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Bioavailability of ibuprofen from hot-melt extruded mini-matrices

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Abstract

The bioavailability of ibuprofen from hot-melt extruded mini-matrices based on ethyl cellulose and a hydrophilic excipient was tested. During the in vivo evaluation an oral dose of 300 mg ibuprofen was administered to healthy volunteers ($n = 9$) in a randomized cross-over study and compared with a commercially available sustained release product (Ibu-slow®). The plasma samples were analysed by a validated HPLC-UV method. One mini-matrix formulation (F-1) consisted of 30% ibuprofen, 35% ethyl cellulose and 35% hydroxypropyl methylcellulose (Metolose® 60 SH 50), while the second formulation (F-2) contained 60% ibuprofen, 20% ethyl cellulose and 20% xanthan gum. These mini-matrices were administered in hard gelatine capsules. Both formulations behaved in vivo as sustained release formulations with an $HVD_{t_{50\%}C_{max}}$ value (time span during which the plasma concentration is at least 50% of the C_{max} value) of 7.6 and 12.0 h for formulations F-1 and F-2, respectively, whereas a value of 5.2 h was obtained for Ibu-slow®. Although a significantly higher C_{max} and $AUC_{0-24\,h}$ was seen for the reference product, the relative bioavailability of both experimental formulations was about 80%.

Keywords: Multiple unit dosage form; Sustained release matrix; Ibuprofen; In vivo

1. Introduction

Ibuprofen, a phenyl propionic acid derivative, is widely accepted as one of the best tolerated non-steroidal anti-inflammatory drugs available for the treatment of rheumatoid arthritis, osteoarthritis, and mild to moderate pain. At lower doses (0.6–1.2 g per day) ibuprofen is well suited for the treatment of fever, pain, migraine and dysmenorrhoea. Effective treatment of chronic painful arthritic conditions requires daily doses between 1.6 and 2.4 g. Using conventional formulations ibuprofen is rapidly absorbed, peak serum concentrations occurring within 1–2 h (Highton, 1999). Its short biological half life, approximately 2 h, requires multiple daily dosing, but slowing down the ibuprofen release from the formulation—using sustained release dosage forms—could reduce the frequency of drug administration, enhancing patient compliance.

Previous work (De Brabander et al., 2003) described the in vitro behaviour of mini-matrices formulated with ibuprofen (model drug), ethyl cellulose and a hydrophilic excipient. The in vitro sustained drug release could be modified by the appropriate selection of hydrophilic excipients at different concentrations. Based on these in vitro data two mini-matrix formulations

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(containing ibuprofen as the model drug) were selected to evaluate their in vivo performance after administration to healthy volunteers. During this study the in vivo behaviour of the controlled release experimental dosage forms was evaluated and compared against a commercial controlled release dosage form.

2. Materials and methods

2.1. Materials

Ibuprofen (IBP) (average diameter: 25 μm) (Knoll Pharmaceuticals, Nottingham, UK) was used as drug. Ethyl cellulose (EC) (ethoxyl content: 48–49.5% (w/w); viscosity: 9–11 mPa s (5% solution in toluene/EtOH, 80:20, 25 °C)) was purchased from Dow Chemical Company (Midland, USA). Hydroxypropyl methylcellulose (HPMC) (Metolose® 60 SH 50) was obtained from Shin Etsu Chemical Company (Tokyo, Japan) and xanthan gum from Federa (Brussels, Belgium).

Ibu-slow® 600 was obtained from Therabel (Brussels, Belgium). These tablets contain 600 mg ibuprofen.

2.2. Production process

Prior to hot-melt extrusion, the different components of the formulations were mixed in a planetary mixer. The powder mixture of the first formulation (F-1) consisted of 30% IBP, 35% EC and 35% HPMC (Metolose® 60 SH 50), while the second formulation (F-2) contained 60% IBP, 20% EC and 20% xanthan gum.

Hot-melt extrusion of the formulations was performed using a laboratory scale co-rotating twin screw extruder (MP19TC-25, APV Baker, Newcastle-under-Lyme, UK) with a length-to-diameter ratio of 25/1. The machine was equipped with a control panel, a standard screw profile with two mixing sections, a cylindrical die of 3 mm for the production of the mini-matrices and a twin screw powder feeder. The screw speed was set at 30 rpm and the powder feed rate at 360 g/h for both formulations. The temperature of the five heating zones along the barrel was set at 60 and 82 °C for the 60 and 30% IBP formulation, respectively. The extrudates (∅: 3 mm) were manually cut into mini-matrices of 2 mm length.

2.3. In vitro characteristics

The drug release from the mini-matrices was evaluated by dissolution testing. A modified paddle method (USP XXIV) was used in which the mini-matrices (approximately 60 mg) were kept in a spherical basket positioned at the bottom of the dissolution vessel. The dissolution was performed in a VK 7000 dissolution system linked to a VK 8000 automatic sampling station (VanKel Industries, New Jersey, USA). The temperature of the medium was kept at 37 ± 0.5 °C, while the rotational speed of the paddles was set at 100 rpm. Phosphate buffer (pH 7.2) was used as the dissolution medium. Samples of 5 ml were withdrawn at 0.5, 1, 2, 4, 6, 8, 12, 16, 20 and 24 h, replaced by fresh medium and spectrophotometrically analysed for ibuprofen at 221 nm by means of a Perkin Elmer Lambda 12 UV-Vis double beam spectrophotometer (Zaventem, Belgium). The ibuprofen concentrations were calculated from a calibration curve between 0 and 40 μg/ml.

To compare the dissolution profiles, the similarity factor (f_2) was used. In this approach, recommended by the FDA Guidance for Industry, similarity between two drug products is defined by an f_2 value between 50 and 100, f_2 being 100 for identical dissolution profiles. An average difference of 10% at all measured time points results in an f_2 value of 50. The similarity factor f_2 can be calculated as follows:

$$f_2 = 50 \log \left\{ \left[1 + \frac{1}{T} \sum_{i=1}^{T} (\bar{x}_{ti} - \bar{x}_{ri})^2 \right]^{-0.5} \times 100 \right\}$$

$\bar{x}_{ti}$ and $\bar{x}_{ri}$ represent the average percentage of drug dissolved from the mini-matrices measured at the ith time point of the test and reference preparations, respectively, and T is the number of time points tested.

2.4. In vivo evaluation

2.4.1. Subjects and study design

A group of nine Caucasian volunteers (three males and six females), aged between 18 and 55 years, gave written informed consent to participate in the study, which was approved by the Medical Ethics Committee of Ghent University Hospital. The study was conducted in accordance with the current ICH-GCP guidelines. The subjects were non-smokers or could smoke

no more than 10 cigarettes (or 2 cigars/2 pipes) a day and their weight was normal as defined by the body mass index. They were judged healthy on the basis of medical history, physical examination, electrocardiogram and evaluation of biochemical and haematological parameters in blood and urine. The subjects abstained from medication (except paracetamol and oral contraceptives) from 2 weeks prior to and during the whole study.

The following drug formulations were tested:

F-1:	30% ibuprofen, 35% ethyl cellulose and 35% hydroxypropyl methylcellulose (Metolose® 60 SH 50)
F-2:	60% ibuprofen, 20% ethyl cellulose and 20% xanthan gum
F-3:	Ibu-slow® 600 (half a tablet was administered)

The formulations were administered in a randomised cross-over sequence with a washout period of at least 6 days between consecutive sessions.

On the experimental days the subjects were fasting since the previous evening at 22:00 h, although the intake of water was allowed up to 2 h before drug administration. Before the administration of a formulation, an intravenous cannula was placed in an antecubital vein and a blank blood sample was obtained. Hard gelatin capsules (size 00), containing an amount of mini-matrices equivalent to 300 mg ibuprofen (i.e., 1000 and 500 mg for formulations F-1 and F-2, respectively), were administered with 200 ml of water. No food or water was allowed up to 2 h after drug intake. From 2 h after dosing, water could be taken freely. A standard breakfast and dinner were provided 3 and 6 h after drug intake, respectively. From 14 h post-administration, the volunteers could leave the clinical unit and resume their usual diet, except for ethanol containing beverages, which were not allowed until 24 h after drug administration. Blood samples (5 ml at each sampling time) were obtained at 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, 14 and 24 h after drug administration. The blood samples were collected in heparinized tubes and centrifuged for 10 min at 3000 rpm within 2 h of sampling. Separated plasma was aspirated and transferred in plastic tubes. The plasma was stored at −20 °C until assay of ibuprofen.

2.4.2. Ibuprofen assay procedure

Ibuprofen plasma concentrations were analysed according to a previously described HPLC-UV method (De Brabander et al., 2000).

2.4.3. Method validation

The mean calibration curve for ibuprofen ($y = 0.3542x - 0.0075$) ($n = 10$) was linear within the concentration range between 0.25 and 7.5 μg/ml ($r^2 = 0.999$). The detection and quantification limits in human plasma were determined at 0.07 and 0.25 μg/ml, respectively. The ibuprofen plasma recovery varied between 93.8 ± 3.0% ($n = 7$) and 98.7±7.7% ($n = 7$), while 93.6±3.3% ($n = 7$) of the internal standard (indomethacin) was recovered. The intra-assay coefficients of variation (CV) for the standards of the calibration curve ($n = 6$) ranged from 1.9 to 6.3%. The inter-assay CV for the same concentrations ($n = 7$) were between 0.7 and 5.6%. The inter- and intraday accuracy (expressed as the percentage error of the determined concentration compared with the theoretical concentration) was lower than 5.5 and 9.7%, respectively. The percentage plasma recovery of ibuprofen and the internal standard as well as the inter- and intra-assay CV were conform to the requirements for validation (Shah et al., 1992).

2.4.4. Data analysis

The peak plasma concentration (C_{max}) and the time to reach C_{max} (t_{max}) were determined from the individual plasma concentration–time profiles. The extent of absorption ($AUC_{0–24\,h}$) was calculated using the MW-Pharm Program version 3.0 (Mediware, 1987–1991, Utrecht, The Netherlands) using the logarithmic and linear trapezoidal rules. Extrapolated AUCs ($AUC_{0–\infty}$) were not calculated from these data since it was not possible to obtain accurate estimates of the terminal elimination constant due to the prolonged drug absorption. The sustained release characteristics of a formulation were evaluated by the time span during which the plasma concentration is at least 50% of the C_{max} value ($HVD_{t_{50\%}C_{max}}$, the width of the plasma concentration profile at 50% of C_{max}). The $HVD_{t_{50\%}C_{max}}$-values were determined from the individual plasma concentration–time profiles. The ratio between $HVD_{t_{50\%}C_{max}}$ of a test formulation and of an immediate release reference formulation (expressed as the quotient, $R\Delta$) is a measure for its sustained

release effect: a ratio of 1.5, 2 and >3 indicating a low, intermediate and strong sustained release effect, respectively (Meier et al., 1974). The immediate release reference formulation used to calculate $R\Delta$ was an ibuprofen suspension (Junifen®, The Boots Pharmaceuticals, Belgium) with a $HVD_{t_{50\%}C_{max}}$-value of 1.8 ± 0.8 h (Ntawukulilyayo et al., 1996).

The pharmacokinetic parameters (C_{max}, $AUC_{0-24\,h}$ and $HVD_{t_{50\%}C_{max}}$) of the formulations were statistically evaluated by a two-way ANOVA. The normality of the data was checked by means of the Shapiro–Wilk test and the homogeneity of variances using the Levene's test. If the variances were found not be equal the data were transformed to their square root. To further compare the effects of the different treatments a multiple comparison among pairs of means was performed using a Scheffé test with $P < 0.05$ as significance level.

3. Results and discussion

Previous work (De Brabander et al., 2003) demonstrated that mini-matrices (cylindrical shape, 2 mm height and 3 mm diameter) manufactured by hot-melt extrusion and consisting of ibuprofen, ethyl cellulose and hydroxypropyl methylcellulose or xanthan gum were able to sustain the in vitro drug release. A flexible drug delivery system was developed whereby the drug release could be modified by changing the viscosity grade and substitution degree of HPMC. The HPMC concentration, the drug load and the HPMC/EC ratio affected the in vitro drug release profile. Instead of HPMC, other hydrophilic excipients (xanthan gum) could also be incorporated into the matrix, a formulation containing xanthan gum having a near zero order drug release. In this paper the bioavailability of ibuprofen after oral administration of these mini-matrices is presented. Selecting the formulations for in vivo evaluation was done after a comprehensive in vitro development study as described by De Brabander et al. (2003).

Fig. 1 shows the in vitro release profiles of ibuprofen from Ibu-slow® and the different mini-matrices under investigation. It can be seen that both mini-matrices had a slower in vitro sustained release when compared with the commercially available reference product (Ibu-slow®). Fig. 2 shows the individual and mean ($n = 9$) plasma concentration–time profiles after oral administration of 300 mg ibuprofen as the commercial Ibu-slow® formulation and as the experimental mini-matrices F-1 and F-2, while Fig. 3 summarises their mean plasma concentration–time profiles. Following the initial peak in ibuprofen plasma concentration a second peak was observed in the profile of several subjects (independent of the formulation used). This bimodal drug absorption is unlikely to be due to enterohepatic recycling since this phenomenon was not observed following intravenous injection or administration of a conventional immediate release preparation (Parr et al., 1987). However, the same bimodal absorption of ibuprofen was visualised in combination with other sustained release dosage forms (Parr et al., 1987; Wilson et al., 1989; Borin et al., 1990; Gharaibeh et al., 1996; Pargal et al., 1996; Halsas et al., 1998). It was claimed that the second plasma peak might be the result of a loss of integrity of the dosage forms during gastrointestinal transit (Parr et al., 1987) or could be due to an increase in drug permeability in the colon (Borin et al., 1990).

The pharmacokinetic parameters are listed in Table 1. C_{max} of the experimental formulations was significantly lower than the corresponding value of the commercial formulation, combined with a delayed onset of action since t_{max} of F-1 and F-2 were 4.1 ± 0.9 h and 6.4 ± 3.8 h, respectively, versus 2.7 ± 0.8 h for Ibu-slow®.

With regard to the extent of absorption, Table 1 shows that the $AUC_{0-24\,h}$ values were very similar for both experimental formulations, but significantly lower than the $AUC_{0-24\,h}$ of Ibu-slow®, yielding a relative bioavailability of about 80% compared with the marketed product. However, it should be emphasised that drug absorption was not complete 24 h after administration of F-1 and F-2 (Fig. 3). A complete absorption of ibuprofen and consequently a higher relative bioavailability versus Ibu-slow® might be expected when the sampling time would be extended. These in vivo data correspond with the in vitro observations shown in Fig. 1, where similar ibuprofen release rates ($f_2 > 50$) for formulations F-1 and F-2 were seen. The f_2 values were less than 50 for the experimentally developed formulations (F-1: 41.9 and F-2: 34.5) using Ibu-slow® as a reference. Despite the similarity (based on the similarity factor, f_2) of the in vitro ibuprofen release for formulations F-1 and F-2, the latter had a near zero order drug

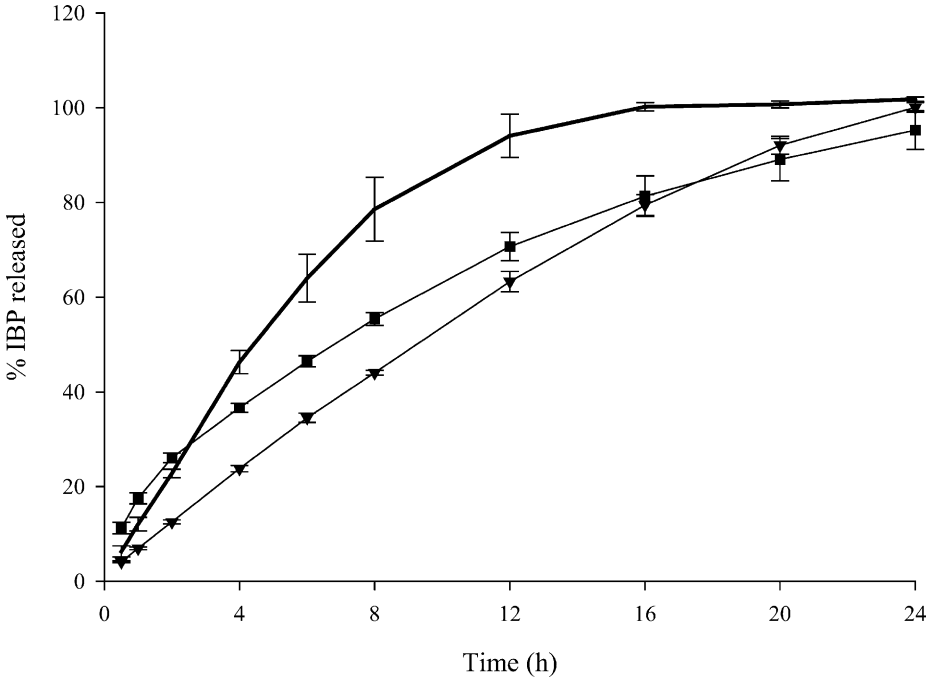

Fig. 1. Mean ibuprofen dissolution profiles (±S.D.) ($n = 6$) in phosphate buffer (pH 7.2): Ibu-slow® 600 (1/2 tablet) (—), mini-matrix F-1 containing HPMC (■) and mini-matrix F-2 containing xanthan gum (▼).

release, whereas some burst effect was seen in the drug release from the mini-matrices formulated with HPMC (F-1). These differences were reflected in the initial phase of the in vivo plasma concentration–time profiles, as initially a slower drug release was seen for the mini-matrices containing xanthan gum (F-2). Both mini-matrix formulations behaved in vivo as sustained release systems with an $HVD_{t_{50\%}C_{max}}$ value of 7.6 and 12.0 h for formulation F-1 and F-2, respectively (versus 5.2 h for the reference formulation) (Table 1). Although the bimodal absorption behaviour was formulation independent, it was interesting to note that for both mini-matrices the second ibuprofen plasma peak exceeded 50% of the C_{max}-value, even

Table 1
Mean pharmacokinetic parameters (±S.D.) after oral administration of 300 mg ibuprofen to healthy volunteers ($n = 9$): Ibu-slow® 600 (1/2 tablet), mini-matrix F-1 containing HPMC and mini-matrix F-2 containing xanthan gum

	Ibu-slow®	F-1	F-2
t_{max} (h)	2.7 ± 0.8	4.1 ± 0.9	6.4 ± 3.8
C_{max} (μg/ml)	14.1 ± 3.4	7.8 ± 2.7[a]	6.1 ± 1.1[a]
$AUC_{0-24\,h}$ (μg h/ml)	104.1 ± 34.0	79.0 ± 24.5[a]	80.9 ± 24.1[a]
F_{rel} (%)	–	76.9 ± 13.3	79.7 ± 17.7
$HVD_{t_{50\%}C_{max}}$ (h)	5.2 ± 2.0	7.6 ± 3.3	12.0 ± 6.3[a]
$R\Delta$	2.8 ± 1.1	4.2 ± 1.8	6.5 ± 3.5
$C_{24\,h}/C_{max}$ (%)	5.9 ± 3.6	26.4 ± 17.3[a]	51.0 ± 31.0[a]

$R\Delta$: ratio between $HVD_{t_{50\%}C_{max}}$ of the test formulation and $HVD_{t_{50\%}C_{max}}$ of an immediate release reference formulation (1.8 h for an ibuprofen suspension, Ntawukulilyayo et al., 1996).

[a] Significantly different from Ibu-slow® according to a two-way analysis of variance ($P < 0.05$).

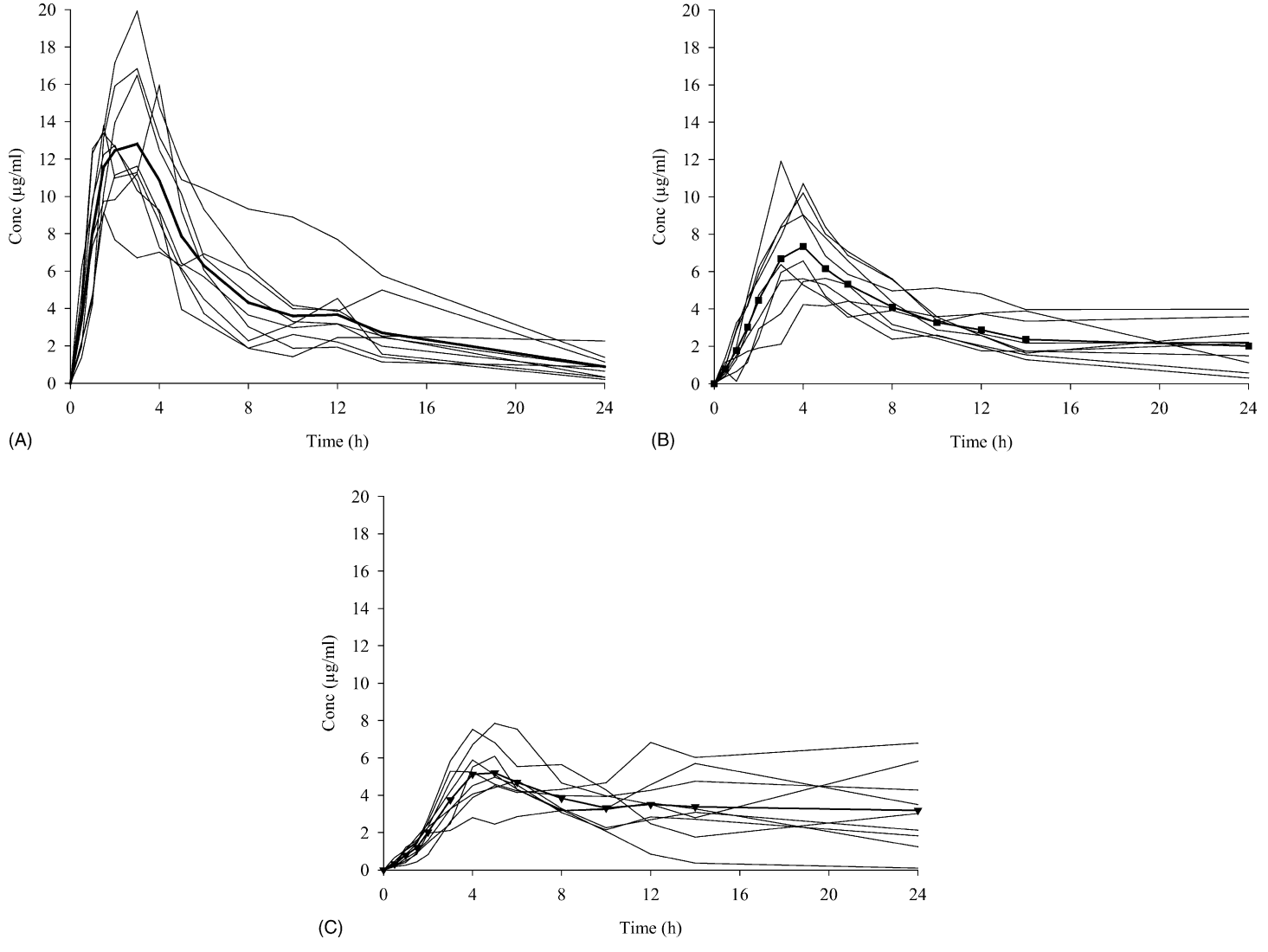

Fig. 2. Individual and mean plasma concentration–time profiles after administration of 300 mg ibuprofen to healthy volunteers ($n = 9$): Ibu-slow® 600 (1/2 tablet) (A), mini-matrix F-1 containing HPMC (B) and mini-matrix F-2 containing xanthan gum (C).

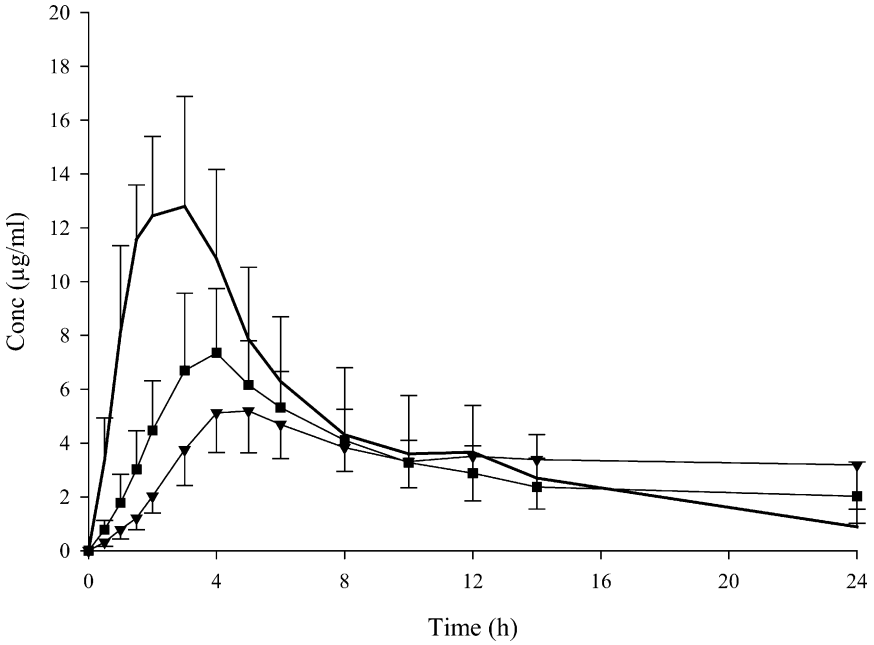

Fig. 3. Mean plasma concentration–time profiles (±S.D.) after administration of 300 mg ibuprofen to healthy volunteers ($n = 9$): Ibu-slow® 600 (1/2 tablet) (—), mini-matrix F-1 containing HPMC (■) and mini-matrix F-2 containing xanthan gum (▼).

prolonging $HVD_{t_{50\%}C_{max}}$ of F-1 and F-2. The $R\Delta$ ratios showed that the experimental formulations exhibited a strong sustained release effect with $R\Delta$ values of 4.2 (F-1) and 6.5 (F-2) when compared with an ibuprofen suspension (Ntawukulilyayo et al., 1996). The experimental formulations performed better than the marketed product, indicated by the lower $R\Delta$ value (2.8) of the Ibu-slow® tablet equivalent to an intermediate sustained release effect.

Examining the plasma concentration–time profiles and the higher $HVD_{t_{50\%}C_{max}}$ values revealed a more constant drug absorption pattern over 24 h for F-2 and to some extent for F-1 compared with the reference formulation. The residual concentration at the end of the sampling period ($C_{24\,h}$) can be used as a simple criterion to differentiate between various formulations after single dose administration (Steinijans, 1990). If the residual concentration is expressed as a percentage of the maximum concentration ($C_{24\,h}/C_{max} \times 100$), it provides an indication of the peak–trough fluctuation to be expected during steady-state. The experimental formulations provided a significantly higher percentage of the $C_{24\,h}/C_{max}$-value than the reference product (Table 1), possibly indicating a better in vivo performance during steady state administration as a sustained release product.

Based on the relatively high plasma concentrations at the end of the sampling period (24 h) for both mini-matrix formulations, this bioavailability study clearly supported the findings of previous studies (Parr et al., 1987; Wilson et al., 1989; Borin et al., 1990; Gharaibeh et al., 1996; Pargal et al., 1996; Halsas et al., 1998) that ibuprofen is absorbed throughout the entire GI tract; the largest portion of the area under the curve most probably being generated when the dosage form resides in the large intestine.

In conclusion, it can be said that the mini-matrices formulated with ethyl cellulose in combination with xanthan gum or hydroxypropyl methylcellulose can be used to prepare sustained release dosage forms. Especially, the formulation with xanthan gum as the hydrophilic excipient was able to maintain the ibuprofen plasma levels during 24 h.

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References

Borin, M.T., Khare, S., Beihn, R.M., Jay, M., 1990. The effect of food on gastrointestinal (GI) transit of sustained-release ibuprofen tablets as evaluated by gamma scintigraphy. Pharm. Res. 7, 304–307.

De Brabander, C., Vervaet, C., Görtz, J.P., Remon, J.P., Berlo, J.A., 2000. Bioavailability of ibuprofen from matrix mini-tablets based on a mixture of starch and microcrystalline wax. Int. J. Pharm. 208, 81–86.

De Brabander, C., Vervaet, C., Remon, J.P., 2003. Development and evaluation of sustained release mini-matrices prepared via hot-melt extrusion. J. Control. Release 89, 235–247.

Gharaibeh, M., Zmeili, S., Saket, M., Arafat, T., Saleh, S., Sallam, E., Shubair, M., Al Deleq, S., 1996. Ibuprofen sustained-release dosage forms. Single- and multiple-dose studies of tablets and spansules in normal male volunteers. Clin. Drug Invest. 11, 174–183.

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

Highton, F., 1999. The pharmaceutics of ibuprofen. In: Rainsford, K.D. (Ed.), Ibuprofen. A Critical Bibliographic Review. Taylor and Francis, London, pp. 53–86.

Meier, J., Nuesch, E., Schmidt, R., 1974. Pharmacokinetic criteria for the evaluation of retard formulations. Eur. J. Clin. Pharmacol. 7, 429–432.

Ntawukulilyayo, J.D., Vervaet, C., Remon, J.P., Görtz, J.P., Berlo, J.A., 1996. In vitro and in vivo evaluation of a xanthan gum-*n*-octenylsuccinate starch mixture tablet containing ibuprofen as model drug. Int. J. Pharm. 139, 79–85.

Pargal, A., Kelkar, M.G., Nayak, P.J., 1996. The effect of food on the bioavailability of ibuprofen and flurbiprofen from sustained release formulations. Biopharm. Drug Dispos. 17, 511–519.

Parr, A.F., Beihn, R.M., Franz, R.M., Szpunar, G.J., Jay, M., 1987. Correlation of ibuprofen bioavailability with gastrointestinal transit by scintigraphic monitoring of ^{171}Er-labeled sustained-release tablets. Pharm. Res. 4, 486–489.

Shah, V.P., Midha, K.K., Dighe, S., McGilveray, I.J., Skelly, J.P., Yacobi, A., Layloff, T., Viswanathan, C.T., Cook, C.E., McDowall, R.D., Pittman, K.A., Spector, S., 1992. Analytical methods validation: bioavailability, and pharmacokinetic studies. Int. J. Pharm. 82, 1–7.

Steinijans, V.W., 1990. Pharmacokinetic characterisation of controlled release formulations. Eur. J. Drug Metab. Pharmacokinet. 15, 173–181.

Wilson, C.G., Washington, N., Greaves, J.L., Kamali, F., Rees, J.A., Sempik, A.K., Lampard, J.F., 1989. Bimodal release of ibuprofen in a sustained-release formulation: a scintigraphic and pharmacokinetic open study in healthy volunteers under different conditions of food intake. Int. J. Pharm. 50, 155–161.