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Bioavailability of ibuprofen from matrix mini-tablets based on a mixture of starch and microcrystalline wax

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Abstract

The bioavailability of ibuprofen from matrix mini-tablets based on microcrystalline wax and a starch derivative was tested. An oral dose of 300 mg of ibuprofen was administered to healthy volunteers ($n = 8$) in a randomized cross-over study design either as a commercial matrix formulation (Ibu-Slow® 600) or as mini-tablets (filled into hard gelatin capsules). The mini-tablets consisted of 60% ibuprofen, 15% Paracera® M (wax), 22.5% DDWM (starch) and 2.5% triacetin (lubricant). $t_{50\%}$ of the in vitro release was 4.5 and 5 h for the mini-tablet and Ibu-slow® formulations, respectively. Both formulations behaved in vivo as sustained-release formulation; their $HVD_{t50\%Cmax}$ value was determined at 5.6 and 5.1 h for the mini-tablet and Ibu-slow® formulations, respectively. A significantly higher value of C_{max} was seen for the mini-tablet formulation, resulting in a relative bioavailability of $116 \pm 22.6\%$ compared to the Ibu-slow® matrix. These data demonstrate that the experimental mini-tablets can be used to formulate sustained-release dosage forms.

Keywords: Mini-tablet; Sustained release; Matrix; Ibuprofen; Bioavailability

1. Introduction

Ibuprofen is a widely prescribed non-steroidal agent with anti-inflammatory, analgesic and antipyretic properties used to treat rheumatoid arthritis, osteoarthritis and mild to moderate pain. Maximum ibuprofen plasma concentrations are achieved within 1–2 h after ingestion of the drug, but due to its short half life of about 2 h (Highton, 1999) therapeutic blood concentrations can only be maintained if the drug is administered frequently. These drug characteristics make ibuprofen a suitable molecule to incorporate in a sustained-release dosage form, reducing the dose regimen to a once or twice a day scheme. Besides, a slower ibuprofen release may also decrease the occurence of gastro-intestinal side-effects (Highton, 1999).

The administration of multiparticulate matrix systems [such as pellets or mini-tablets (2–3 mm)] filled into hard gelatin capsules offers several advantages over conventional single-unit matrix for-

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mulations: less risk of dose-dumping, less inter- and intra-subject variability, higher degree of dispersion in the gastro–intestinal tract thus minimizing irritation due to high local drug concentrations (Bechgaard and Nielsen, 1978; Follonier and Doelker, 1992).

Recently, De Brabander et al. (in press) described the in vitro behaviour of mini-tablets formulated with microcrystalline waxes and starch derivatives and showed that the drug release rate from these mini-tablets can be modified by proper selection of the type and concentration of both the hydrophobic microcrystalline wax and the hydrophilic starch component. This paper deals with the bioavailability of ibuprofen from wax/starch matrix mini-tablets after administration to healthy male volunteers and relates the bioavailability of this experimental formulation to the in vivo behaviour of a commercial sustained-release dosage form.

2. Materials and methods

2.1. Materials

Ibuprofen (Knoll Pharmaceuticals, Nottingham, UK) was selected as a model drug. The matrix consists of a hydrophobic component: microcrystalline wax (Paracera® M (melting range: 68–72°C) Paramelt, Heerhugewaard, The Netherlands); and of a hydrophilic component: Drum Dried Waxy Maize Starch (DDWM), a pregelatinized starch derivative supplied by Eridania–Béghin Say–Cerestar (Vilvoorde, Belgium). Triacetin, acting as a lubricant during extrusion and tabletting, was purchased from Vel (Leuven, Belgium).

Ibu-slow® 600, a commercially available matrix formulation (Therabel, Brussels, Belgium) containing 600 mg of ibuprofen was used as a reference formulation.

2.2. Production of the matrix mini-tablets

Prior to melt extrusion, all components of the formulation containing 60% ibuprofen, 15% Paracera® M, 22.5% DDWM and 2.5% triacetin were homogenized in a planetary mixer. Melt extrusion was performed using a laboratory scale co-rotating twin screw extruder (MP19TC-25, APV Baker, Newcastle-under-Lyme, UK). The material was extruded at a screw speed of 100 rpm, while the powder feed rate was set at about 700 g/h. Binding of the formulation was ensured using the following temperature profile at the different sections of the extrusion barrel: 64–62–62–59–58°C from the powder feeder towards the die. Afterwards the extrudates (Ø: 3 mm) were cooled to room temperature, milled using a Kenwood® mill and sieved to isolate the 250–500 μm granule fraction. These granules (250–500 μm) were compressed, using an eccentric tabletting machine, (Korsch EK 0, Frankfurt, Germany) equipped with 2 mm flat punches at a compaction pressure of $\pm$ 150 MPa; yielding 7.5 mg mini-tablets.

2.3. In vitro characterisation

A modified paddle method (Zhou et al., 1996) was used in which the mini-tablets were kept in a spherical basket at the bottom of the dissolution vessel. The dissolution of both the experimental mini-tablet formulation and the Ibu-slow® 600 reference formulation was performed in a Van Kel 7000 dissolution system (Van Kel Industries, New Jersey, USA) using phosphate buffer pH 7.2 (USP 23) at 37°C and a paddle speed of 100 rpm. Samples were withdrawn at regular intervals and analyzed at 221 nm by means of a UV–VIS double beam spectrophotometer (Lambda 12, Perkin Elmer, Zaventem, Belgium).

2.4. In vivo evaluation

2.4.1. Subjects and study design

Eight male, Caucasian volunteers, aged between 22 and 57 years, gave written informed consent before participating in the study, which was appoved by the Medical Ethics Committee. All subjects were non-smokers and their weight was within 15% of their ideal weight. They were judged healthy based on their medical history, a physical examination, an electrocardiogram and a biochemical and haematological analysis of blood

and urine. The subjects had to abstain from medication from 2 weeks prior to and during the study. Formulations, containing 300 mg ibuprofen, were orally administered in a randomized cross-over study; either as half a tablet of the commercial Ibu-Slow® 600 delivery system or as mini-tablets filled into hard gelatin capsules. The wash-out period between both sessions was at least 1 week. On the experimental day, the volunteers were fasting since the previous evening at 20 h, but the intake of water was allowed until 6.30 h. Before administration of the formulation, an intravenous cannula was placed in one of the anticubical veins and a blank blood sample was obtained. The formulations were administered with 200 ml of water. During the first 2 h after intake, the subjects remained in a sitting position. Water was available from 2 h after drug intake, while a standard lunch and dinner were provided after 4 and 10 h. Twelve hour post-administration, the volunteers were allowed to resume their usual diet except for ethanol-containing beverages, which were not allowed until after 24 h after the ingestion of ibuprofen. The blood samples were collected in dry heparinized tubes before and 0.5, 1, 2, 3, 4, 5, 6, 8, 10, 12, 24 h after ibuprofen intake. Within 1 h of collection of the samples, the blood was centrifuged for 5 min at 3000 rpm and the plasma was stored at −20°C until assay of ibuprofen.

2.4.2. Ibuprofen assay

Ibuprofen plasma concentrations were determined using a HPLC–UV method. All chemicals were of analytical or HPLC grade.

Fifty microlitres of an internal standard solution (20 μg/ml indometlacin in ethanol), 50 μl ethanol, 500 μl plasma, 100 μl HCl (2N) and 4 ml hexane/ether mixture (ratio: 4/1; v/v) were transferred into a borosilicate glass tube. After 3 min of vortexing and 5 min centrifuging at 4000 rpm, the upper organic layer was transferred into a new glass tube and evaporated to dryness under a nitrogen stream. The residue was dissolved in 100 μl mobile phase and 25 μl of this solution was injected onto the column. The plasma concentrations were determined via a calibration curve. These standards containing 500 μl blank plasma spiked with 50 μl of internal standard solution and 50 μl of a standard solution (with a known ibuprofen concentration in ethanol) were extracted using the same procedure.

The HPLC equipment consisted of a solvent pump (L-6000 pump, Hitachi, Tokyo, Japan) set at a constant flow-rate of 1.5 ml/min, a variable wavelength detector (L-4000 UV, Hitachi, Tokyo, Japan) set at 220 nm, a reversed-phase C-18 column (125 × 4 mm — 5 μm) (LiChrospher®, Merck, Darmstadt, Germany) equipped with a precolumn (4 × 4 mm — 5 μm) and an automatic integrator (D-2000 Chromato-Integrator, Hitachi, Tokyo, Japan). The mobile phase consisted of 0.1 M KH_2PO_4 (adjusted to pH 7.0 with 2M NaOH) and acetonitrile (ratio: 11/4; v/v).

2.4.3. Method validation

The mean calibration curve ($y = 0.3241x + 0.0112$) ($n = 6$) was linear between 0.25 and 15 μg/ml ibuprofen ($r^2 = 0.999$). The correlation coefficient of the separate calibration curves varied between 0.998 and 0.999. The ibuprofen plasma recovery of the 1, 5 and 10 μg/ml samples was 99.3 ± 8.27%, 91.5 ± 4.13% and 91.6 ± 0.44%, respectively; while 92.7 ± 1.65% of the internal standard was recovered after extraction. The intra assay coefficients of variation for the 1, 5 and 10 μg/ml ibuprofen standards ($n = 6$) ranged from 5.7 to 7.5%; while their inter assay coefficients of variation ($n = 6$) were between 2.1 and 5.1%.

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 ($AUC_{0\text{-}24h}$) was calculated using the MW-Pharm Software version 3.0 (Mediware, Utrecht, The Netherlands). The $AUC_{0\text{-}24h}$ was calculated using logarithmic and linear trapezoidal rules. An additional parameter characterising the in vivo behaviour of sustained release formulations is by means of $HVD_{t50\%Cmax}$. This is the time span during which the plasma concentrations are at least 50% of the C_{max} value or the width of the plasma profile at 50% of C_{max}. The $HVD_{t50\%Cmax}$ was determined from the individual plasma concentration–time profiles.

The pharmacokinetic parameters were statistically evaluated using a paired Sample's t-test in case of normal distributed results (Kolmogorov–Smirnov analysis), while the non-parametric Wilcoxon Signed Ranks test was used for non-normal distributed data. All tests were performed at a level of significance of $P < 0.05$.

3. Results and discussion

Previous work (Zhou et al., 1996, De Brabander et al., in press) demonstrated that a multi-particulate system based on a combination of starch and microcrystalline wax offers a flexible system capable of sustaining drug release even at high drug loadings. These studies showed that the in vitro drug release of pellets (Zhou et al., 1996) and mini-tablets (De Brabander et al., in press) based on this system could be "tailor-made" by modifying the type and concentration of the components of the formulation.

This paper describes the bioavailability of ibuprofen after oral administration of matrix mini-tablets. Based on the in vitro dissolution data (De Brabander et al., in press) mini-tablets consisting of 60% ibuprofen, 15% Paracera® M, 22.5% DDWM and 2.5% triacetin were selected for in vivo evaluation, as this formulation had an in vitro release profile similar to Ibu-Slow® 600 (Fig. 1). The $t_{50\%}$ were 4.5 and 5 h for the mini-tablet formulation and Ibu-slow® system, respectively. Figs. 2a and 2b shows the plasma concentration–time profiles after oral administration of 300 mg ibuprofen to eight healthy volunteers, both as the commercial Ibu-slow® formulation (Fig. 2a) and as the experimental matrix mini-tablets (Fig. 2b), while Fig. 3 summarises their mean plasma concentration–time profiles ($\pm$SD; $n = 8$). The results demonstrated that both formulations behaved in vivo as sustained release systems as indicated by their $HVD_{t50\%Cmax}$ values of 5.1 and 5.6 h for the Ibu-slow® and the mini-tablet formulation, respectively. All the pharmacokinetic parameters ($AUC_{0\rightarrow 24h}$, C_{max}, T_{max}, $HVD_{t50\%Cmax}$) are listed in Table 1. The matrix mini-tablets containing 60% drug had a relative bioavailability of 116 $\pm$ 22.6% ($n = 8$) compared to the marketed product. The C_{max} value of the wax–starch matrix mini-tablets was higher than for the Ibu-slow® ($P = 0.034$).

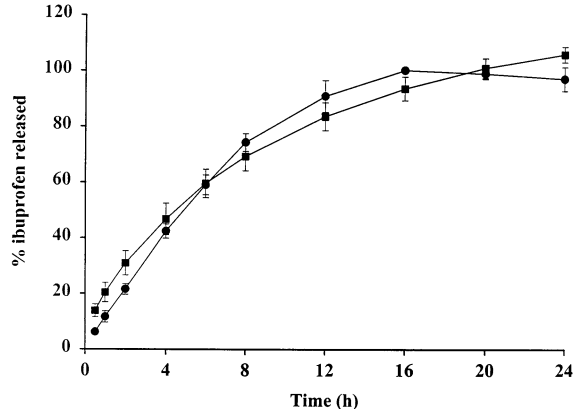

Fig. 1. In vitro dissolution profiles (phosphate buffer pH 7.2) of half a tablet of Ibu-slow® 600 (●) and of a mini-tablet formulation (■) consisting of 60% ibuprofen, 15% Paracera® M, 22.5% DDWM and 2.5% triacetin (all percentages are expressed as weight fractions).

The in vivo data of the mini-tablet formulation were compared to those previously obtained after oral administration of matrix pellets based on the same wax/starch system (Zhou et al., 1998) These pellets which have a similar in vitro dissolution profile compared to the mini-tablets,

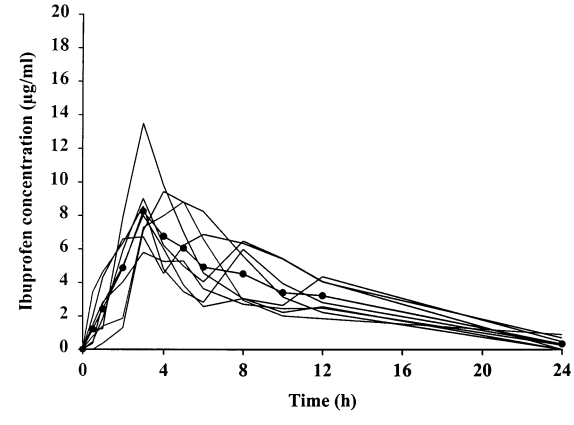

Fig. 2a. Individual and mean (●) plasma concentration-time profiles ($n = 8$) after administration of half a tablet Ibu-slow® 600 containing 300 mg ibuprofen.

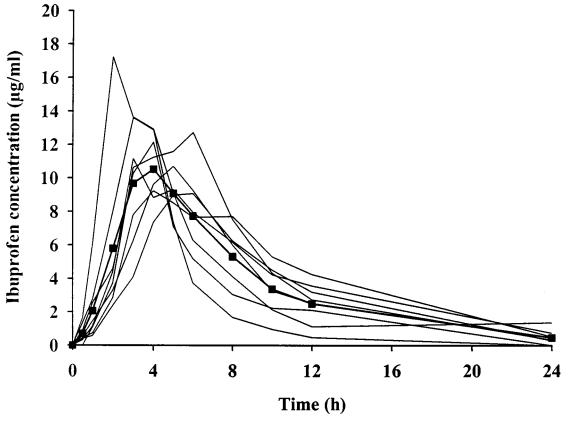

Fig. 2b. Individual and mean (■) plasma concentration-time profiles ($n = 8$) after administration of matrix mini-tablets (60% ibuprofen, 15% Paracera® M, 22.5% DDWM and 2.5% triacetin) containing 300 mg ibuprofen (all percentages are expressed as weight fractions).

Table 1
Mean pharmacokinetic parameters ($\pm$SD; $n = 8$) after oral administration of 300 mg ibuprofen either as $\frac{1}{2}$ tablet Ibu-slow® 600 and as a mini-tablet formulation consisting of 60% ibuprofen, 15% Paracera® M, 22.5% DDWM and 2.5% triacetin (all percentages are expressed as weight fractions)

	Mini-tablet formulation	$\frac{1}{2}$ tablet of Ibu-slow® 600
C_{max} (µg/ml)	11.9 ± 2.64[a]	8.7 ± 2.26
t_{max} (h)	4.1 ± 1.46	3.7 ± 1.16
$HVD_{t50\%Cmax}$ (h)	5.6 ± 1.90	5.1 ± 1.36
$AUC_{0\rightarrow 24h}$ (µg.h/ml)	82.8 ± 9.75	73.3 ± 13.93
F_{rel} (%)	116 ± 22.6	

[a] Significantly different from the Ibu-slow® formulation ($P < 0.05$; Paired Sample's t-test).

consist of 60% ibuprofen, 15% waxy maltodextrin and 25% Paracera® P and were processed by melt pelletisation in a high shear mixer (Zhou et al., 1996). Similar in vivo ibuprofen plasma profiles were seen, only C_{max} was significantly lower for the pellet formulation ($P < 0.05$; One-way ANOVA: 11.9 and 8.5 µg/ml for the mini-tablet and pellet formulation, respectively).The bioavailability of the mini-tablet formulation was 109.5% relative to the pellet formulation.

This bioavailability study clearly demonstrated that the matrix mini-tablets formulated with wax and starch can be used to prepare sustained release dosage forms. As a multiparticulate drug delivery system matrix mini-tablets offered the main advantage of an easier scaling up procedure in comparison with the matrix pellet system (De Brabander et al., in press).

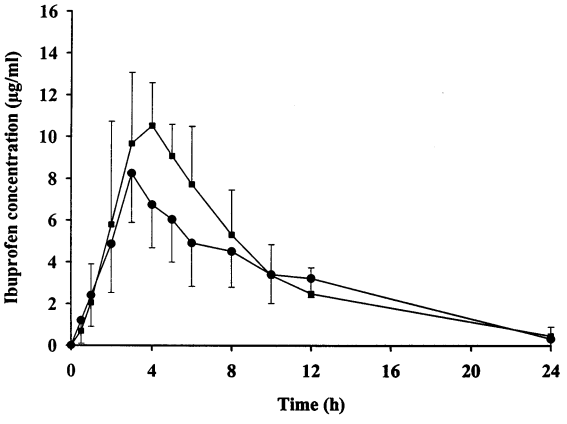

Fig. 3. Mean plasma concentration-time profiles after administration of half a tablet Ibu-slow® (●) and matrix mini-tablets (60% ibuprofen, 15% Paracera® M, 22.5% DDWM, 2.5% triacetin) (■).

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