinical situations.

Comparison of in vitro and in vivo results

Results of in vitro studies in acid environments, e.g. at pH 1.2, are often thought to allow optimum prediction of the in vivo fate of a drug product. In the study reported here, there were no differences between formulations at pH 1.2 (Fig. 1). In vivo, however, differences between formulations were evident (Figs. 3 and 4, Table 1).

It is possible that the capsules remained for 0.5 to 2 h in the stomachs of volunteers. During this time, an outer layer consisting of precipitated alginic acid is formed. A similar layer is also seen in vitro studies (Fig. 2). The alginic acid layer, which is not hydrophillic does not favour adherence of the formulation to the gastric mucosa for a long time. Under fasting conditions, movements of the migrating myoelectric complex ("housekeeper" wave), appearing approximately every second hour (Minami and McCallum, 1984), therefore sweep the capsule to the small intestine. The solution subsequently penetrating into the capsule is no longer acid. The rest of the sodium alginate in the core forms a gel. Its tightness depends on the viscosity grade of the polymer. This is why the in vivo absorption rate correlates with the viscosity grade of sodium alginate although no differences were seen in dissolution studies at pH 1.2.

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