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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, 1994) 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., 1994) 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,

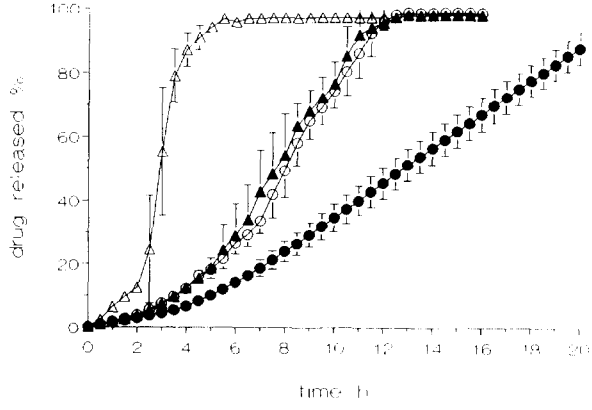

Fig. 1. Release of ibuprofen from press-coated tablets containing different viscosity grades of sodium alginate: (△) Manucol LF, (○) Manucol DM, (▲) Manugel GHB and (●) Manugel DPB. The amount of sodium alginate in the coat was always 360 mg. Each point is the mean + SD, $n = 6$.

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.

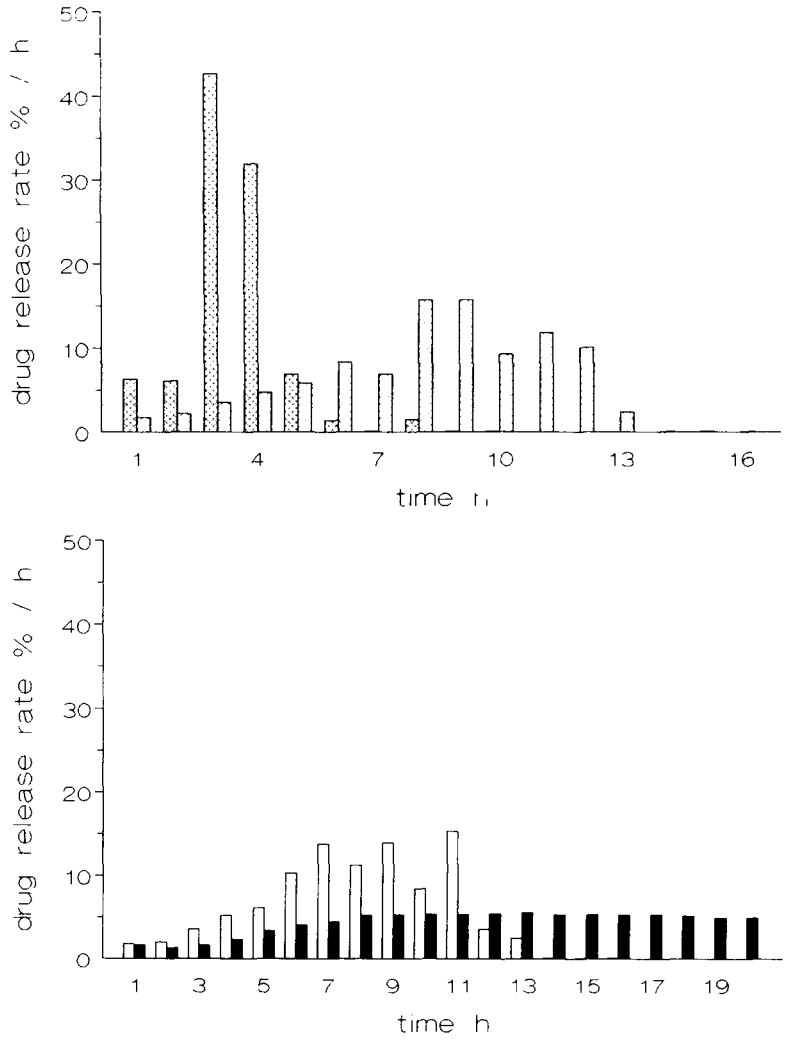

Fig. 2. Rate of drug release (per cent dissolved/h) vs time. (Upper panel) Manucols (cross-hatched bars) LF and (diagonally hatched bars) DM; (lower panel) Manugels (empty bars) GHB and (filled bars) DPB.

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

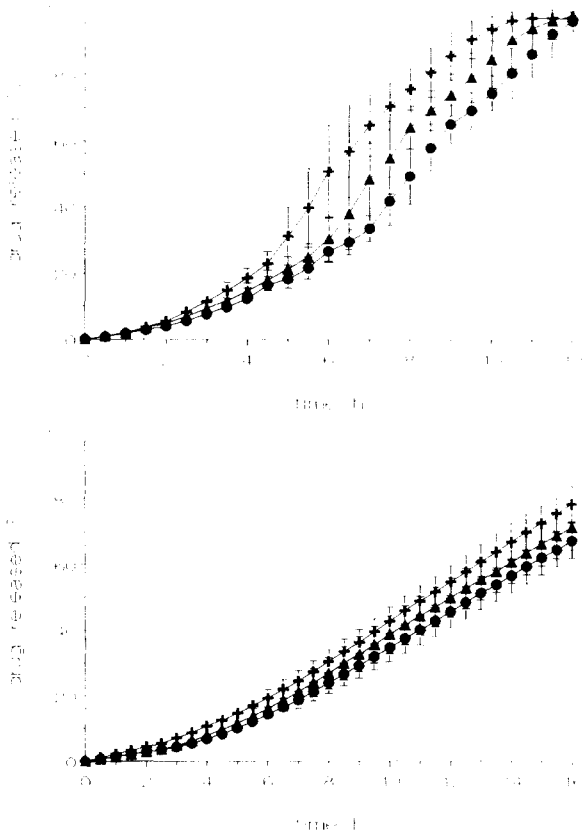

Fig. 3. Release of ibuprofen from press-coated tablets containing different amounts of sodium alginate: (+) 300 mg, (▲) 340 mg and (●) 360 mg in the coats. Each point is the mean ± SD, $n = 6$. The polymers used were Manucol DM (upper panel) and Manugel DPB (lower panel).

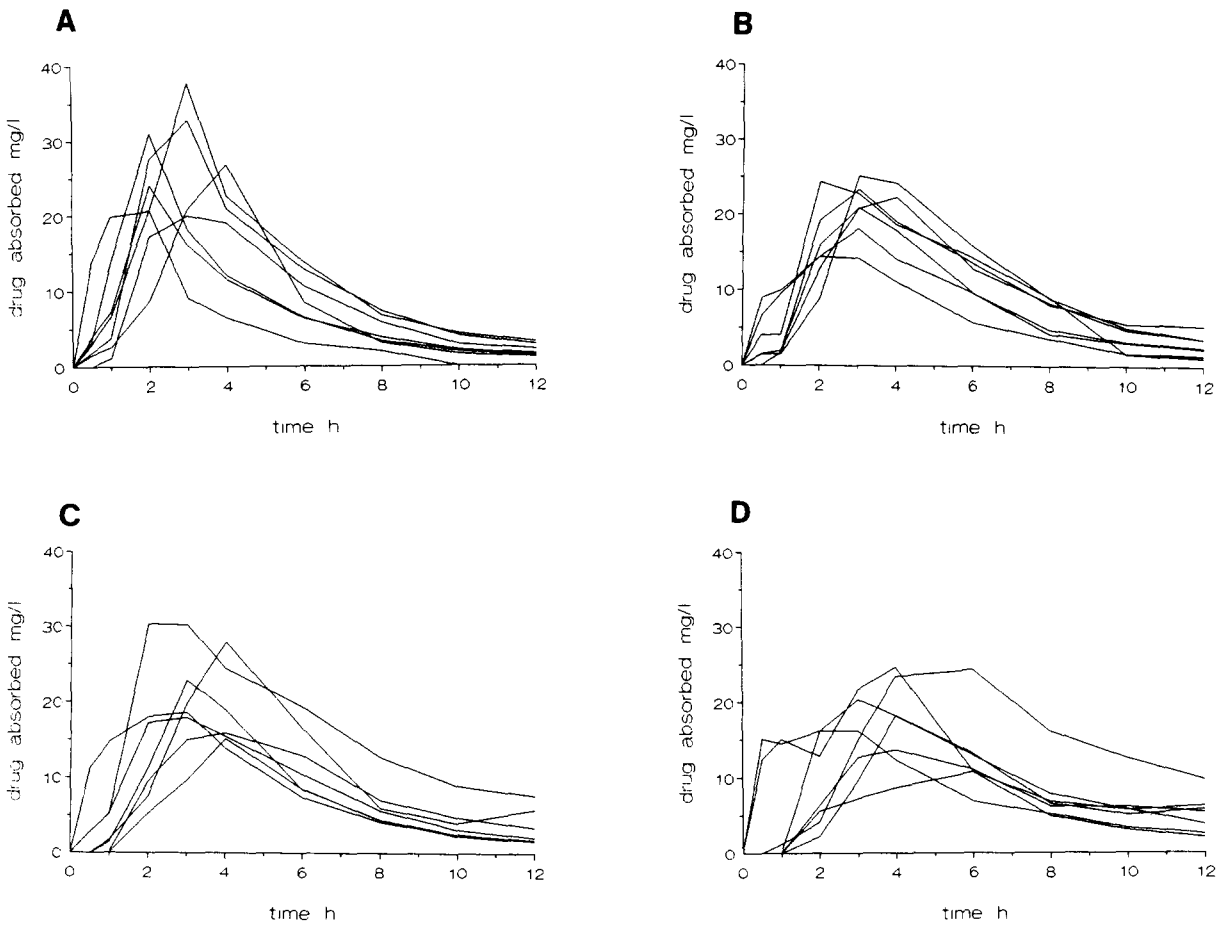

Fig. 4. Individual blood concentration curves of ibuprofen after administration of dose via test preparations: (A) Manucol LF, (B) Manucol DM, (C) Manugel GHB and (D) Manugel DPB.

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.

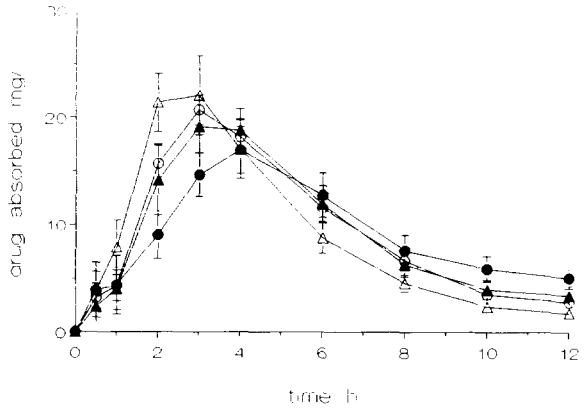

Fig. 5. Mean blood concentrations of ibuprofen after administration of 400 mg via test preparations: (△) Manucol LF, (○) Manucol DM, (▲) Manugel GHB and (●) Manugel DPB (means ± SE, $n = 7$).

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.

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