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Research paper

Xanthan gum to tailor drug release of sustained-release ethylcellulose mini-matrices prepared via hot-melt extrusion: in vitro and in vivo evaluation

E. Verhoeven, C. Vervaet, J.P. Remon *

Laboratory of Pharmaceutical Technology, Ghent University, Gent, Belgium

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Abstract

Mini-matrices (multiple-unit dosage form) with release-sustaining properties were developed by means of hot-melt extrusion using ibuprofen as the model drug and ethylcellulose as sustained-release agent. Xanthan gum, a hydrophilic polymer, was added to the formulation to increase the drug release since ibuprofen release from the ibuprofen/ethylcellulose matrices (60/40, w/w) was too slow (20% in 24 h). Changing the xanthan gum concentration as well as its particle size modified the in vitro drug release. Increasing xanthan gum concentrations yielded a faster drug release due to a higher liquid uptake, swelling and erosion rate. Regarding the effect of the xanthan gum particle size, no difference was observed for formulations containing 10% and 20% xanthan gum. However, using 30% xanthan gum, drug release was influenced by the particle size of the hydrophilic polymer due to the susceptibility of the coarser xanthan gum particles to erosion. Drug release from the mini-matrices was mainly diffusion controlled, but swelling played an important role to obtain complete drug release within 24 h. Drug release was influenced by the ionic strength of the medium as the conformation of xanthan gum molecules is determined by the salt concentration. An oral dose of 300 mg ibuprofen was administered to dogs ($n = 6$) in a cross-over study design either as an immediate-release preparation (Junifen®), as a sustained-release formulation (Ibu-Slow® 600 mg (1/2 tablet)) or as the experimental mini-matrices (varying in xanthan gum concentration). Administration of the experimental formulations sustained the ibuprofen release. Although a significant difference in dissolution rate of the 20% and 30% xanthan gum mini-matrices was detected in vitro, the difference in relative bioavailability was limited (70.6% and 73.8%, respectively).

Keywords: Hot-melt extrusion; Sustained release; Multiple-unit dosage form; Matrix system; Xanthan gum; Ibuprofen

1. Introduction

Hot-melt extrusion is becoming a widely used technology in the pharmaceutical industry to produce matrix formulations into which a drug is homogeneously embedded. Its major advantage over conventional techniques for manufacturing matrices is the continuity of the production process as the different steps (mixing, melting, homogenizing and shaping) are carried out on a single machine. This implicates a decrease in investment costs and offers more opportunities for automation of the production. Furthermore, this technique has a high throughput and limited material loss, yielding material having excellent homogeneity [1–3].

The excellent feasibility of ethylcellulose, a polymer with thermoplastic properties, for hot-stage extrusion has been established in a variety of applications [4–6]. Previous work [7–9] has shown that hot-melt extrusion can be used as an appropriate technique to develop mini-matrices using ethylcellulose to sustain the release of ibuprofen, selected as the model drug. The combination of ethylcellulose and a hydrophilic component such as hydroxypropylmethylcellulose (HPMC) offered a flexible system to tailor the drug

* Corresponding author. Laboratory of Pharmaceutical Technology, Ghent University, Harelbekestraat 72, 9000 Gent, Belgium. Tel.: +32 9 2648054; fax: +32 9 2228236.
E-mail address: JeanPaul.Remon@UGent.be (J.P. Remon).

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release by changing the viscosity, substitution type and concentration of HPMC. Substituting HPMC for xanthan gum yielded formulations having a nearly zero-order drug release without burst effect [7]. In addition, the incorporation of xanthan gum resulted in a longer sustained-release effect, allowing to use a lower concentration of hydrophilic polymer [10]. Rheological and drug diffusion studies in hydrated HPMC and xanthan gum compacts elucidated the difference in the release-controlling ability of both polymers [11–13].

In the present study, sustained-release mini-matrices were developed by hot-melt extrusion of an ibuprofen/ethylcellulose-mixture with the addition of xanthan gum to tailor drug release, whereby the influence of the concentration as well as the particle size of xanthan gum on the in vitro characteristics of the mini-matrices was investigated. The in vivo performance of these experimental formulations was evaluated in dogs and compared with an equivalent dose of a sustained-release ibuprofen matrix tablet (Ibu-Slow® 600 mg).

2. Materials and methods

2.1. Materials

Ibuprofen (IBP) (average diameter: 25 μm) (Knoll Pharmaceuticals, Nottingham, UK) was selected as the model drug. The matrix consisted of ethylcellulose (Ethocel Std 10 FP Premium) (EC) kindly donated by the Dow Chemical Company (Midland, USA), and a hydrophilic component: xanthan gum (XG), available in different particle sizes (Xantural® 75 (XG75), Xantural® 180 (XG180) and Xantural® 11K (XG11K) having a mean particle size of 75, 180 and 1180 μm, respectively) supplied by CP Kelco (Liverpool, UK). Ibu-Slow® 600 mg, a commercially available hydrophilic matrix tablet containing 600 mg of ibuprofen, was obtained from Therabel Pharma (Brussels, Belgium) and Junifen®, a sugar-free solution of ibuprofen (100 mg/5 ml), was purchased from Boots Healthcare (Wemmel, Belgium). All other chemicals were at least of analytical grade (VWR, Leuven, Belgium).

2.2. Composition of the mixtures

The ibuprofen content was 60% (w/w) and the remaining part of the formulation consisted of ethylcellulose and xanthan gum. The xanthan gum concentration varied between 10% and 30% (w/w). All formulations are listed in Table 1.

Table 1
Composition (w/w, %) of the hot-melt extruded formulations

	10% XG	20% XG	30% XG
Ibuprofen	60	60	60
Xanthan gum (XG75, XG180 or XG11K)	10	20	30
Ethylcellulose	30	20	10

2.3. Production of the mini-matrices

Prior to hot-melt extrusion the formulations were blended in a planetary mixer (15 min, 90 rpm) (Kenwood Major Classic, Hampshire, UK). Hot-melt extrusion was performed using a lab-scale intermeshing 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 Brabender twin-screw powder feeder, a screw with two mixing sections and a cylindrical die of 3 mm for the production of the mini-matrices. For all formulations, the following extrusion conditions were used: a screw speed of 30 rpm, a powder feed rate of 6 g/min and a temperature of 50 °C for the five heating zones along the barrel. After cooling down to room temperature, the extrudates ($\varnothing = 3$ mm) were manually cut into mini-matrices of 2 mm length.

2.4. In vitro evaluation

2.4.1. In vitro drug release

The mini-matrices (approximately 60 mg) were introduced in a basket (USP 27, dissolution apparatus 1). The dissolution was performed in a VK 7010 dissolution system combined with a VK 8000 automatic sampling station (VanKel Industries, New Jersey, USA). Phosphate buffer KH_2PO_4 (pH 7.2, $\mu = 0.11$) was used as the dissolution medium. The temperature of the medium (900 ml) was kept at 37 ± 0.5 °C, while the rotational speed of the baskets was set at 100 rpm. Samples of 5 ml were withdrawn at 0.5, 1, 2, 4, 6, 8, 12, 16, 20 and 24 h 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 50 μg/ml. The dissolution was simultaneously performed in 6 dissolution vessels, each vessel containing 4 mini-matrices.

Additional rotational speeds of 50 and 200 rpm were used during dissolution testing in order to evaluate the influence of matrix erosion on drug release.

The susceptibility of the mini-matrices to ionic strength was verified by dissolution testing in diluted phosphate buffer and phosphate buffer with increasing NaCl concentrations: $\mu = 0.011$ (10-fold dilution), $\mu = 0.022$ (5-fold dilution), $\mu = 0.055$ (2-fold dilution), $\mu = 0.11$, $\mu = 0.15$ and $\mu = 0.2$. Sodium chloride was added to the medium, since these are the main electrolytes in the gastrointestinal fluid [14].

To determine the in vitro release properties of the formulations used for in vivo evaluation, a dissolution was also performed on a hard-gelatin capsule (n° 00) filled with 500 mg mini-matrices. To understand the drug release mechanism from swellable matrices, the data (M_t/M_∞) were fitted to the following exponential equation (Eq. 1) proposed by Ritger and Peppas [15]:

$$\frac{M_t}{M_\infty} = kt^n \quad (1)$$

This equation generally holds for the initial phase of the release profile ($M_t/M_\infty \leqslant 60\%$). M_t/M_∞ is the amount drug released at time t, k denotes a constant incorporating the structural and geometric characteristics of the release device and the exponent n is a release constant used to characterize the transport mechanism.

Images of the mini-matrices, after immersion in the dissolution medium, were made with a digital camera (C3030 Olympus) attached to an image analysis system (analySIS®, Soft Imaging system, Münster, Germany).

2.4.2. Liquid uptake, erosion and swelling measurements

The mini-matrices were introduced into USP dissolution apparatus 1 and submitted to a dissolution test ($n = 3$) under the conditions described above (100 rpm, $\mu = 0.11$), each vessel containing one mini-matrix. At predetermined time intervals (dissolution sampling points), they were withdrawn from the medium and weighed after removing excess surface water. Liquid uptake (expressed as % weight gain of the polymer content (ethylcellulose and xanthan gum)) was determined from the weight of the mini-matrices, taking into account the drug released (Eq. 2):

$$\%\ \text{liquid uptake} = \frac{(W_\text{w} - \text{DR}_t) - (W_\text{i} - \text{DR}_0)}{(W_\text{i} - \text{DR}_0)} \times 100 \quad (2)$$

where W_w = weight of the mini-matrix at time 't' after immersion in the dissolution medium, W_i = initial weight of the mini-matrix at time '0', DR_0 = amount of drug in the mini-matrix at time '0', DR_t = amount of drug in the mini-matrix at time 't'.

The degree of erosion (expressed as % erosion of the polymer content) was determined based on the weight difference between the dried mini-matrix and its initial weight, considering the amount of drug released (Eq. 3):

$$\%\ \text{erosion} = \frac{(W_\text{i} - \text{DR}_0) - (W_\text{d} - DR_t)}{(W_\text{i} - DR_0)} \times 100 \quad (3)$$

where W_d = dry weight of the mini-matrix at time 't' after immersion in the dissolution medium, W_i = initial weight of the mini-matrix at time '0', DR_0 = amount of drug in the mini-matrix at time '0', DR_t = amount of drug in the mini-matrix at time 't'.

The height and diameter of the mini-matrices were measured using an electronic digital calliper (Bodson, Luik, Belgium) to determine the axial and radial swelling, respectively.

2.4.3. Porosity

The porosity of the mini-matrices was calculated, based on the difference between the apparent and true volume of the extrudates. After measuring the exact height and diameter of the extrudate ($\varnothing = 3$ mm, length = 30 mm), the total apparent volume was calculated ($n = 10$). The true volume of 10 extrudates was measured using a helium pycnometer (AccuPyc 1330, Micromeritics, Norcross, USA) ($n = 10$). The porosity was expressed as a percentage of the apparent volume.

2.4.4. Stability study

The XG75-formulations were selected for stability testing according to the USP guidelines [16]. Mini-matrices were stored at 25 ± 2 °C/60 ± 5% relative humidity (RH) and at 40 ± 2 °C/75 ± 5% RH. The in vitro drug release and the moisture content of the mini-matrices were determined as a function of storage time (12 months), storage conditions and XG concentration.

The moisture content of the mini-matrices was determined using a Mettler Toledo DL35 Karl Fisher titrator (Mettler Toledo, Beersel, Belgium) in combination with a Mettler DO337 oven operated at 170 °C. The samples (approximately 100 mg) were placed in the oven and the moisture evaporated from the sample during 10 min was carried to the titration vessel by a nitrogen stream (300 ml/min), after which the titration was started. Hydroquant Uniquant 2® (Biosolve LTD, Valkenswaard, The Netherlands) with a theoretical titre of 2 mg H_2O/ml was used as the titrant solution. The analysis was performed in triplicate.

2.4.5. Statistical analysis

The effect of xanthan gum concentration and particle size on the release mechanism and the drug release (AUC levels) was assessed by a two-way ANOVA. To further compare the main effect of the different treatments, a multiple comparison among pairs of means was performed using a Bonferroni post-hoc test with $P < 0.05$ as significance level. If a significant interaction between both factors was present, the simple effects were investigated with a Bonferroni post-hoc test. The normality of the residuals was tested with a Kolmogorov–Smirnov test. The homogeneity of variances was tested with Levene's test. SPSS version 12.0 was used to perform the statistical analysis.

2.5. In vivo evaluation

All procedures were performed in accordance with the guidelines and approval of the local Institutional Animal Experimentation Ethics Committee.

2.5.1. Subjects and study design

A group of 6 male mixed-breed dogs (weight 26.0–45.5 kg) was used in this study. To investigate the influence of the xanthan gum concentration in the experimental mini-tablets on the bioavailability of ibuprofen, the following drug formulations were administered:

F-1: hot-melt extruded mini-matrices, consisting of 60% ibuprofen, 30% ethylcellulose and 10% Xantural® 75 (XG75 10%).

F-2: hot-melt extruded mini-matrices, consisting of 60% ibuprofen, 20% ethylcellulose and 20% Xantural® 75 (XG75 20%).
F-3: hot-melt extruded mini-matrices, consisting of 60% ibuprofen, 10% ethylcellulose and 30% Xantural® 75 (XG75 30%).
F-4: Ibu-Slow® 600 mg.
F-5: Junifen® (100 mg/5 ml).

The mini-matrices of the experimental formulations were filled in hard-gelatin capsules n° 00, each capsule containing 300 mg ibuprofen. Ibu-Slow® 600 mg (1/2 tablet) and Junifen® (15 ml) were administered as sustained- and immediate-release reference formulations, respectively. The formulations were administered in a cross-over sequence with a wash-out period of at least 8 days between consecutive sessions. On the experimental days the dogs were fasted for 12 h prior to the study period, although water was available ad libidum. Before administration of the formulations, an intravenous cannula was placed in the lateral saphenous and a blank blood sample was obtained. The formulations were then orally administered with 10 ml water. The blood samples (2 ml at each sampling) were collected in dry heparinized tubes before and 1, 2, 4, 6, 8, 12, 24 and 36 h after intake of F-1, F-2, F-3, F-4, and at 0.25, 0.5, 1, 1.5, 2, 4, 6, 8, 12, 24 and 36 h after ibuprofen ingestion of F-5. No food was administered to the dogs during the initial 24 h of the test, afterwards they resumed their usual diet. Water could be taken freely. Within 1 h after collection, the blood was centrifuged for 10 min at 1450*g* and the plasma was immediately assayed for ibuprofen.

2.5.2. Ibuprofen assay

The plasma ibuprofen concentrations were determined by a validated HPLC-UV method. All chemicals were of analytical HPLC grade.

Fifty microlitres of an internal standard solution (30 μg/ml indomethacin in ethanol), 50 μl ethanol and 500 μl plasma were transferred into a borosilicate glass tube. After 1 min of vortexing, 100 μl HCl (2 N) was added and homogenized by 1 min of vortexing. Consecutively, 4 ml hexane/ether mixture (4:1, v:v) was added. After 3 min of vortexing and 5 min of centrifuging at 2500*g*, the upper organic layer was transferred into a new glass tube and evaporated to dryness under a nitrogen stream. The residue was dissolved in 200 μl mobile phase and 50 μl of this solution was injected onto the column. The ibuprofen plasma concentrations were determined via a calibration curve. These standards for the calibration curve were extracted using the same procedure as described above: 500 μl blank plasma was spiked with 50 μl of internal standard solution and 50 μl of a standard solution with a known concentration of ibuprofen in ethanol (0, 3, 6, 12, 30, 60, 90, 180 and 240 μg/ml).

The HPLC equipment consisted of a solvent pump (L-7100, Merck-Hitachi, Darmstadt, Germany) set at a constant flow-rate of 1.5 ml/min, a variable wavelength UV-detector (L-7400, Merck-Hitachi, Darmstadt, Germany) set at 220 nm, a reversed-phase column and precolumn (LiChroCART® 125-4 and 4-4, LiChrospher® 100 RP-18 (5 μm); Merck, Darmstadt, Germany), an auto-sampler (L-7200, Merck-Hitachi, Darmstadt, Germany) injection system with a 50 μl loop (Valco Instruments Corporation, Houston, Texas, USA) equipped with an automatic integration system (software D-7000 Multi-Manager, Merck, Darmstadt, Germany). The mobile phase consisted of 0.1 M KH_2PO_4 (adjusted to pH 7.0 with 2 M NaOH)/acetonitrile (12:3, v:v).

2.5.3. Data analysis

The peak plasma concentration (C_{max}), the time to reach C_{max} (T_{max}) and the extent of absorption ($AUC_{0–36h}$) were calculated using the MW-Pharm Program version 3.0 (Mediware 1987-1991, Utrecht, The Netherlands). The $AUC_{0–36h}$ was calculated using logarithmic and linear trapezoidal rules. The relative bioavailability (F_{rel}, expressed in %) was calculated as the ratio of $AUC_{0–36h}$ between a test formulation and the sustained-release reference formulation (Ibu-Slow® 600 mg). The sustained-release characteristics of a formulation were evaluated by the time span during which the plasma concentrations were at least 50% of the C_{max} value ($HVD_{t50\%C_{max}}$, the width of the plasma concentration profile at 50% of C_{max}) [17,18]. The $HVD_{t50\%C_{max}}$ values were determined from the individual plasma concentration–time profiles. The ratio between the $HVD_{t50\%C_{max}}$ values of a test formulation and the immediate-release reference formulation (Junifen®) (expressed as R_D) is indicative of sustained-release effect: a ratio of 1.5, 2 and >3 indicating a low, intermediate and strong sustained-release effect, respectively [17].

2.5.4. Statistical analysis

The effect of ibuprofen formulation on the bioavailability was assessed by repeated-measures ANOVA (univariate analysis). To further compare the effects of the different treatments, a multiple comparison among pairs of means was performed using a Bonferroni post-hoc test with $P < 0.05$ as significance level. The normality of the residuals was tested with a Kolmogorov–Smirnov test. The sphericity of covariances was tested with Mauchly's test. If the assumption of sphericity was not fulfilled, the Huynh–Feldt correction was performed. SPSS version 12.0 was used to perform the statistical analysis.

3. Results and discussion

3.1. In vitro drug release: influence of xanthan gum concentration and particle size

Hot-melt extrusion was performed at 50 °C and produced smooth extrudates without sharkskin. This rather low extrusion temperature, far below the glass transition temperature of EC (130 °C), can be explained by the

plasticizing effect of IBP on EC, favourably affecting the stability of both the drug and the polymer [19].

The drug release from the IBP/EC matrix was too slow as only 20% of IBP was released in 24 h (Fig. 1) and hydrophilic polymers such as HPMC [7] and XG had to be added to enhance the drug release rate. This sustained-release effect was attributed to the integrity of the matrix structure which was maintained during the dissolution experiment. Changing the XG/EC ratio allowed to modify the drug release rate as increasing concentrations of XG (type XG75) enhanced drug release (Fig. 1): after 24 h, only 50% IBP was released from formulations containing 10% XG, whereas the total drug load was released within this time from mini-matrices containing 20% and 30% XG. Conventionally, in case of XG as a hydrophilic matrix tablet, the drug release rate from matrices decreased at higher XG concentrations, due to an increase in viscosity and thickness of the hydrated gel layer, instantly formed around the dosage form upon contact with the dissolution medium [10,20]. This gel barrier restricted water penetration into and drug diffusion from the tablet, delaying drug release [11–14,21–23]. However, as the system under investigation is not a pure hydrophilic matrix but a combination of a hydrophobic matrix and a hydrophilic additive the higher degree of swelling did not impede drug release as the swelling of XG opened the structure of the mini-matrices, creating pores in the lipophilic EC matrix through which IBP was released. The XG particle size had no effect on the drug release from formulations containing 10% and 20% XG since the formulations containing XG180 and XG11K (results not shown) yielded similar release profiles as presented in Fig. 1 for the XG75 mini-matrices. However, at 30% XG, the drug release was influenced by the particle size of the hydrophilic polymer: an accelerated drug release from the mini-matrices formulated with coarser XG. Those data are in agreement with the results reported by Dhopeshwarkar and Zatz [10] on XG hydrophilic matrix tablets: a fine particle size of XG produced the slowest and most reproducible sustained-release profiles, whereas the coarser XG fractions did not hydrate fast enough to form a protective layer and the matrix tablet disintegrated during dissolution testing. To evaluate the susceptibility of the coarser XG fractions to erosion, the erosion behaviour (including liquid uptake and swelling) of the hydrated mini-matrices was determined since these parameters affect the mechanism and kinetics of drug release.

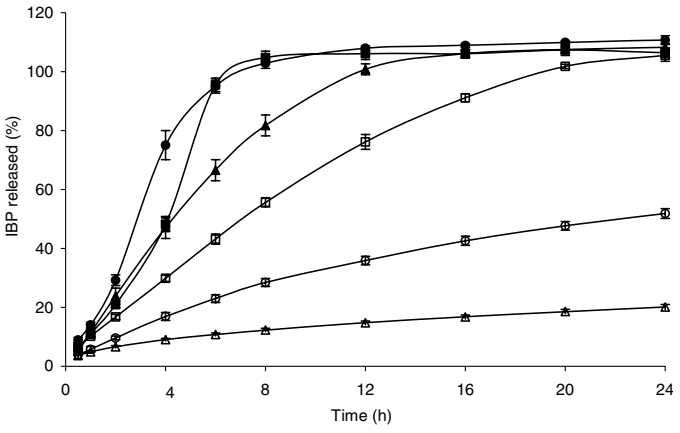

Fig. 1. Influence of xanthan gum (XG) concentration and particle size on the dissolution profiles (mean ± SD, $n = 6$) of the mini-matrices containing 60% IBP, EC and XG. (△) 0% XG, (○) 10% XG75, (□) 20% XG75, (▲) 30% XG75, (■) 30% XG180 and (●) 30% XG11K.

The porosity data of the mini-matrices (1.4–5.5%) indicated that the initial porosity is independent of the composition of the mini-matrices and therefore not responsible for any difference in drug release.

3.2. Liquid uptake, erosion and swelling

The influence of XG concentration and particle size on the liquid uptake, swelling and erosion is presented in Fig. 2. A higher liquid uptake (Fig. 2a) was observed at increasing XG180 concentrations: as expected from the hydrophilic nature of the polymer, the mini-matrices became more accessible to the dissolution medium with increasing XG concentration, resulting in a higher weight gain of the mini-matrices after immersion in the medium (Eq. 2). Radial (Fig. 2b) as well as axial (data not shown) swelling also depended on the concentration of XG and was in all cases directly proportional to the liquid uptake. Formulations containing 10% and 20% XG (XG180 grade) did not swell to a great extent, in contrast to the swelling capacity of the 30% XG formulation: for the latter, the hydrated polymer layer was less cohesive and therefore more sensitive to erosion (Fig. 2c). After 4 h immersion in the medium, these mini-matrices became brittle and as a consequence a higher erosion rate was seen, the matrix was completely eroded after 6 h. The liquid uptake, swelling and erosion profiles for the 10% and 20% XG75 and XG11K formulations (data not shown) coincided with those presented for the XG180 mini-matrices, so no influence of the particle size was observed at these concentrations. However, when comparing formulations containing 30% XG, the erosion rate was affected by the XG grade (Fig. 2c): using the coarser XG types, the mini-matrices were more susceptible to erosion, whereas the gelled surface of the mini-matrices formulated with the XG75 grade seemed to be stronger and therefore these mini-matrices were more resistant to erosion. The lower liquid uptake and swelling of the XG180 and XG11K matrices at 4 h are also due to the higher erosion rate of these formulations as a smaller amount of material was recovered. The difference in gel strength of XG when using different grades was confirmed by visual inspection of the mini-matrices after 4 h immersion in the dissolution medium (Fig. 3): the mini-matrices containing XG75 were embedded in a gel layer, and the inner core was not yet fully hydrated. In contrast, the entire matrix was hydrated when using the coarsest XG grade (XG11K), only a few non-hydrated individual particles remained. These pictures also

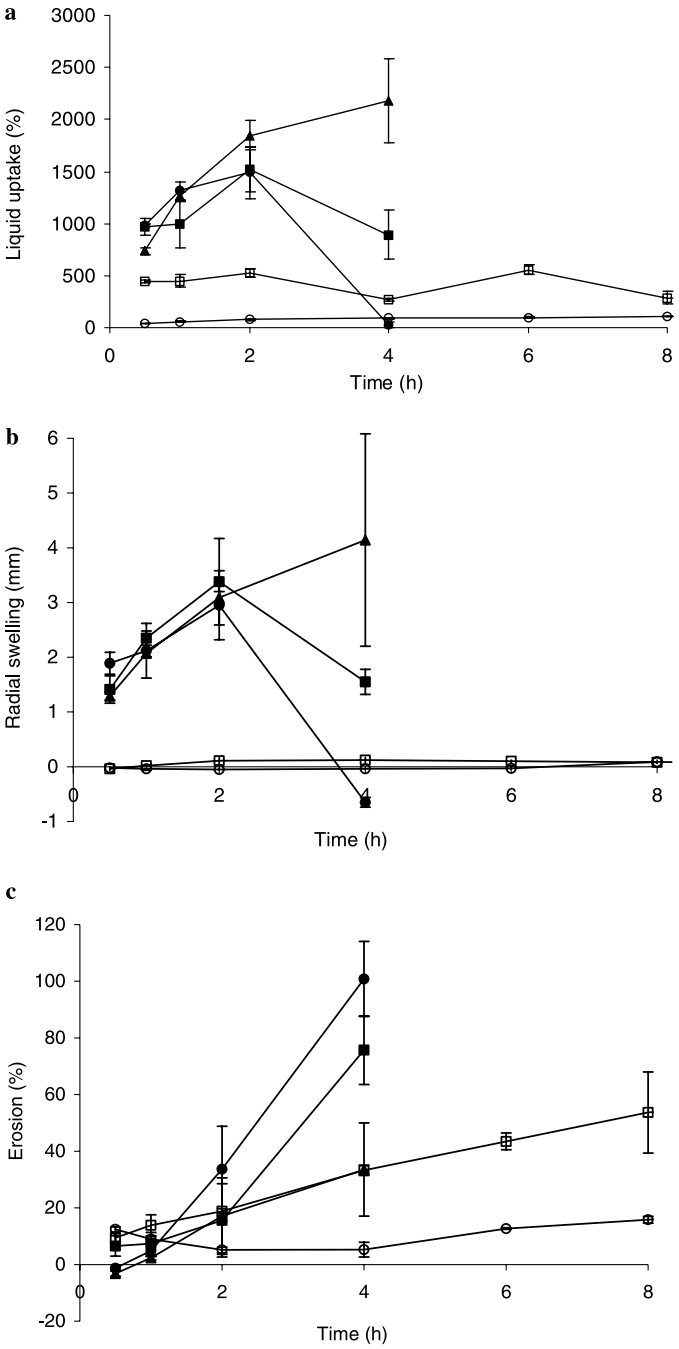

Fig. 2. Influence of xanthan gum (XG) concentration and particle size on the liquid uptake (a), radial swelling (b) and erosion (c) (mean ± SD, $n = 3$) of the mini-matrices containing 60% IBP, EC and XG. (○) 10% XG180, (□) 20% XG180, (▲) 30% XG75, (■) 30% XG180 and (●) 30% XG11K.

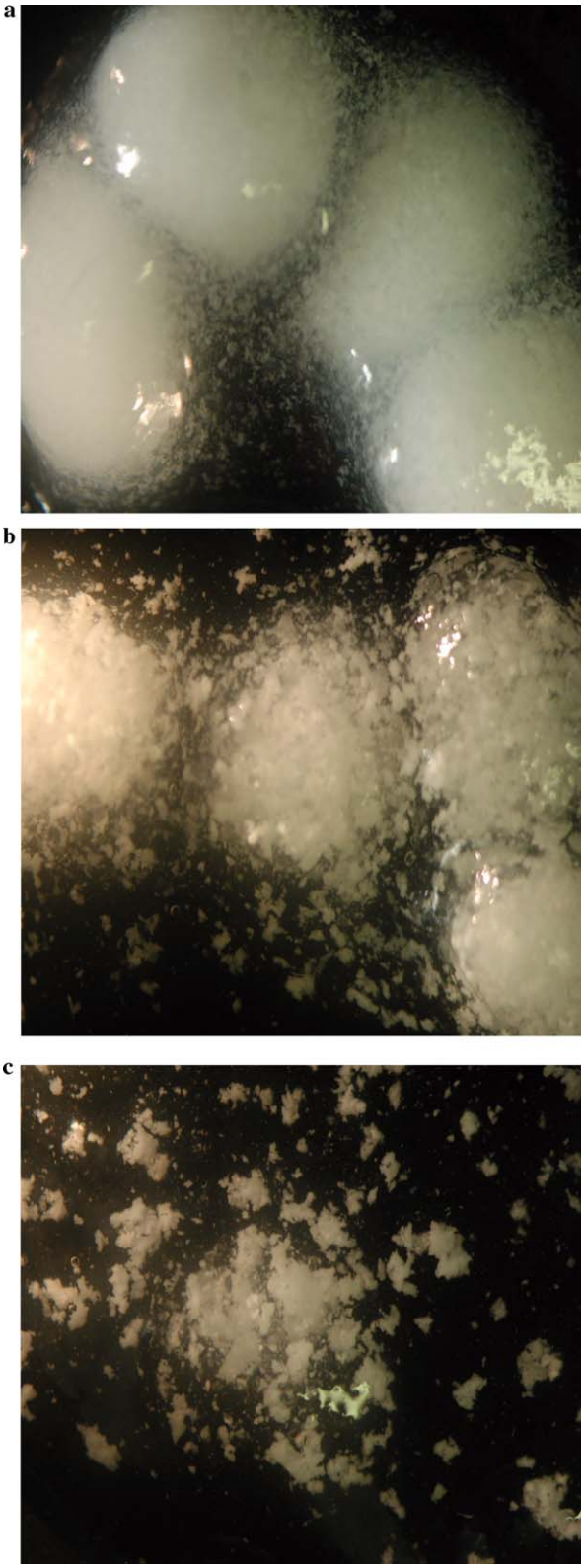

Fig. 3. Mini-matrices containing 60% IBP, 10% EC and 30% XG after 4 h immersion in the dissolution medium. (a) XG75, (b) XG180 and (c) XG11K.

confirmed a decrease in diffusion path length with increasing XG particle size, resulting in a faster drug release from the 30% XG11K mini-matrices (Fig. 1).

3.3. Analysis of drug release mechanism

To investigate if the XG concentration and particle size had an effect on the IBP release mechanism, the exponent characterizing drug release (n) and the area under the curve (AUC) were compared. As the ranking of n (Table 2) and AUC (Table 3) in function of concentration was independent

Table 2
Influence of xanthan gum concentration and particle size on the calculated n values (mean ± SD, $n = 6$) from the dissolution profiles (100 rpm)

	10%	20%	30%
XG75	0.58 ± 0.08^{a}	0.77 ± 0.03^{a}	0.86 ± 0.07^{a}
XG180	0.64 ± 0.03^{a}	0.85 ± 0.09^{a}	1.00 ± 0.07^{b}
XG11K	0.55 ± 0.05^{a}	0.85 ± 0.10^{a}	1.06 ± 0.05^{b}
Main effect concentration	0.59 ± 0.07^{A}	0.82 ± 0.08^{B}	0.97 ± 0.11^{C}

For a cylinder, Fickian or Case I diffusion is defined by $n = 0.45$, zero-order drug release due to erosion or relaxation (Case II diffusion) by $n = 0.89$ and anomalous behaviour or non-Fickian transport is indicated by values between 0.45 and 0.89. Super Case II transport is defined by n values > 1.0 [15,28].
[a,b] Means in the same column with different superscript are different at the 0.05 level of significance.
[A,B,C] Means in the same row with different superscript are different at the 0.05 level of significance.

Table 3
Influence of xanthan gum concentration and particle size on the calculated AUC values (mean ± SD, $n = 6$) from the dissolution profiles (100 rpm)

	10%	20%	30%
XG75	794 ± 32^{a}	1637 ± 27^{a}	1993 ± 36^{a}
XG180	792 ± 31^{a}	1412 ± 28^{b}	2136 ± 33^{b}
XG11K	981 ± 23^{b}	1469 ± 12^{c}	2236 ± 25^{c}
Main effect concentration	856 ± 95^{A}	1506 ± 101^{B}	2122 ± 107^{C}

[a,b,c] Means in the same column with different superscript are different at the 0.05 level of significance.
[A,B,C] Means in the same row with different superscript are different at the 0.05 level of significance.

of particle size, the main effect of XG concentration could be analysed (comparison of the overall mean of each column). However, as the ranking in function of particle size depended on XG concentration only the simple effect could be analysed (at each specific XG concentration, i.e., within each column). When increasing the XG concentration in the mini-matrices (regardless of the XG particle size), the drug release tended towards transport by Case II diffusion (i.e., erosion) as indicated by a significantly increasing exponent n (Table 2) (coefficient of determination of 0.9943 ± 0.0076 ($n = 162$)). This observation was confirmed by the erosion study (Fig. 2c) and the dissolution profiles (Fig. 1) and correlated with AUC values (Table 2), since a higher contribution of erosion resulted in a faster drug release. Regarding the effect of XG particle size, the IBP drug release mechanism did not differ significantly for the 10% and 20% XG formulations, although a significant, but not relevant, higher AUC value was obtained for the XG11K and XG75 formulations, respectively. Both formulations followed a similar release pattern: in all cases anomalous transport with n values from 0.55 up to 0.85. As the core of these mini-matrices could be recovered after 24 h, there is a strong indication that the drug release mechanism is not primarily erosion controlled. However, for the 30% XG formulation, anomalous transport was seen for the XG75 type ($n = 0.86$), whereas the release mechanism was mainly erosion controlled for the mini-matrices with a coarser XG particle size ($n = 1.06$). This observation was expected based on the erosion study (Figs. 2c and 3) since a higher erosion rate was seen for the XG180 and XG11K mini-matrices.

3.4. In vitro drug release: influence of hydrodynamics

The influence of the hydrodynamic stress on the release rate is negligible for a diffusion-controlled system, but has a great influence on an erosion-based system [24]. Therefore, dissolution experiments were carried out at different stirring rates (50, 100 and 200 rpm). The n and AUC values for IBP release (50 and 200 rpm data not shown) clearly indicated that for all formulations, regardless of the XG concentration and particle size, the drug release mechanism was not affected by the rotational speed. For the 30% XG formulations, this was surprising in view of the high erosion rates observed for the XG11K formulations (Fig. 2c). Since drug release was unaffected by the hydrodynamic conditions, we concluded that, although erosion of the mini-matrix is contributing to the faster drug release from the 30% formulations, the drug release mechanism from the mini-matrices was mainly diffusion controlled. The faster drug release observed using a coarser particle size (XG11K type) for the 30% XG formulations was more related to the faster hydration of the polymer particles.

3.5. In vitro drug release: influence of ionic strength of the dissolution medium

The susceptibility of the 20% XG75 containing matrices to the ionic strength of the dissolution medium is shown in Fig. 4. The slowest drug release was seen at the lowest ionic strength: after 24 h in a medium of $\mu = 0.011$, only 50%

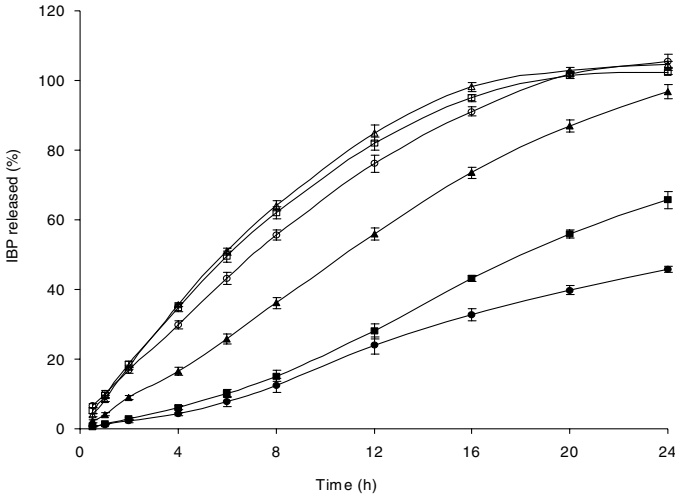

Fig. 4. Dissolution profiles (mean ± SD, $n = 6$) of the mini-matrices containing 60% IBP, 20% EC and 20% XG75 at different ionic strengths. (●) $\mu = 0.011$, (■) $\mu = 0.022$, (▲) $\mu = 0.055$, (○) $\mu = 0.11$, (□) $\mu = 0.15$ and (△) $\mu = 0.2$.

IBP was released, whereas the total drug load was released in a medium of $\mu = 0.055$ or higher. Above an ionic strength of 0.11 no differences in drug release profiles were observed, which was also reported by Talukdur and Kinget [14], since under these conditions XG formed a helical structure and further addition of salts had no influence on its rheological properties [25]. A similar drug release dependency on the ionic strength was noticed for the 10% and 30% XG75 mini-matrices (data not shown). Visual inspection of the XG matrices (Fig. 5) after 24 h of dissolution testing showed enhanced swelling of the mini-matrices in a dissolution medium of high ionic strength, which correlated with a higher IBP release. This behaviour might be attributed to the conformation of XG molecules which depended on the salt concentration. In aqueous solutions, a transition of XG occurs from a random coil at low ionic strength to an ordered elongated double helix with increasing salt concentrations. The ordered elongated conformation is able to form a gel, unlike the random coil [14]. Hence, at the lower ionic strengths, the disordered XG molecules resulted in less gel formation, a reduced swelling of the mini-matrices and a slower drug release rate. Based on these findings it is likely that within the physical range of gastric and intestinal ionic strengths ($\mu = 0.01$–0.166 according to Johnson et al. [26]) the drug release of XG containing formulations would be affected. The higher drug release in media of increasing salt concentrations is consistent with data reported by other investigators [11,12,14,20,27].

3.6. Stability study

Due to the presence of hydrophilic polymer, these formulations might be susceptible to storage conditions due to the effect of relative humidity and temperature. Therefore, the stability of these mini-matrices was evaluated under specific conditions. The release profiles indicated that all experimental mini-matrices were stable for at least 12 months during storage at 25 °C/60% RH. Storage at 40 °C/75% RH did not affect ibuprofen release from 10% XG mini-matrices. However, the drug release from the 20% and 30% XG formulations was increased: after 12 months, the amount of drug released after 4 h increased from 30% to 42% for the 20% and 30% XG mini-matrices, respectively, to 51% and 75%, respectively.

Immediately after production of the mini-matrices, the water content was similar (0.04, 0.08 and 0.09% for the 10, 20 and 30% XG formulations, respectively). Storage during 12 months at both conditions resulted in an increase of the water uptake which depended on XG concentration and storage conditions: 3.6% and 4.6% for the 20% and 30% XG formulations, respectively, when stored at 25 °C/60% RH; 4.3% and 6.8%, respectively, when stored at 40 °C/75% RH. No difference was seen in water uptake for the 10% XG formulations between both storage conditions (2.3% and 2.0% for 25 °C/60% RH and 40 °C/75% RH, respectively).

The stability data revealed that drug release and water uptake of formulations containing 20% and 30% XG changed when stored at 40 °C/75% RH and therefore these mini-matrices should be appropriately packaged.

3.7. In vivo performance

An in vitro burst release was observed at 30% XG when using the coarsest particle size XG11K (Fig. 1). Therefore, to prevent a burst release in vivo, the formulations containing XG75 were selected for in vivo analysis.

Fig. 6 shows the mean plasma concentration–time profiles after oral administration of 300 mg ibuprofen to 6 dogs as Junifen®, Ibu-Slow® 600 mg (1/2 tablet) and the experimental mini-matrices. The pharmacokinetic parameters are reported in Table 4.

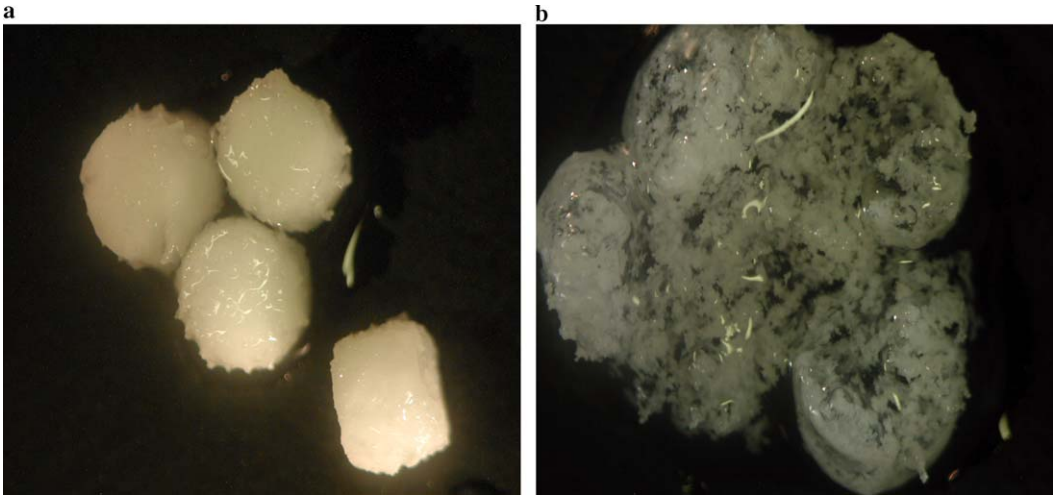

Fig. 5. Mini-matrices containing 60% IBP, 20% EC and 20% XG75 after 24 h immersion in the dissolution medium at different ionic strengths. (a) $\mu = 0.011$, (b) $\mu = 0.2$.

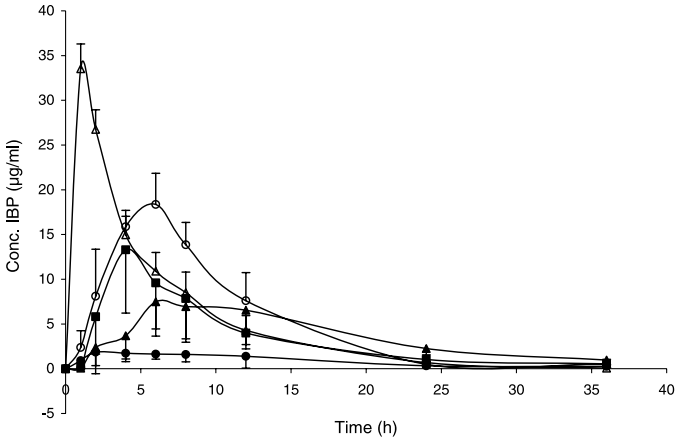

Fig. 6. Mean plasma concentration–time profiles (±SD, $n = 6$) after oral administration of 300 mg ibuprofen to dogs: (●) 10% XG75, (▲) 20% XG75, (■) 30% XG75, (○) Ibu-Slow® 600 (1/2 tablet) and (△) Junifen® (15 ml).

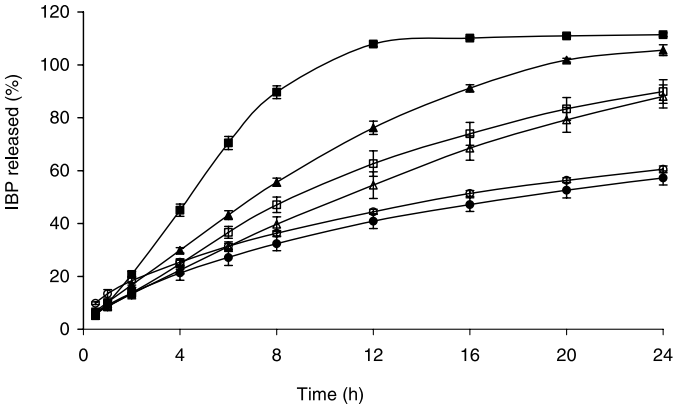

Fig. 7. Influence of XG concentration and sample size introduced in the dissolution medium on the drug release profiles (mean ± SD, $n = 6$) of the mini-matrices containing 60% IBP, EC and XG: (●) 10% XG75 60 mg, (○) 10% XG75 500 mg, (▲) 20% XG75 60 mg, (△) 20% XG75 500 mg, (■) 30% XG75 60 mg and (□) 30% XG75 500 mg.

With regard to the extent of absorption, the mean AUC_{0-36h} of the formulations F-1, F-2, F-3 and Ibu-Slow® 600 mg (1/2 tablet) were 34.8, 129.7, 134.9 and 186.2 µg/ml h, respectively; yielding relative bioavailabilities of the mini-matrices versus Ibu-Slow® 600 mg (1/2 tablet) of 19.3, 70.6 and 73.8%, respectively. The similar in vivo behaviour of the 20% and 30% XG formulations was not reflected in their in vitro dissolution profiles (Fig. 1) since a significant difference in drug release was noticed for these formulations. Therefore, it was investigated if the drug release properties were altered when a larger sample size (500 mg) of mini-matrices is filled into a capsule (similar to the dosage form that was administered to the dogs). Similar dissolution profiles (Fig. 7) and swelling (Fig. 8) were obtained for the 10% XG75 formulation, irrespective of the amount of mini-matrices. However, the release rate for the mini-matrices containing 20% and 30% XG was reduced (Fig. 7) by increasing the sample size in the dissolution basket, although sink conditions were maintained (solubility of ibuprofen: 4.48 ± 0.08 mg/ml at 37 °C [7]). Due to the rapid swelling of XG at 20% and 30% after hydration by the dissolution medium, the mini-matrices stick together with increasing sample size (Fig. 8): the increased diffusion path length reduced the drug release rate and similar drug release profiles were obtained at both XG concentrations. The formulations F-2 and F-3 had a pronounced sustained-release profile with R_D values of 3.1 and 2.2, respectively. In comparison with the 30% XG mini-tablets, the 20% XG formulation is characterized by a higher T_{max} (3.7 and 6.3 h, respectively) and a lower C_{max} (15.8 and 9.8 µg/ml, respectively), which is typical for sustained-release formulations and which is reflected in its higher $HVD_{t50\%C_{max}}$ and R_D. It was interesting to observe that during the initial phase of the plasma concentration–time profiles a slower absorption was seen for the mini-matrices containing 20% XG. This delayed onset of action can be seen as an advantage since it could favourably affect the clinical effect of an ibuprofen dose administered in the evening by preventing the morning stiffness typically associated with rheumatoid arthritis. Examining the plasma concentration–time profiles revealed a constant drug absorption pattern over 36 h for the 20% XG mini-matrices compared with the 30% XG mini-matrices and the reference formulation. From the data in Table 4, it can be concluded that C_{max} and T_{max} are similar for the 30% XG mini-tablets and Ibu-Slow® 600 mg (1/2 tablet). The similar pharmacokinetic parameters of both formulations supported the hypothesis that the 30% XG mini-matrices behaved in vivo as a single-unit dosage form instead of multiparticulates due to the immediate swelling

Table 4
Mean pharmacokinetic parameters (±SD, $n = 6$) after oral administration of 300 mg ibuprofen to dogs as the XG75 10% mini-matrices, XG75 20% mini-matrices, XG75 30% mini-matrices, Ibu-Slow® 600 (1/2 tablet) and Junifen® (15 ml)

	C_{max} (µg/ml)	T_{max} (h)	AUC_{0-36h} (µg h/ml)	$HVD_{t50\%C_{max}}$ (h)	F_{rel}* (%)	R_D
XG75 10%	3.0 ± 0.5^{a}	$5.7 \pm 3.9^{a,b}$	34.8 ± 8.8^{a}	$10.6 \pm 3.8^{a,b}$	19.3 ± 5.5^{a}	3.6 ± 1.4^{a}
XG75 20%	9.8 ± 2.3^{b}	$6.3 \pm 2.9^{a,b}$	129.7 ± 40.0^{b}	$9.5 \pm 4.0^{a,b}$	70.6 ± 22.9^{b}	3.1 ± 1.2^{a}
XG75 30%	$15.8 \pm 4.6^{b,c}$	3.7 ± 0.8^{b}	134.9 ± 32.6^{b}	6.9 ± 2.1^{b}	73.8 ± 19.5^{b}	2.2 ± 0.6^{a}
Ibu-Slow® 600 (1/2 tablet)	18.4 ± 5.7^{c}	$4.3 \pm 2.0^{a,b}$	186.2 ± 39.8^{b}	8.5 ± 1.8^{b}	–	2.8 ± 0.7^{a}
Junifen® (15 ml)	32.1 ± 3.7^{d}	1.0 ± 0.0^{a}	175.4 ± 46.9^{b}	3.1 ± 0.4^{a}	–	–

–: not applicable.
[a,b,c,d] Means in the same column with different superscript are different at the 0.05 level of significance.
* Ibu-Slow® 600 (1/2 tablet).

Fig. 8. Mini-matrices containing 60% IBP, EC and XG after 6 h immersion in the dissolution medium: (a) 10% XG75 60 mg, (b) 20% XG75 60 mg, (c) 30% XG75 60 mg, (d) 10% XG75 500 mg, (e) 20% XG75 500 mg and (f) 30% XG75 500 mg.

of the 30% XG mini-matrices upon contact with the GI-fluids and the formation of a plug. Although swelling was also noticed for the 20% XG mini-tablets, they performed in vivo as a multiparticulate dosage form since they differ in C_{max} and T_{max} values from Ibu-Slow® 600 mg (1/2 tablet). This bioavailability study demonstrated that the matrix

mini-matrices formulated with EC and XG can be used to prepare sustained-release dosage forms.

4. Conclusions

The present work was conducted in order to assess the influence of xanthan gum parameters (concentration and particle size) on the in vitro release of ibuprofen from ethylcellulose mini-matrices manufactured by hot-stage extrusion. Since the drug release was modified by changing the xanthan gum concentration as well as the xanthan gum particle size, the mini-matrices based on a combination of ethylcellulose and this hydrophilic additive offered a flexible system to tailor the drug release to the required specifications. Increasing xanthan gum concentrations yielded a faster drug release, higher liquid uptake, swelling and erosion rate.

The low susceptibility to the agitation speed suggested that diffusion is the predominant mechanism of drug release. However, diffusion was not the only mechanism controlling drug release from these systems as the rate and extent of drug release was also dependent on the swelling (relaxation) of the hydrated polymer mass.

In vivo data showed that oral administration of a xanthan gum/ethylcellulose formulation was able to sustain plasma levels in dogs.

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