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Bioavailability of ibuprofen from matrix pellets based on the combination of waxes and starch derivatives

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Abstract

The bioavailability of ibuprofen from pellets based on microcrystalline wax and starch derivatives was tested. During the in vivo evaluation an oral dose of 300 mg ibuprofen was administered to healthy human volunteers. F-1 and F-2 pellets were filled into hard gelatin capsules and were formulated with 60% ibuprofen, 15% waxy maltodextrin and 25% wax (a mixture of Lunacera M® and Lunacera P® (ratio 7/3) in the case of F-1 pellets and pure Lunacera P® in case of the F-2 pellets). In vitro, $t_{50\%}$ was 20 and 4 h for F-1 and F-2 pellets, respectively. Both formulations behaved in vivo as sustained release formulations with a $HVD_{t_{50\%}C_{max}}$ value of 6.4 and 5.6 h for F-1 and F-2, respectively. Bioavailability depended on the composition of the formulation as the C_{max}-values were 5.3 and 8.5 μg/ml and the $AUC_{0\rightarrow 24h}$-values 49.0 and 75.6 $\mu g \times h$/ml for the F-1 and F-2 pellets, respectively. The bioavailability of a chewable tablet, made of F-3 pellets (30% ibuprofen, 40% drum dried corn starch and 30% Lunacera P®) and showing an immediate in vitro drug release, was similar to the bioavailability of an ibuprofen suspension. The C_{max} and $AUC_{0\rightarrow 24h}$ of F-3 pellets were 31.9 μg/ml and 121.1 $\mu g \times h$/ml, respectively. These data demonstrate that pellets based on the combination of microcrystalline wax and starch derivatives can be used to formulate sustained as well as immediate release formulations.

Keywords: Matrix; Pellets; Bioavailability; Sustained release; Starch; Microcrystalline wax

1. Introduction

As matrix pellets do not require an expensive and time consuming coating step a growing interest in matrix pellets resulted in the development of several matrix pellet delivery systems. Sustained release from these pellets was obtained by the incorporation of release retarding agents such as chitosan (Goskonda and Upadrashta, 1993; Tapia et al., 1993), cellulose-derivatives (O'Connor and Schwartz, 1985; Ghali et al., 1989a; Bianchini et

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al., 1992; Goskonda and Upadrashta, 1993; Goskonda et al., 1994a,b), pH-adjusters (Bianchini et al., 1992; Goskonda et al., 1994a,b), methacrylic acid (Bianchini et al., 1992; Goskonda et al., 1994a,b) or hydrophobic components (Briquet et al., 1986; Ghali et al., 1989b; Wong et al., 1992).

A new matrix pellet system, produced by a melt pelletization process in a high shear mixer, was described by Zhou et al. (1996) and used a flexible matrix system based on the combination of microcrystalline wax and starch derivatives. It was demonstrated that this system was able to sustain in vitro drug release, the release rate being dependent on the type and the concentration of both the hydrophobic and the hydrophilic component. The aim of this study was to evaluate the in vivo behaviour of matrix pellets based on microcrystalline waxes and starch derivatives. In the first part of the study the bioavailability of two sustained release matrix pellet formulations was investigated, while in a second in vivo study the bioavailability of a chewable tablet based on the wax–starch combination was evaluated. Both studies used ibuprofen as a model drug.

2. Materials and methods

2.1. Materials

Micronised ibuprofen (Knoll Pharmaceuticals, Nottingham, UK) was used as the model drug. Lunacera M® (melting range 68–72°C) and Lunacera P® (melting range 58–62°C), both microcrystalline waxes, were used as hydrophobic binders (Füller, Lüneburg, Germany). Waxy maltodextrin (WMD) and drum dried corn starch (DDCS) were used as fillers. Both starch derivatives were supplied by Eridania-Béghin Say-Cerestar (Vilvoorde, Belgium).

2.2. Formulations and preparation of the pellets

The bioavailability of two sustained release pellet formulations was evaluated. Both contained 60% (w/w) ibuprofen and 15% (w/w) WMD, while the binders used in the two formulations were different. Formulation 1 (F-1) contained 25% of a mixture of Lunacera P® and Lunacera M® (ratio 3/7), while formulation 2 (F-2) contained 25% Lunacera P®. The second part of the study evaluated the in-vivo behaviour of immediate release pellets consisting of 30% ibuprofen, 40% DDCS and 30% Lunacera P® (formulation 3, F-3). The pellets were prepared in a jacketed lab-scale high-shear mixer (Gral 10, Machines Collette, Wommelgem, Belgium), using a method described by Zhou et al. (1996).

2.3. In vitro dissolution testing

The in vitro ibuprofen release from the pellets was evaluated using the dissolution test described by Zhou et al. (1996).

2.4. Bioavailability testing

Both sustained release ibuprofen formulations (F-1 and F-2) were filled into hard gelatin capsules (no. 0), while F-3 pellets were compressed into a 13 mm tablet using a compression force of 2.7 kN. For the first study, an oral dose of 300 mg ibuprofen (as F-1 and F-2 pellets) was administered to eight volunteers, according to a randomized cross-over trial design. The washout period between drug administrations was at least 6 days and maximally 14 days. During the second in vivo study, eight other volunteers received a chewable tablet made from F-3 pellets and containing 300 mg ibuprofen.

The volunteers were Caucasian males, aged between 18 and 40 years, non-smoking and within 15% of their ideal weight as described in the Height and Weight Table of the Metropolitan Life Insurance Company (1983). They were allowed to participate in the study after giving informed written consent. Their medical condition was judged on the basis of their medical history, a physical examination, an electrocardiogram and the determination of biochemical and hematological parameters in the blood and urine.

On the experimental day, the volunteers were fasting from the previous evening at 20:00, but the intake of water was allowed until 06:30. Before administration of the formulation, an intravenous

cannula was placed in one of the anticubital veins and a blank blood sample was obtained. The cannula was kept patent using a heparinized saline solution. The hard gelatin capsules containing F-1 or F-2 pellets were swallowed with 200 ml water. The tablet, made from F-3 pellets, had to be chewed and was then swallowed with 200 ml water. Blood samples were obtained 0.5, 1, 2, 3, 4, 5, 6, 8, 10, 12 and 24 h after drug intake. During the first 2 h, the subjects remained in a sitting position. No food or water was taken until 2 h after drug intake. After 2 h water could be taken freely. A standard lunch and supper was provided 4 and 10 h after drug intake. 12 h post-administration the volunteers resumed their usual diet except for ethanol-containing beverages, the intake of ethanol not being allowed until 24 h after the ingestion of the ibuprofen formulations.

Blood samples were collected in heparinized tubes and were centrifuged for 5 min at 3000 rpm. The plasma was transferred into 5-ml polyethylene tubes and stored at -20°C until assay of ibuprofen.

2.5. Chromatography

Ibuprofen plasma concentrations were determined using a RP C-18 column (125 mm × 4 mm—5 μm) (LiChrospher®, Merck, Darmstadt, Germany) equipped with a precolumn (4 mm × 4 mm—5 μm). The mobile phase consisted of 0.1 M phosphate buffer (pH 7.0) and acetonitrile (ratio 11/4 (v/v)). The flow rate was set at 1.5 ml/min and the detector wavelength at 220 nm. Indomethacin was used as the internal standard.

500 μl Plasma, 100 μl HCl (2 N), 40 μl indomethacin solution (0.05 μg/ml) and 4 ml of a hexane–ether mixture (ratio 4/1 (v/v)) were transferred into a borosilicate glass tube. After 3 min vortexing and 5 min centrifuging at 4000 rpm, the upper organic layer was transferred into a new glass tube and evaporated at 45°C under a nitrogen stream. The residue was dissolved in 100 μl mobile phase and homogenized. 25 μl of this solution was injected into the column.

2.6. HPLC validation

The ibuprofen plasma recovery (1–50 μg/ml range) varied between 92.0 and 99.2%, while 97.0% of the internal standard was recovered. Both standard curves were linear over the entire concentration range ($r^2 = 0.9983 \pm 0.0023$ and 0.9989 ± 0.0011 for a concentration ranging from 0 to 10 and from 0 to 50 μg/ml, respectively) ($n = 10$). The within-day variability was 1.0–6.2% in the 1–50 μg/ml range, while the between-days variability for the same concentration range was determined at 0.2–6.5%. The detection and quantification limit in human plasma were determined at 0.09 and 0.32 μg/ml, respectively.

2.7. Pharmacokinetic analysis

The C_{max}, t_{max} and $HVD_{t_{50\%}C_{max}}$ values were determined from the individual plasma concentration–time profiles, while the $AUC_{0\rightarrow 24h}$ was calculated using the MW/Pharm software package (v. 3.0, Mediware 1987–1991, Utrecht, The Netherlands). The pharmacokinetic parameters of the F-1 and F-2 formulations were compared using the Wilcoxon signed ranked test for paired observations (Siegel and Castellan, 1988), while the F-3 formulation was compared to both matrix formulations using the Wilcoxon–Mann–Whitney test for two independent groups (Siegel and Castellan, 1988).

3. Results and discussion

Zhou et al. (1996) demonstrated that matrix pellets based on the combination of microcrystalline waxes and starch derivatives could be formulated using a melt pelletization technique. This matrix system provides a flexible drug delivery system, whereby the drug release rate depends on the type and the concentration of the hydrophobic and the hydrophilic component. This study evaluated the bioavailability of these wax–starch formulations using ibuprofen as a model drug.

Fig. 1 shows the in vitro release profiles of ibuprofen from the different pellet formulations. It can be seen that both F-1 and F-2 pellets

showed an in vitro sustained release profile. The drug release rate of F-2 was higher compared to F-1 with a $t_{50\%}$ value of 20 and 4 h for F-1 and F-2, respectively. This is due to the Lunacera M® incorporated in the F-1 pellets as this type of microcrystalline wax has a higher melting range (68–72°C) compared to Lunacera P® (58–62°C). Zhou et al. (1996) demonstrated that the drug release from the wax–starch system depended on the melting range of the hydrophobic component; pellets formulated with the wax having the highest melting range gave the slowest drug release rate. Fig. 1 indicates that F-3 pellets failed to form a sustained release matrix system as 90% of the dose was released within 45 min of the dissolution test. This was due to the swelling ability of DDCS in aqueous medium, res2ulting in a fast disintegration of the wax–starch pellets.

The intake of ibuprofen was well tolerated in both studies. During the first study, one volunteer complained of mild abdominal pain for 1 h from 2 h after intake of F-1. During the second study no adverse effects were reported.

The ibuprofen plasma concentration–time profiles, after oral administration of F-1 and F-2 containing 300 mg ibuprofen, are shown in Fig. 2, while the pharmacokinetic parameters are listed in Table 1. The results demonstrated that both formulations behaved in vivo as sustained release formulations as indicated by the high $HVD_{t_{50\%}C_{max}}$ values (6.4 and 5.6 h for F-1 and F-2, respectively). These $HVD_{t_{50\%}C_{max}}$ val-

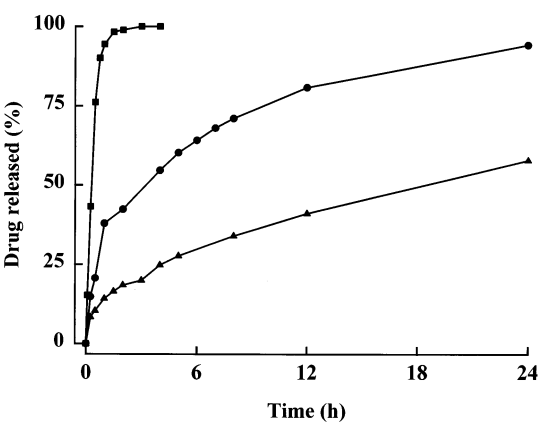

Fig. 1. Dissolution profile of the wax–starch pellet formulations containing ibuprofen. ▲, F-1: ibuprofen–WMD–Lunacera P® and Lunacera M® mixture (ratio 3/7) 60/15/25 (w/w/w); ●, F-2: ibuprofen–WMD–Lunacera P® 60/15/25 (w/w/w); ■, F-3: ibuprofen–DDCS–Lunacera P® 30/40/30 (w/w/w).

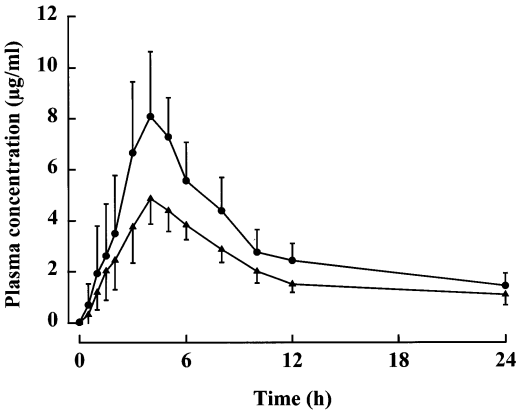

Fig. 2. Mean plasma concentration–time profiles (± S.D.; $n = 8$) obtained after oral administration of 300 mg ibuprofen as matrix pellets. Both formulations (F-1 and F-2) were filled into hard gelatin capsules. ▲, F-1: ibuprofen–WMD–Lunacera P® and Lunacera M® mixture (ratio 3/7) 60/15/25 (w/w/w); ●, F-2: ibuprofen–WMD–Lunacera P® 60/15/25 (w/w/w).

Table 1
Mean bioavailability parameters (± S.D.; $n = 8$) after oral administration of 300 mg ibuprofen

	F-1	F-2	F-3
C_{max} (μg/ml)	5.3 ± 0.9	8.5 ± 2.0[a]	31.9 ± 6.9[b]
t_{max} (h)	4.5 ± 0.9	4.1 ± 0.4	2.2 ± 0.7[b]
$AUC_{0\rightarrow 24h}$ ($\mu g \times h/ml$)	49.0 ± 6.8	75.6 ± 16.1[a]	121.1 ± 22.9[b]
$HVD_{t50\%Cmax}$ (h)	6.4 ± 1.9	5.6 ± 1.2	2.5 ± 0.7[b]

The drug was administered as sustained release pellets (F-1 and F-2 pellets filled into hard gelatin capsules) and as a chewable tablet (compressed out of F-3 pellets). F-1: ibuprofen–WMD–Lunacera P® and Lunacera M® mixture (ratio 3/7) 60/15/25 (w/w/w); F-2: ibuprofen–WMD–Lunacera P® 60/15/25 (w/w/w); F-3: ibuprofen–DDCS –Lunacera P® 30/40/30 (w/w/w).

[a] Significantly different from F-1 ($p \leq 0.01$; Wilcoxon signed ranked test).

[b] Significantly different from F-1 and F-2 ($p \leq 0.01$; Wilcoxon–Mann–Whitney test for two independent groups).

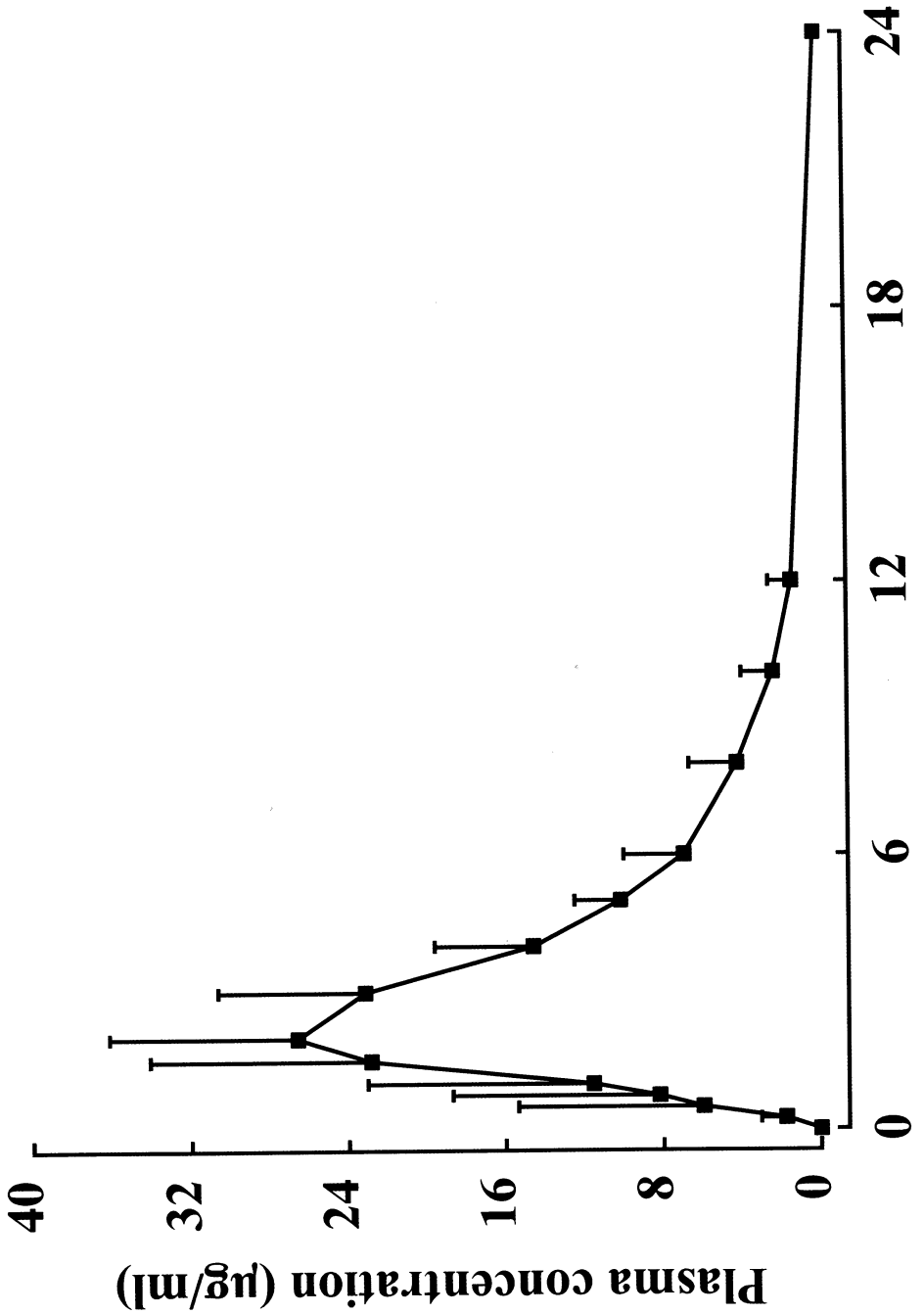

Fig. 3. Mean plasma concentration–time profiles (± S.D.; $n = 8$) obtained after oral administration of 300 mg ibuprofen as F-3 pellets, administered as a chewable tablet made from the wax–starch pellets. ■, F-3: ibuprofen–DDCS–Lunacera P® 30/40/30 (w/w/w).

ues are similar to those obtained by Ntawukulilyayo et al. (1996), when formulating an ibuprofen matrix tablet based on xanthan gum and on the combination of xanthan gum and *n*-octenylsuccinate starch. The plasma profiles also indicated that the absorption of ibuprofen depended on the composition of the matrix pellet formulation. This was shown by the significantly higher C_{max} and $AUC_{0\rightarrow 24h}$ values for F-2 compared to F-1 ($p \leq 0.01$; Wilcoxon signed ranked test) (Table 1). These differences can be attributed to the slower release rate of ibuprofen from the F-1 matrix.

Fig. 3 shows the ibuprofen plasma concentration profiles after administration of 300 mg ibuprofen formulated as a chewable tablet made from F-3 pellets. The pharmacokinetic parameters of this formulation are listed in Table 1. Oral administration of F-3 resulted in a faster ibuprofen absorption rate and higher plasma concentrations compared to the sustained release pellets (F-1 and F-2) (Figs. 2 and 3). The chewable tablet (F-3) yielded a bioavailability similar to the value obtained after oral administration of an ibuprofen suspension (Ntawukulilyayo et al., 1996). This indicated that ibuprofen is rapidly released from pellets containing microcrystalline wax and DDCS.

Compared to the chewable tablet the relative bioavailability of F-1 and F-2 pellets was 40.5 and 62.4%, respectively. This suggests that the in vivo release from both matrix pellets formulations was probably too slow to release its dose within 24 h. But as the drug release depends on the type and the concentration of both the microcrystalline wax and the starch derivative, the absorption from the wax–starch matrix system in the gastrointestinal tract can be enhanced by an appropriate selection of the composition of the formulation.

From these in vivo studies it can be concluded that the bioavailability of pellet formulations based on the combination of microcrystalline waxes and starch derivatives can be adjusted by means of varying the type and the content of both the waxes and the starch derivatives. Pellets with a sustained as well as an immediate drug release could be formulated using the wax–starch delivery system.

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