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In vitro and in vivo evaluation of a xanthan gum-*n*-octenylsuccinate starch matrix tablet containing ibuprofen as a model drug

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Abstract

The bioavailability after oral administration of two sustained release ibuprofen formulations using xanthan gum and a combination of *n*-octenylsuccinate starch (CL490) and xanthan gum has been investigated in healthy human volunteers and compared with a commercial suspension formulation. The ibuprofen-xanthan gum and the ibuprofen-xanthan gum-CL490 matrix tablets were prepared by direct compression. Three different xanthan gum/CL490 ratios (1:1; 1:4 and 1:10) were investigated in vitro. The xanthan gum/CL490 matrix tablets of a 1/4 and a 1/10 ratio both released nearly 100% after 24 h. No difference was observed in the release profiles between the matrix tablets prepared with 1/1 ratio of xanthan gum and CL490 and with pure xanthan gum during the first 8 h of dissolution test. After 8 h, the release rate from the pure xanthan gum matrix increased (nearly 90% after 24 h) while matrix tablet with a 1/1 ratio of xanthan gum and CL490 released 60% after 24 h. A dry core remained after a 24 h dissolution time period for matrix tablets prepared with the 1/1 ratio of xanthan gum and CL490, while the pure xanthan gum matrix had completely eroded. For the in vivo study, a xanthan gum/CL490 (1:1) matrix tablet was compared to a xanthan gum matrix tablet and a conventional suspension formulation. In comparison with the conventional suspension, the oral bioavailability was 86.83% ± 25.80% ($n = 6$) and 75.50% ± 17.18% ($n = 6$) for the tablets made with xanthan gum and with a combination of xanthan gum and CL490 (ratio 1/1), respectively. The combination of a xanthan gum and CL490 seemed to avoid the initial slow absorption phase in vivo that occurred with a pure xanthan gum matrix tablet. The combination of xanthan gum and *n*-octenylsuccinate starch could offer some advantages in the formulation of sustained release hydrophilic matrix tablets.

Keywords: Xanthan gum; *N*-octenylsuccinate starch; Hydrophilic matrix; In vitro release; Bioavailability

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1. Introduction

In this study, ibuprofen, a non steroidal anti-inflammatory drug with a half-life of 2–3 h, was used as a model drug to investigate the bioavailability of hydrophilic matrix formulations based on xanthan gum and on the combination of xanthan gum and *n*-octenylsuccinate starch. Xanthan gum is a high molecular weight biosyntethic polysaccharide produced by the micro-organism *Xanthamonas campestris* in a pure culture fermentation process and is ordinarily enzymatically resistant. The viscosity of its gel is also nearly independent of the pH, ionic strength and temperature (Ingani and Moës, 1988; Lu et al., 1991; Dhopeshwarkar and Zatz, 1993). Xanthan gum is compatible with virtually all salts. For these reasons, it seemed an interesting polymer for the preparation of hydrophilic matrix tablets. Xanthan gum has been frequently used in aqueous suspension formulations and in food products such as stabilisers and thickeners (Tempio and Zatz, 1980; Sanderson, 1982; Teague et al., 1982). Recently, a number of studies have discussed gel swelling release mechanism from xanthan gum hydrogels (Ingani and Moës, 1988; Lu et al., 1991; Talukdar and Plaizier-Vercammen, 1993; Talukdar and Kinget, 1995). The combination of xanthan gum and pure or modified starch has been of great interest for the stability of many food preparations (Christianson et al., 1981; Sanderson, 1982; Laura, 1987; Urlacher and Dalbe, 1992). This combination generally gives a positive synergetic effect, such as the enhancement of the viscosity or gelation and pseudoplastic properties. It was demonstrated that this behaviour was due to the interaction between the xanthan gum and the amylose fraction of the starch. The main interest of the present work was to investigate whether a xanthan gum-*n*-octenylsuccinate starch matrix could provide additional controlled release characteristics in comparison with a pure xanthan gum matrix.

2. Materials and methods

2.1. Materials

Ibuprofen 25 (average particle size of 31 μm) was purchased from Knoll Pharmaceuticals (Nottingham, England). *n*-Octenylsuccinate ester of waxy corn starch was kindly provided by Eridania-Beghin Say-Cerestar (Vilvoorde, Belgium) and is indicated as CL490.

n-Octenylsuccinate starch is obtained after treatment of a waxy corn starch suspension with succinic acid anhydride containing a 1-octenyl substituent group. It has a degree of substitution (DS) below 0.03 (BeMeller and Paschall, 1984). Xanthan gum (Rhodigel®) and magnesium stearate were purchased from Rhône-Poulenc (Brussels, Belgium) and Flandria (Zwijnaarde, Belgium), respectively. A commercially available ibuprofen suspension (Junifen® Batch 93I08) (The Boots Pharmaceuticals, Groot-Bijgaarden, Belgium) was purchased.

2.2. Methods

2.2.1. Tablet preparation

Three different xanthan gum/CL490 ratios (1:1; 1:4 and 1:10) were used for in vitro dissolution experiments. The amount of drug was kept constant at 100 mg per tablet while the amount of magnesium stearate was 4 mg per tablet. For the in vivo study, xanthan gum/CL490 (ratio 1:1) tablets were used and compared with pure xanthan gum tablets and the conventional suspension formulation. The amount of drug was kept constant at 300 mg per tablet while the amount of magnesium stearate was 10 mg per tablet and the total weight was set at 500 mg. Before use, all ingredients were sieved through a 90 μm sieve, weighed and mixed during 10 min in a Turbula mixer (Type T2A, W.A. Bachofen, Maschinen Fabriek, Basel, Switzerland). Finally, the magnesium stearate was added and mixed for an additional 2 min. Tablets were compressed on an eccentric tabletting machine (Korsch type EKO, Frankfurt, Germany) fitted with 9 and 13 mm flat punches for tablets containing 100 and 300 mg of ibuprofen, respectively. The tablets were compressed in order to obtain an 8 kg hardness (Heberlein α Co.AG, Wattwil, Switzerland).

The ibuprofen content was 100.1% and 99.7% for the tablets prepared with xanthan gum alone

and combined with CL490, respectively (high performance liquid chromatography (HPLC) method, USP XXIII).

2.2.2. Dissolution testing

The matrix tablets and the suspension (5 ml of suspension contains 100 mg of ibuprofen) were subjected to the paddle dissolution method (USP XXIII, 1995) using 900 ml of phosphate buffer pH 7.2 as the dissolution medium. The temperature was set at 37°C (± 1°C). In order to study the influence of the rotational speed on the release rate from the matrix tablets, the dissolution test was performed at 50, 100 and 150 rev./min. At 1 h intervals over a 24 h period, 5 ml samples were withdrawn, filtered through a 0.2 μm filter (Minisart, Sartorius GmbH, Heidelberg, Germany) and assayed spectrophotometricaly at 221 nm (Shimadzu UV-140-02, Kyoto, Japan) after appropriate dilution. All experiments were run four times and the calibration curve specifications were y = 0.045237x (S.D. ± 0.00216) + 0.00102 (S.D. ± 0.0005) (n = 4).

2.2.3. Bioavailability study

Six healthy male volunteers aged between 21–37 years with an average weight of 79.3 kg (range 67–101 kg) were selected for the study. The volunteers gave written informed consent to participate in the study. The study was conducted in accordance with the declarations of Helsinki (1964), Tokyo (1975) and Venice (1983) and approved by an independent medical ethics committee. The volunteers were judged healthy on the basis of medical history, physical examination, electrocardiogram and routine laboratory tests. None of them took drugs regularly. The subjects abstained from intake of any medication 2 weeks prior to and during the whole study. The volunteers were not allowed to consume xanthine-containing foods and drinks from 3 days before each experimental day. Each volunteer took 3 single-dose applications of oral medication (300 mg ibuprofen/xanthan gum tablets, 300 mg ibuprofen/xanthan gum/CL490 tablets and 15 ml of the ibuprofen suspension) in a crossover randomized sequence.

Each administration was separated by a 6 days wash out period. Drugs were administered with 250 ml of water at 8 a.m. after an overnight fast. Standard lunch and dinner were provided at 4 and 10 h after drug intake. Blood samples (10 ml) were taken from the jugular vein and collected in heparinized tubes before and 15, 30, 45, 60 min, 1 h 30, 2 h, 3 h, 4 h, 5 h, 6 h, 8 h, 10 h, 12 h and 24 h after drug administration. The blood was centrifuged at 3000 rev./min for 10 min and the plasma was stored at −15°C until determination.

2.2.4. Ibuprofen assay determination

Plasma ibuprofen concentrations were determined by a validated HPLC method. All chemicals were of analytical or HPLC grade and naproxen was used as the internal standard. To plasma and control solutions, 100 μl of HCl (2 N) and 20 μl of the internal standard solution (containing 100 μg/ml of naproxen) were added. The extraction was performed during 30 min on a rotary mixer using 4 ml of an hexane/ether mixture (4:1, v/v). After centrifugation, the upper organic layer was transferred to 16 × 100 mm disposable tubes and evaporated at 45°C under an

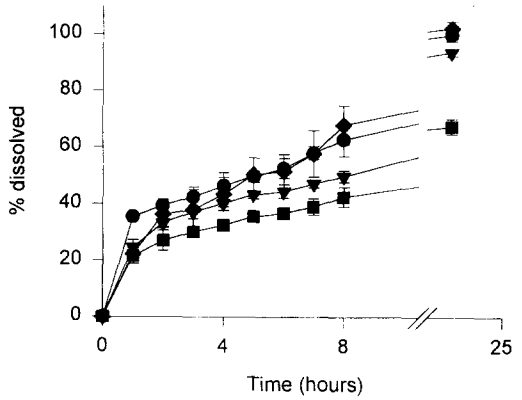

Fig. 1. Release profiles of ibuprofen (rotational speed of 50 rev.min) from matrix tablets containing 100 mg ibuprofen and prepared by direct compression of a blend of ibuprofen and a 1/1 (■), 1/4 (▼), 1/10 (◆) ratio of xanthan gum and CL490 in comparison to a matrix tablet prepared with pure xanthan gum (●).

Table 1
Drug release from matrix tablets containing pure xanthan gum and a combination of xanthan gum and *n*-octenylsuccinate starch (ratio 1/1, 1/4 and 1/10) in function of paddle rotational speed

Tablets	% Drug released					
	50 rev./min		100 rev./min		150 rev./min	
	4 h	24 h	4 h	24 h	4 h	24 h
Matrix with pure xanthan gum	46.45	99.87	47.23	99.55	46.26	99.81
Matrix with 1/1 ratio	30.10	67.36	31.19	67.36	30.19	70.05
Matrix with 1/4 ratio	34.16	93.38	37.07	100.10	54.97	*
Matrix with 1/10 ratio	38.00	102.20	44.55	102.30	93.68	*

*100% drug released after 6 h.

air stream. The residue was redissolved in 100 μl mobile phase: phosphate buffer pH 7 (13.6 g KH_2PO_4 dissolved in 900 ml of distilled water HPLC grade and the pH was adjusted using NaOH 2N) and acetonitrile (75:25, v/v). Twenty five μl was injected into the insert vial and fixed on the rack of the autosampler (AS 2000 S autosampler Merck-Hitachi). The HPLC equipment consisted of a solvent pump (L 6200 A Merck-Hitachi, Overyse, Belgium) set at constant flow rate of 1.5 ml/min, a variable wavelength detector UV (L4500 Diode Array Merck-Hitachi, Overyse, Belgium) set at 220 nm, a reversed phase column C18 Symmetry (3.9 mm × 15 cm) (Waters, Massachusettes, USA) and an automatic integrator system. The HPLC method was validated (Algranti et al., 1992a,b). The retention time was 6.04 and 2.04 min for ibuprofen and the internal standard, respectively. The mean calibration curve (y = 4304.84 + 606.7x) between 0 and 50 μg/ml ibuprofen showed a correlation coefficient of 0.99926 (r^2). The accuracy and precision were tested by analysing five samples of blank plasma containing 10 μl/ml of ibuprofen. The repeatability and reproducibility were 3.27% and 3.75%, respectively. The detection and quantification limits were 0.09 μg/ml and 0.3 μg/ml, respectively. No interfering peaks were observed in the chromatograms of blank plasma samples.

2.2.5. Data analysis

The area under the plasma concentration time curve (AUC_{0-24}) was calculated using the 'Kinbes 3.01 (Medware, New Pharm., The Netherlands, 1993)'. The C_{max} was defined as the maximum observed ibuprofen concentration from the individual plasma concentration time profiles, and t_{max} was the time corresponding to C_{max}. Meier et al. (1974) suggested evaluating the sustained-release characteristics of formulations at the time at which the plasma concentration was at least 50% of the C_{max} ($HVD_{t50\%Cmax}$). The C_{max}, t_{max} and the $HVD_{t50\%Cmax}$ were taken from each individual plasma concentration-time profile for the three formulations. The pharmacokinetic parameters of the three formulations were compared by the multiple case Friedman test at the significance level $P = 0.05$ (Siegel and Casrellan, 1988).

3. Results and discussion

3.1. In vitro evaluation

In our previous work, the interaction between xanthan gum and *n*-octenylsuccinate amylopectine was reported in suspension formulations (Ntawukulilyayo et al., 1995). The association of xanthan gum and *n*-octenylsuccinate starch gave specific visco-elastic properties and inhibited crystal growth. Due to those observations, the aim of this study is to investigate the possible use of the combination of both polymers in hydrophilic matrix formulations. Fig. 1 shows the influence of different xanthan gum/CL490 ratios on the release profile of ibuprofen in a phosphate buffer

pH 7.2. In the case of a 1/1 ratio, about 65% of the drug was released after 24 h. The pure xanthan gum matrix and the xanthan gum/CL490 matrices with a 1/4 and a 1/10 ratio behaved differently, all three matrices released nearly 100% of ibuprofen after 24 h. The increased release rate observed with xanthan gum/CL490 matrices with a 1/4 and a 1/10 ratio could be due to the powerful wettability of *n*-octenylsuccinate starch (CL490), causing a faster erosion of the matrix tablets. The rotational speed of the paddle did influence the dissolution profile of the matrix tablets prepared with the 1/4 and 1/10 ratio matrices. From the 1/10 and the 1/4 matrices, 93.68% and 54.67% of ibuprofen was released after 4 h at 150 rev./min, respectively, whereas only 38% and 34.16% of ibuprofen was released after 4 h at 50 rev./min (Table 1). As the rotational speed increased, the hydrated gelatinous layer surrounding the intact tablet core eroded more rapidly, resulting in an increased release rate of the drug from the 1/10 and 1/4 ratio matrix tablets. The release profile from pure xanthan gum and 1/1 ratio matrix tablets was less sensitive to changes of the rotational speed (Table 1). In function of the results of the in vitro dissolution experiments, it was decided to compare the bioavailability and $HVD_{t50\%Cmax}$ of pure xanthan gum and xanthan gum/CL490 (1/1) matrix tablets containing 300 mg of ibuprofen. Fig. 2 shows the in vitro release profiles of ibuprofen obtained with the matrix tablets containing 300 mg of ibuprofen and pre-

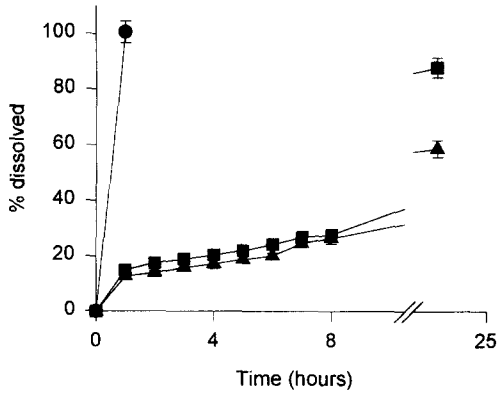

Fig. 2. Release profiles of ibuprofen (rotational speed of 50 rev./min) from matrix tablets containing 300 mg ibuprofen and prepared with pure xanthan gum (■) and with a xanthan gum/CL490 combination (1/1 ratio) (▲) in comparison to a conventional suspension containing 300 mg of ibuprofen in 15 ml (●).

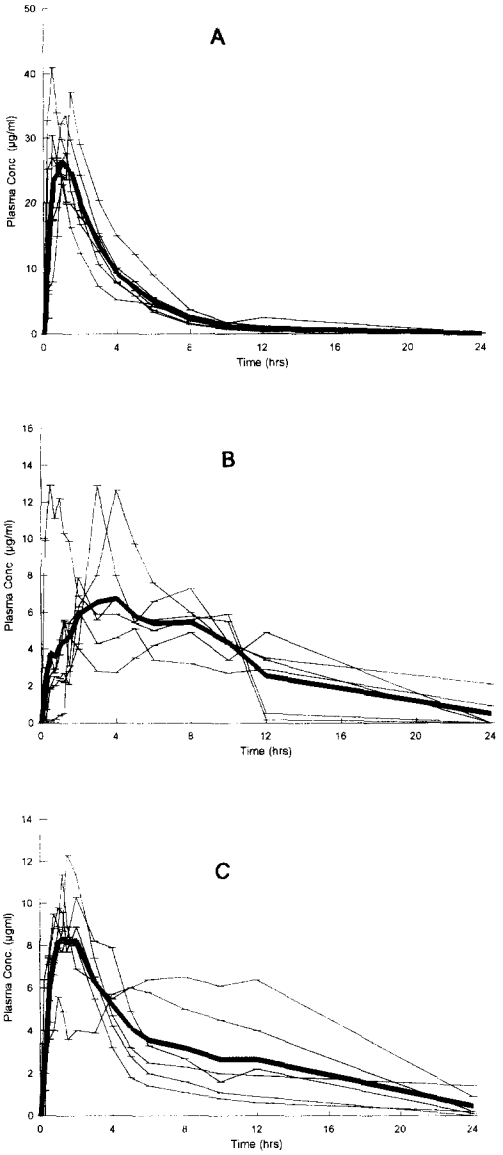

Fig. 3. Individual and mean (n = 6) plasma concentration-time profiles after oral administration of 300 mg ibuprofen as a conventional suspension (A) and as matrix tablets prepared with xanthan gum (B) and with xanthan gum-*n*-octenylsuccinate starch at a 1/1 ratio (C).

Table 2
Pharmacokinetic parameters for the conventional preparation and for the two matrix tablets after oral administration of 300 mg ibuprofen as a conventional suspension, as a xanthan gum matrix and as a xanthan gum-*n*-octenylsuccinate starch matrix at a 1/1 ratio.

Products	t_{max} (h), mean ± S.D. (n = 6)	C_{max} (μg/ml), mean ± S.D. (n = 6)	AUC_{0-24} (μg·h/ml), mean ± S.D. (n = 6)	$HVD_{t50\%Camax}$ (h), mean ± S.D. (n = 6)
Ibuprofen suspension	1.17 ± 0.61	31.98 ± 6.34*	98.16 ± 24.92	1.83 ± 0.78*
Matrix with pure xanthan gum	2.67 ± 1.67	9.67 ± 3.53	78.92 ± 17.30	7.28 ± 2.82
Matrix with the 1/1 ratio	3.40 ± 3.50	9.97 ± 1.99	71.40 ± 25.99	5.25 ± 4.37

*Significantly different from matrix tablets (Friedman test; P = 0.05).

pared with the 1/1 ratio of xanthan gum and CL490 and with pure xanthan gum in comparison to the dissolution profile of the conventional suspension. Nearly 25% of ibuprofen was released within 8 h for both matrices. Differences were observed in the release profile of those two matrix tablets after 8 h. It was noticed that a dry core remained after a 24 h dissolution time period for matrix tablets prepared with the 1/1 ratio of xanthan gum/CL490 while the pure xanthan gum matrix had completely disintegrated.

3.2. *In vivo evaluation*

All preparations were well tolerated by the volunteers. Fig. 3 shows the individual and the mean (n = 6) plasma concentration-time profiles of the three products tested. With 4 volunteers, an initial slow absorption of about 2 h was observed for xanthan gum tablets, while this was not seen for the matrix tablets prepared with the 1/1 ratio of xanthan gum/CL490. The matrix tablets prepared with pure xanthan gum and with a xanthan gum-*n*-octenylsuccinate starch combination (1/1 ratio), compared to the ibuprofen suspension, showed a relative bioavailability of 86.8% (± 15.3%) (n = 6) and 75.5% (± 17.2%) (n = 6), respectively. Those values were not significantly different (Friedman P = 0.05). The pharmacokinetic parameters (AUC_{0-24}, C_{max}, t_{max} and $HVD_{t50\%Cmax}$) are shown in Table 2 and were not significantly different for the two matrix tablets (Friedman, P = 0.05). The AUC_{0-24} and t_{max} values were not significantly different after administration of the suspension formulation and the two matrix tablets. The C_{max} and the $HVD_{t50\%Cmax}$ values differed significantly between the matrix tablets and the suspension formulation. After a dissolution time of 24 h at a rotational speed of 50 rev./min, a dry core remained in the case of the xanthan gum/CL490 matrix tablet, suggesting that plasma levels might be sustained a longer time for the xanthan gum/CL490 matrix tablets in comparison to the xanthan gum matrix tablets, but the in vivo study did not reveal a significant difference in $HVD_{t50\%Cmax}$ values between the two preparations. The combination of xanthan gum and *n*-octenylsuccinate starch seemed to avoid the initial slow absorption phase that occurred in vivo with a pure xanthan gum matrix tablet.

In conclusion, it can be said that the pure xanthan gum and the xanthan gum/CL490 (1:1 ratio) matrices behaved differently after 8 h of dissolution testing. A dry core remained after a 24 h dissolution time period for matrix tablets prepared with the 1/1 ratio while the pure xanthan gum matrix had completely disintegrated. The release profile from pure xanthan gum and 1/1 ratio matrix tablets was less sensitive to changes of the rotational speed. The combination of xanthan gum and *n*-octenylsuccinate starch avoided the initial slow absorption phase that occurred in vivo with a pure xanthan gum matrix tablet. The

combination of xanthan gum and *n*-octenylsuccinate starch could offer some advantages in the formulation of sustained release matrices based on hydrophilic matrices, especially in avoiding an initial slow absorption phase.

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