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In vivo evaluation of xanthan gum as a potential excipient for oral controlled-release matrix tablet formulation

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Abstract

The controlled-release (CR) properties of xanthan gum (XG) matrix tablets were investigated in vivo. Indomethacin and the sodium salt of indomethacin were selected as model drugs to examine the properties of formulations of a very poorly soluble and a highly soluble drug, respectively. The performance of XG matrices was compared with a marketed CR product containing an equivalent dose of indomethacin. A single oral dose pharmacokinetic study was conducted according to a randomised crossover design in six healthy male volunteers with three dosage forms: (A), 50 mg indomethacin tablets; and (B), 50 mg sodium indomethacin tablets both prepared with XG; and (C) Flexin® tablets. Dosage forms A and C showed the same in vitro release profile, while dosage form B demonstrated a faster release of the drug. There was no statistically significant difference in the time to reach the maximal plasma concentration between dosage form A and B or the reference product. Whereas the maximal plasma concentrations were varied considerably and found to be 1.73, 1.07, and 0.73 μg/ml for the dosage form A, B, and C, respectively. No statistically significant difference in AUC_{0-32} was found between either of the two test products and the reference product, but three way analysis of variance indicated an influence of the variable 'volunteers' on this parameter, indicating that interpretation of these data must be done with great caution. Based on these findings, the three products can be considered as bioequivalent. However, it seems that the drug released from the test products reached the minimum effective concentration earlier and remained longer within the therapeutic range. Based on these findings, it can be concluded that, although the common pharmacokinetic parameters of the drug from the test products are not significantly different from those of the marketed product, the therapeutic efficacy of the drug from the former may be superior to that of the latter.

Keywords: Xanthan gum; Hydrophilic matrices; Controlled-release; Indomethacin; Sodium indomethacin; In vivo study

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1. Introduction

In earlier studies, the performance of xanthan gum (XG) as a potential excipient for oral controlled-release (CR) tablet dosage forms was thoroughly evaluated and characterised by in vitro tests (Talukdar and Kinget, 1995; Talukdar et al., 1996a,b; Talukdar and Kinget, 1997a; Talukdar et al., 1997b). In vitro dissolution tests seem to be sensitive and reliable predictors of bioavailability as evaluated in vivo, yet in vitro testing cannot always predict in vivo performance. Therefore, validation of the final product accomplished by in vivo testing in human subjects remains the ultimate test of any dosage form. The ultimate goal of formulating a CR dosage form, is to achieve the drug concentration in the blood level within the therapeutic range for an extended period of time thereby eliminating high peaks of drug concentration.

Particularly in the case of oral CR drug delivery, poor correlation between in vitro and in vivo performance has been observed due to various unpredictable physiological factors and states that affect drug release and absorption. Intra- and intersubject differences can exist in gastrointestinal pH, volume, blood flow, electrolyte concentration, motility, gastric emptying, and residence times, etc. The rate and/or extend of drug absorption for any oral dosage form can be affected by these factors, but CR products are considerably more susceptible to variation, since they are intended to sustain a more precise delivery (Boxenbaum, 1984).

The objective of this study was to evaluate the in vivo performance of XG as a potential excipient to prepare a hydrophilic matrix (HM) tablet for oral CR delivery of indomethacin or sodium indomethacin. In vitro dissolution studies of these matrix tablets using both active agents have shown satisfactory drug release. The in vivo performance of the formulations in human subjects was evaluated and compared with an equivalent dose of a marketed sustained-release indomethacin tablet (Flexin®-LS Continus® tablets).

2. Materials and methods

2.1. Materials

Xanthan gum (Rheogel®) (Iranex, Rouen, France), 200 mesh; indomethacin (BP.80), mean particle size 8.4 μm; the sodium salt of indomethacin trihydrate (MSD Research Laboratory, Rahway, NJ); lactose 200 mesh (Ph.Belg. VI.); mean particle dimension 73 μm and analytical grade sodium dihydrogen phosphate, sodium hydroxide, and sodium chloride were used. Flexin®-LS Continus® tablets (Controlled Release Indomethacin B.P.; BN 06564K; Napp Laboratories, Cambridge, UK) was used as reference marketed CR product. Reagents and organic solvents used were of analytical or HPLC grade. Preparation of buffer and its dilutions were done with Milli-Q water (Millipore, Bedford).

2.2. Tabletting and in vitro drug release study

A 100 g batch size containing the drug (50 mg), polymer (20 or 40 mg), and lactose (130 or 110 mg) was thoroughly mixed in a small blender. Predetermined amounts (200 ± 2 mg) of the powder mixture were fed manually into the die of a flat-surface single punch (11 mm diameter) instrumented tabletting machine (Korsch MP1) and compressed to matrix tablets with a porosity of $15 \pm 2\%$ at a constant relative humidity (RH) of 42% (Talukdar and Kinget, 1995). After compaction, the tablets were stored in an atmosphere of 42% RH until use.

Drug release was measured according to the method described in the USP XXIII using apparatus 2 with the paddle rotating at 50 rpm in 1000 ml of USP phosphate buffer (pH 7.4), unless otherwise stated, at 37°C. At predetermined time intervals (10 min), samples were continuously assayed at 320 nm with a diode array spectrophotometer (Hewlett Packard 8452A) using a peristaltic pump and an automated dissolution testing system (Hewlett Packard 89550A Dissolution Testing System Software).

Drug release data were fitted according to the exponential Eq. (1).

Table 1
Treatment schedules for in vivo study of XG matrices with indomethacin (form A)/sodium indomethacin (form B), and Flexin® (form C)

Treatment #	Volunteer # 1	Volunteer # 2	Volunteer # 3	Volunteer # 4	Volunteer # 5	Volunteer # 6
1	A	A	B	B	C	C
2	B	B	C	C	A	A
3	C	C	A	A	B	B

$$\frac{M_t}{M_a} = Kt^n \quad (1)$$

where, M_t/M_a is the fractional (0.1–0.8) drug released at time t; k is a constant incorporating the properties of the macromolecular polymeric system and the drug, and n is a kinetic constant which depends on and is used to characterize the transport mechanism. For example, $n = 0.45$ for Case I or Fickian diffusion, $n = 0.89$ for Case II transport, $0.45 < n < 0.89$ for anomalous behaviour or non-Fickian transport, and $n > 1.0$ for Super Case II transport (Ritger and Peppas, 1987).

In order to characterize the drug release, the mean dissolution time (MDT) was calculated according to Eq. (2) (Möckel and Lippold, 1993).

$$MT = \frac{n}{n+1} K^{-\left(\frac{1}{n}\right)} \quad (2)$$

Where, k and n have the same meaning as in Eq. (1).

2.3. Selection of volunteers

Six healthy male volunteers (weight $= 68.35 \pm 8.41$ kg; height $= 1.74 \pm 0.09$ m) aged between 20 and 35 years were selected for this study. The volunteers were judged healthy on the basis of medical history, physical examination, electrocardiogram, and routine laboratory tests, 2 weeks before starting the study. None of them were allowed to take drugs regularly and to consume xanthine-containing foods and drinks from 3 days before each experimental day. They gave written informed consent to participate in the study. This study was conducted in accordance with the declarations of Helsinki (1964), Tokyo (1975), and Venice (1983). The study was approved by an independent Ethics and Project Review Board of Universitaire Ziekenhuizen, Gasthuisberg, K.U. Leuven (Belgium).

2.4. Protocol of the in vivo study

Subjects were fasted for at least 10 h before ingesting the tablet. The daily dose of all the preparations was equivalent to 50 mg of indomethacin or the sodium salt of indomethacin, and the wash out period between the treatments was 7 days. Each volunteer received 3 different formulations:Form A, Indomethacin 50 mg matrix tablet prepared with xanthan gum, Form B, Sodium indomethacin 50 mg matrix tablet prepared with xanthan gum and Form C, Flexin®-LS Continus® tablets, 50 mg marketed controlled-release form of indomethacin from Napp Laboratories.

Volunteers were allocated at random to one of the three treatment schedules according to the scheme shown in Table 1. Fluid intake was restricted for at least 2 h after administration and no food was allowed up to 4 h after administration. A standard lunch was given to all volunteers at 4 h after administration.

2.5. Blood sampling

Blood samples of 5 ml were collected in heparinized vials at time 0 (before dosing), 0.5, 1.0, 1.5, 2.0, 3.0, 4.0, 6.0, 8.0, 10.0, 12.0, 18.0, 24.0, and 32.0 h after dosing. An indwelling cannula was used for drawing blood samples by means of a catheter. The blood samples were centrifuged for 10 min at 15000 rpm within 10 min after collection. All plasma samples were stored at -20°C until assayed by HPLC.

2.6. Sample preparation

After the addition of 50 μl of the internal standard solution (flurbiprofen 6.22 μg/ml, made up in 0.01 M phosphate buffer pH 7.0) to 500 μl of plasma sample, the mixture was acidified by adding 100 μl of 0.6 M H_2SO_4. Subsequently, the mixture was extracted with 3.00 ml of *n*-hexane-diethylether (50:50 v/v) by vortexing for 1 min. After centrifugation at $3000 \times g$ for 10 min, 2.0 ml of the organic phase was transferred to a dry test tube with a pasteur pipette and evaporated at room temperature under a gentle stream of air. The residue was dissolved in 100 μl of the mobile phase and injected into the HPLC system. The extraction yield was 94 ± 9, 93 ± 5, and $94 \pm 4\%$ for indomethacin, sodium indomethacin and flurbiprofen, respectively at a concentration of 0.26, 0.21, and 0.10 μg/ml, respectively.

2.7. High performance liquid chromatographic (HPLC) method

Isocratic HPLC was performed using a LiChroGraph L-6000 HPLC pump (Merck-Hitachi, Darmstadt, Germany), a Rheodyne Model 7125 Injector (Rheodyne, Cotati, CA) equipped with a 20 μl loop, a LiChroGraph L-4000 UV detector (Merck-Hitachi), set at 254 nm, and a Merck-Hitachi Model D-2500 Chromato-Integrator. The 24.4×0.4 cm column was packed with LiChrospher 100 RP-18 (5 μm) (Merck, Darmstadt, Germany). A guard column (0.4×0.4 cm) with the same packing material was used to protect the analytical column. The mobile phase, which consisted of 0.03 M phosphate buffer (pH 4.0): acetonitrile (55:45 v/v), was filtered through a nylon membrane filter (0.45 μm) and degassed by ultrasonication before use. The flow rate was 1.4 ml/min. The retention time of the internal standard and drug was 9.7 and 11.8 min, respectively. The detection limit of the drug was 0.05 μg/ml. The relationship between peak area ratio and the drug concentration was found to be linear ($r > 0.999$) in the investigated concentration range.

2.8. Data analysis

The area under the plasma concentration versus time curve (AUC_{0-32}) from the time of drug administration up to 32 h after administration, maximum concentration (C_{max}) in the plasma, time (T_{max}) to reach C_{max}, time to reach minimum therapeutic concentration (T_{ther}), and total duration (D_{ther}) within the therapeutic range (TR = 0.5–3.0 μg/ml) of each volunteer were calculated directly from the plasma concentration versus time profile. The AUC_{0-32} was calculated using the trapezoidal rule.

All statistical calculations were performed using SAS version 6.12. In order to make a judgement about the effect of the formulations, a three-way analysis of variance for repeated measurements was performed with the following influence factors: effect of formulation, volunteers, and order of treatment. Multiple comparison was carried out using the Scheffé test to establish differences between two formulations at a time. Differences were considered to be statistically significant when $P < 0.05$.

3. Results and discussion

3.1. In vitro drug release

The in vitro drug release profiles, in USP phosphate buffer pH 7.4, of the three dosage forms selected for in vivo studies are shown in Fig. 1. The release profile of indomethacin from dosage forms A and C are comparable, indicating that the release rate of indomethacin from these two dosage forms are similar. The in vitro release rate of sodium indomethacin from dosage form B is notably higher compared to the other two dosage forms, as reflected in the mean dissolution time (MDT) of indomethacin and the sodium salt of indomethacin from these three profiles. The calculated MDT (Möckel and Lippold, 1993) of indomethacin was found to be 12.88 ± 0.63 h for dosage form A and 12.16 ± 0.26 h for dosage form C, while the MDT of sodium indomethacin from dosage form B was found to be 6.40 ± 0.12 h. This difference in release behaviour between

indomethacin and its sodium salt has already been explained (Talukdar and Kinget, 1995) by their difference in solubility properties and release mechanisms. Being a sparingly soluble drug, indomethacin is released by a swelling-controlled erosional mechanism (Talukdar et al., 1997b), while as a freely soluble drug, the sodium salt of indomethacin is released by a swelling-controlled diffusional mechanism (Talukdar and Kinget, 1997a).

The in vitro drug release behaviour of these dosage forms obtained by pH gradient (half change) method is shown in Fig. 2. The pH gradient dissolution tests were started with 0.1 N HCl (pH ~ 1.2) as an initial medium and every 2 h, half of the medium (i.e. 500 ml) was withdrawn and replaced by an equal volume of USP phosphate buffer pH 7.4 during 8 h of dissolution testing. Fig. 2 indicates that despite the absolute values, the release rate of indomethacin from dosage forms A and C is smaller than the release rate of sodium indomethacin from dosage form B, as shown in Fig. 1. Xanthan gum being an anionic polymer, following exposure to an acidic media the matrix hydration process differs, irrespective of the drug in its acidic or salt form. This may impede gel formation and change its structure. This may be the reason for initial smaller

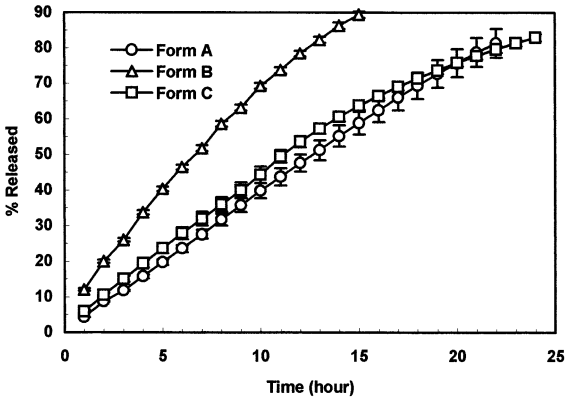

Fig. 1. In vitro release profiles of indomethacin (form A) and its sodium salt (form B) from xanthan gum matrices and Flexin® LS Continus® tablets (form C) in USP buffer pH 7.4 at 50 rpm. Each data point represents the mean of three experiments and the bar represents the standard deviation from the mean.

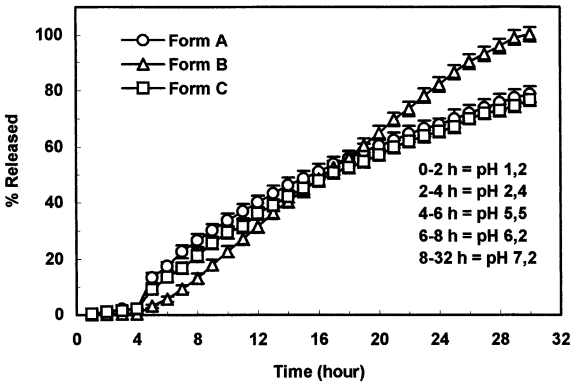

Fig. 2. pH gradient in vitro release profiles of indomethacin (form A) and its sodium salt (form B) from xanthan gum matrices and Flexin® LS Continus® tablets (form C) at 50 rpm. Each data point represents the mean of three experiments and the bar represents the standard deviation from the mean.

values in the release profile of sodium indomethacin, though its overall release rate (indicated by the slope) is higher than that of indomethacin.

Fig. 2 also clearly indicates that indomethacin, whether it is in its salt form or not, started to release from the dosage forms when the pH of the release medium was above 4.5 (i.e. pK_a of indomethacin). This result is in agreement with a recent finding by other investigators (Deasy and Law, 1997), where a similar result was obtained when pH-shift dissolution tests of indomethacin from pellets were carried out. Moreover these observations predict that irrespective of the dosage form, the in vivo release of indomethacin and its sodium salt in extreme acidic medium will be negligible and thereby bioavailability of the drugs from these dosage forms will be largely dependent on the gastric emptying time.

3.2. In vivo evaluation

The individual and mean plasma concentration versus time profiles of indomethacin following administration of the three dosage forms in six healthy volunteers are presented in Figs. 3 and 4, respectively. The mean pharmacokinetic parameters ($AUC_{(0-32)}$, T_{max}, and C_{max}) from the in vivo experiments are shown in Table 2.

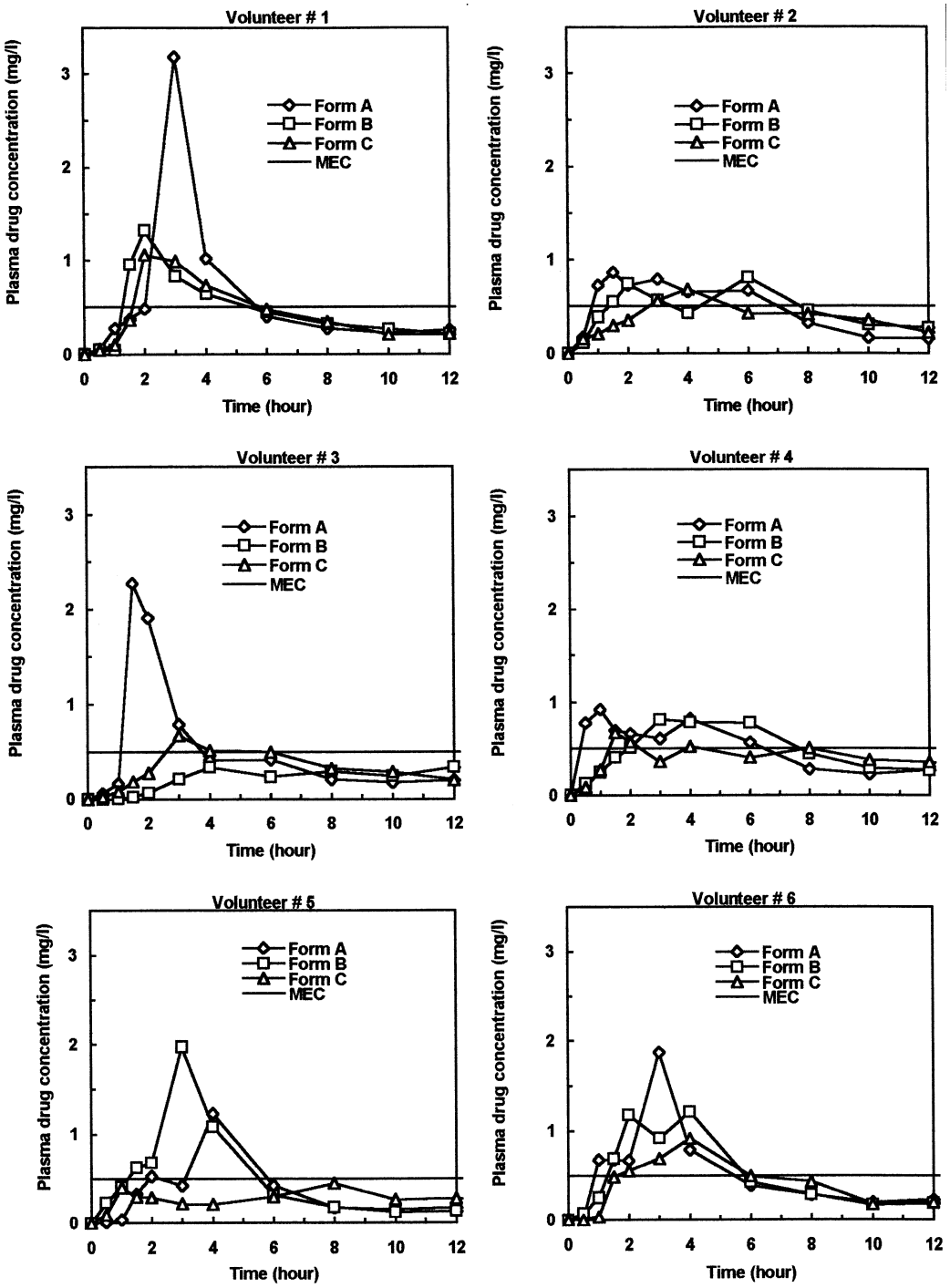

Fig. 3. Individual plasma drug concentration profiles after oral administration of the three dosage forms in six volunteers.

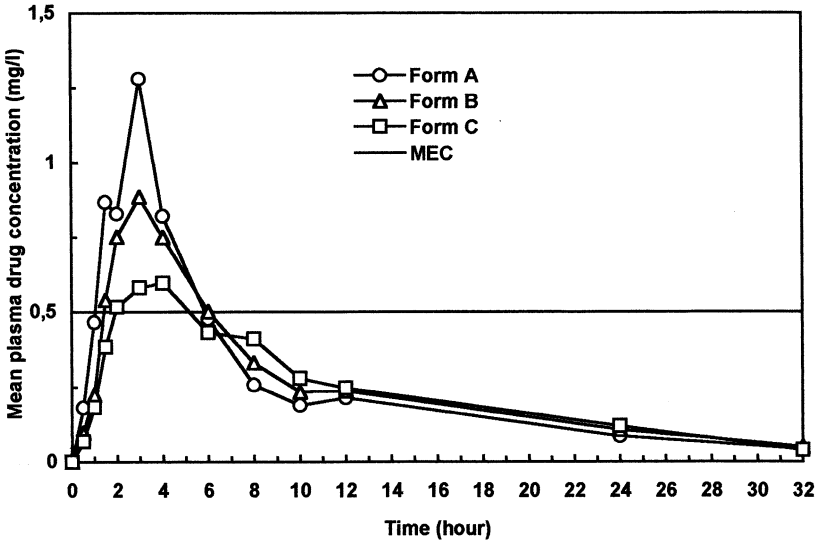

Fig. 4. Mean plasma level profiles of indomethacin (form A) and the sodium salt of indomethacin (form B) from xanthan gum matrices and Flexin® LS Continus® tablets (form C) after oral administration in six volunteers.

Three-way analysis of variance (formulation, volunteers, and order of treatment) indicated no significant difference between T_{max}, $AUC_{(0-32)}$, T_{ther}, and D_{ther} of the three formulations, while a marginally significant difference was observed for C_{max} ($P = 0.045$). However, the results obtained for $AUC_{(0-32)}$ must be interpreted with caution since a significant influence was observed from the variable 'volunteers', which can be attributed to the small number of volunteers.

Fig. 3 also shows that the performance of XG matrix containing indomethacin (dosage form A) and Flexin® tablets (dosage form C) in individual subjects are quite similar. This was confirmed from the calculation of the common pharmacokinetic parameters as $AUC_{(0-32)}$, T_{max}, and C_{max} which are listed in Table 2. No statistically significant difference was observed between the two products in T_{max} and $AUC_{(0-32)}$. These results are in accordance with the in vitro observations shown in Figs. 1 and 2, where it can be seen that the release rates of indomethacin from dosage forms A and C are comparable. However, a statistically significant ($P = 0.02$) difference was observed in C_{max}; this can be attributed to the high plasma levels observed in the concentration-time profiles with dosage form A in volunteers # 1 and 3 (Fig. 3). A similar peak in plasma drug concentration-time profiles after oral administration of ibuprofen tablets, prepared with XG, was also found in a recent study carried out by Ntawukulilyayo et al. (1996). This peak with dosage form A in volunteers # 1 and 3 may be related to some physiological factors, much likely a short gastric emptying time or higher GI motility. This could be elucidated by large meal in vivo tests and simultaneous measurement of gastric emptying and residence times. Alternatively a dosage form inherent failure due to the unsuitability of a tablet preparation by direct compression may be another explanation for this peak. At this moment it is unclear, what causes the appearance of this particular peak. If it is only due to the dosage form failure, compression of the tablets after wet granulation of the powdered drug and excipients and/or increasing XG content in the formulation can eliminate this plasma peak. More recently, a similar study (Vial-Bernasconi et al., 1995), carried out in six healthy volunteers in order to evaluate an extended release formulation of indomethacin, also exhibited a high intersubject variability. For two volunteers out of six, peaks in the plasma drug concentration-time profiles were observed.

Table 2
In vivo data from six volunteers after oral administration of XG and Flexin

T_{max}			
Volunteer #	Form A	Form B	Form C
1	3	2	2
2	1.5	2	4
3	1.5	4	3
4	1	3	1.5
5	4	3	1
6	3	3	4
Mean	2.33	2.83	2.58
S.D.	1.117	0.75	1.28
C_{max}			
Volunteer #	Form A	Form B	Form C
1	3.19	1.32	1.06
2	0.86	0.74	0.68
3	2.28	0.34	0.67
4	0.92	0.82	0.68
5	1.23	1.97	0.40
6	1.87	1.22	0.92
Mean	1.73	1.07	0.73
S.D.	0.91	0.57	0.21
AUC_{max}			
Volunteer #	Form A	Form B	Form C
1	10.19	7.98	7.40
2	7.68	8.63	7.48
3	7.68	5.93	6.69
4	9.34	9.29	8.67
5	6.29	7.79	6.97
6	8.39	8.31	7.73
Mean	8.26	7.99	7.49
S.D.	1.38	1.14	0.69
T_{ther}			
Volunteer #	Form A	Form B	Form C
1	2	1.25	1.70
2	0.75	1.45	2.80
3	1.05		2.6
4	0.3	2	1.3
5	2	1.25	
6	0.8	1.40	1.60
Mean	1.15	1.47	2
S.D.	0.64	0.31	0.66
D_{ther}			
Volunteer #	Form A	Form B	Form C
1	3.7	4.15	4.05
2	6.15	6.30	2.65
3	2.75	0	1.55
4	6.1	5.7	0.95
5	3.85	4.25	0
6	4.60	4.45	4.25
Mean	4.53	4.14	2.24
S.D.	1.37	2.21	1.71

A study by Seideman (1991), in which a conventional (immediate release) oral tablet formulation of indomethacin (50 mg) was given to 10 healthy volunteers, revealed the following mean $\pm$ S.D. value for C_{max}, T_{max}, and $AUC_{(0-32)}$: 4.57 ± 2.06 μg/ml, 1.3×0.64 h, and 10.4 ± 4.21 μg/ml per hour, respectively. The values of the different standard deviations point out also the high intersubject variability with indomethacin. To a first approximation, comparison of the AUC value with ours suggests that, the relative bioavailavility of the present formulations is above 90%. This comparison was done assuming that the physiological conditions of volunteers used in both studies are comparable. A higher T_{max} with dosage form A compared to that of an immediate-release tablet indicates the ability of the former to retard the in vivo drug release. A lower C_{max} with the present formulations indicates that after administration of XG matrices, the drug concentration in the blood plasma will never pass the upper limit of the therapeutic concentration (0.5–3.0 μg/ml; Clarke, 1986). Therefore, the side effect related to a high plasma peak concentration of this drug may be reduced with CR formulations. This is in accordance with a published report (Bacon et al., 1990) from an in vivo study in which it was reported that Flexin® showed less side effects as observed by a reduced incidence of abdominal/epigastric pain compared to an equivalent dose of an indomethacin immediate release product.

Although no statistically significant difference was found between dosage from A and C with respect to T_{ther} and D_{ther}, it seems that, following a single dose administration, the drug concentration from dosage form A tends to reach MEC earlier and remains within the TR for longer periods of time than that from dosage form C. With respect to T_{ther}, it should be mentioned that in one subject receiving dosage form C, it failed to reach the MEC at all (Fig. 3 with volunteer # 5). Thus, on the basis of these results, it could be concluded that the therapeutic effectiveness of indomethacin from dosage form A would probably be better than that from dosage form C.

Although the statistical analysis of pharmacokinetic data (Table 2), clearly indicates that formu-

lations A and C can be considered as bioequivalent, the mean plasma concentration-time profiles of indomethacin (Fig. 4) demonstrate marked differences in the performance of XG matrix and Flexin®.

Fig. 3 also demonstrates that the in vivo performance of tablets made with XG and indomethacin (i.e. dosage form A) or the sodium salt of indomethacin (i.e. dosage form B) are alike. This is also evident from the pharmacokinetic data, shown in Table 2. None of the calculated pharmacokinetic parameters (T_{max}, C_{max}, $AUC_{(0-32)}$, T_{ther}, and D_{ther}) exhibit a statistical difference ($P > 0.05$). This was not in accordance with what was expected from the in vitro dissolution data of these two dosage forms as the in vitro release profile of indomethacin was different from that of sodium indomethacin (Figs. 1 and 2). A similar discrepancy between in vitro and in vivo performances of $TimeR_x$®, a directly compressible XG excipient for CR formulation introduced by Edward Mendell , was found by McCall and Baichwal (1994). In their study using metoprolol tartrate as a model drug, they also found no significant differences in in vivo results with different formulations, although in vitro profiles of the same formulations had suggested different rates of drug release from the matrices. This again illustrates the imperfection of in vitro dissolution studies, which should mainly be used for determining the pharmaceutical availability and a preliminary screening of forms to be used.

In conclusion, this study shows that the common pharmacokinetic parameters of the drug from XG matrices are statistically equal to those from a marketed controlled-release product included in this study, indicating that the XG can be considered as a potential excipient for formulation of oral controlled-release tablets.

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