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Development and evaluation of a multiple-unit oral sustained release dosage form for *S*(+)-ibuprofen: preparation and release kinetics

Philip J. Cox [a,*], Karrar A. Khan [b], Dale L. Munday [a], Jomjai Sujja-areevath [a]

[a] *School of Pharmacy, The Robert Gordon University, Aberdeen AB10 1FR, Scotland, UK*
[b] *Knoll Pharmaceuticals, Pennyfoot Street, Nottingham NG1 1GF, UK*

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Abstract

Mini-matrix tablets containing *S*(+)-ibuprofen have been prepared by the wet granulation method. The hydrophilic matrix was formed with either xanthan gum, karaya gum or hydroxymethylcellulose (HPMC) together with a choice of additives from lactose, Encompress®, Avicel® PH101, talc and Lubritab®. Multiple unit dosage forms (MUDFs) were subsequently obtained by encapsulating the mini-matrix tablets into hard gelatin capsules. Preparation, in vitro release profiles and release kinetics are presented.

Keywords: *S*(+)-ibuprofen; Xanthan gum; Karaya gum; Mini-matrix tablets; Sustained release

1. Introduction

Ibuprofen (2-(4-isobutylphenyl) propionic acid) is a non-steroidal anti-inflammatory drug (NSAID) used widely in rheumatoid arthritis, osteoarthritis and a number of other painful conditions. It has a chiral carbon atom on the propionic side-chain and therefore exists in two enantiomeric forms. *S*(+)-ibuprofen is the pharmacologically active form and 160 times more potent than *R*(−)-ibuprofen (Adams et al., 1976). *R*(−)-ibuprofen is inverted to *S*(+)-ibuprofen in vivo (Hutt and Caldwell, 1983) to the extent of 57–69% (Lee et al., 1985; Cheng et al., 1994).

In this study, hydrophilic mini-matrix tablets were encapsulated in hard gelatin capsules to produce multiple unit dosage forms (MUDFs) which have distinct advantages over single-unit dosage forms (SUDFs), e.g. uniform plasma levels (Edgar et al., 1984) and reproducible bioavailability (Graffner et al., 1986). The production of mini-matrices uses a tabletting technique that is widely understood, diverse and offers less constraints than, for example extrusion or spheronisation. In addition, the mini-matrices have dosing flexibility.

The aim of this work was to prepare mini-matrix tablets containing *S*(+)-ibuprofen, used as a model drug, and xanthan gum or karaya gum as the hydrophilic matrix to retard drug release. Hydroxypropyl methylcellulose (HPMC) was also

* Corresponding author.

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used as a hydrophilic matrix for comparative purposes. In vitro dissolution studies were performed on the formulations. Drug release from hydrophilic matrices is known to be a complex interaction between dissolution, diffusion and erosion mechanisms. This work was an attempt to determine the relative contribution of the various drug release mechanisms from these mini-matrix formulations.

2. Materials and methods

2.1. Materials

S(+)-ibuprofen was a gift from Knoll Pharmaceuticals (formerly Boots) (Nottingham, UK). Natural hydrophilic gums; xanthan gum ($M_r = 2 \times 10^6$ approx.) and karaya gum (from Sterculia tree, $M_r = 9.5 \times 10^6$ approx.), were purchased from Sigma Chemical Company (St. Louis, MO). The synthetic hydrophilic polymer, HPMC (Methocel K4M, nominal viscosity of a 2% aqueous solution at 20°C is 4000 cP), was purchased from Colorcon Ltd. (Orpington, Kent, UK). Spray-dried lactose (α-monohydrate) was obtained from Borculor Whey Product (Holland). Dicalcium phosphate (Encompress®) was supplied by Forum Chemical (Surrey, UK). Microcrystalline cellulose (Avicel® PH101) was purchased from Honeywill and Stein (Surrey, UK). Sodium hydroxide, potassium dihydrogen orthophosphate and potassium chloride were purchased from BDH (Poole, UK). Talc, hydrochloric acid and citric acid were supplied by Fisher (Leicestershire, UK). Sodium phosphate was purchased from Fisons (Loughborough, UK). All other materials were of analytical reagent grade.

2.2. Preparation of mini-matrices

All materials were passed through a mesh sieve with an aperture of 250 μm before use. Matrix tablets were prepared by the wet granulation method. The composition of the formulations are given in Table 1. All materials, with the exception of lubricants (talc or Lubritab®), were thoroughly mixed in a tumbling mixer for 5 min and then wetted in a mortar with 50% v/v aqueous ethanol. The wet mass was then passed through a 500 μm mesh sieve and dried at a temperature not greater than 40°C (well below the melting point of *S*(+)-ibuprofen) for 18 h. The dried granules were then rescreened through a 300 μm mesh sieve, lubricated with 2% w/w talc and compressed into flat-faced mini-matrices of diameters 4.5 mm each weighing 30.61 ± 1.0 mg and containing 10 ± 0.33 mg of *S*(+)-ibuprofen. An instrumented Manesty F3 single punch tablet machine (Manesty Machines Ltd., Liverpool, UK) was used to compress the mini-matrices. The crushing strength of ten matrices was measured individually using an Erweka hardness tester (Erweka TBH 28, Germany). The mean crushing strength and standard deviation were calculated. Eight mini-matrices were encapsulated in size 1 hard gelatin capsules

Table 1
Composition (%) of the mini-matrices containing *S*(+)-ibuprofen, hydrophilic gums (xanthan gum, karaya gum) or HPMC, and various excipients

	Formulations [a]			
	1A–C	2A–C	3A	4A
S(+)-ibuprofen	32.67	32.67	32.67	33
Xanthan gum	32.67	–	–	33
Karaya gum	–	32.67	–	–
HPMC K4M	–	–	32.67	–
Excipients (lactose, Encompress® and Avicel® PH101)	32.67	32.67	32.67	33
Talc	2	2	2	–
Lubritab®	–	–	–	1

[a] A, B and C series for each formulation number contain lactose, Encompress® and Avicel® PH101, respectively.

to produce a multiple unit dosage form with a total dose of 80 mg of $S(+)$-ibuprofen.

2.3. Compression study

There have been reports in the literature that compression force has a negligible influence on the drug release rate from compressed hydrophilic matrices (Huber and Christenson, 1968; Lapidus and Lordi, 1968; Ford et al., 1985; Hogan, 1989; Talukdar and Plaizier-Vercammen, 1993). However, these studies were conducted using active ingredients with much higher melting points than $S(+)$-ibuprofen. Due to the low melting point of $S(+)$-ibuprofen (53–55°C) there is a greater tendency for capping to occur. Mini-matrices containing $S(+)$-ibuprofen, xanthan gum or karaya gum and lactose in a ratio of 1:1:1 (formulations 1A and 2A, Table 1) were produced using a compression force in the range of 11–26 kN (F3 Compression Cycle Analysis System, BWI Manesty, UK). For this study, the punch diameter was increased from 4.5 to 5.5 mm. The larger diameter punches made it easier to observe the tendency of tablets to cap. A larger diameter punch using compression forces within the suitable range would produce tablets with different crushing strengths than the smaller punches. However, this was a comparative study only, plotting compression force against crushing strength and therefore similar results would not necessarily be obtained using the smaller punches.

2.4. Mini-matrix dissolution study

The USP XXIII basket method (Copley Dissolution System and Drive Control, Copley Instruments, Nottingham, UK) was used with a constant temperature water bath at 37 ± 0.5°C. The dissolution medium used was 0.05 M phosphate buffer pH 7.0 (US Pharmacopeia XXIII, 1995). The speed of rotation was 100 ± 1 rpm. The dissolution apparatus was connected to a flow-through UV spectrophotometer (Ultrospec II, LKB Biochrom Ltd., UK) via a peristaltic pump. The absorbance was measured automatically at 231 nm in a 10-mm cell at 30-min intervals over a 12-h period. The studies were carried out in triplicate. The cumulative percentage of $S(+)$-ibuprofen released was calculated and plotted against time.

The pH change dissolution method (changing the pH of the dissolution medium while running the dissolution test) was also used with mini-matrices formulations 1A and 3A in order to simulate the environment of the gastro-intestinal tract. The dissolution media used were 0.05 M hydrochloric acid buffer pH 1.5 (US Pharmacopeia XXIII, 1995) for the first hour, citrate–phosphate buffer pH 5 (Pharmaceutical Handbook, 1980) for the second hour, 0.05 M phosphate buffer pH 6.5 (US Pharmacopeia XXIII, 1995) for the next 3 h and finally 0.05 M phosphate buffer pH 7.2 (US Pharmacopeia XXIII, 1995) for 3 h. Each medium was warmed to 37 ± 0.5°C. At defined time intervals, the dissolution medium was removed and fresh medium added. The amount of drug released in the dissolution medium at pH 1.5 was determined by the first order derivative spectrophotometric method to enhance analytical sensitivity. For the other media, the simple UV absorption at wavelength 231 nm was used.

2.5. Data analysis

Korsmeyer et al. (1983) derived a simple relationship which described drug release from a polymeric system

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

where M_t/M_α is the fraction of drug released, t is the release time, k is a kinetic constant (with units of t^{-n}) incorporating structural and geometric characteristics of the release device and n is the release exponent indicative of the mechanism of release. This equation can be used to analyse the first 60% of a release curve where the release is linearly related to t^n, regardless of geometric shape.

Sinclair and Peppas (1984), Peppas (1985) have shown also that two competing release mechanisms, a Fickian diffusional release and a case-II relaxational release, are the limits of this phenomenon. Fickian diffusional release occurs by the usual molecular diffusion of the drug due to a

Table 2
Diffusion exponent and solute release mechanism for cylindrical shape

Diffusion exponent (n)	Overall solute diffusion mechanism
0.45	Fickian diffusion
$0.45 < n < 0.89$	Anomalous (non-Fickian) diffusion
0.89	Case-II transport
$n > 0.89$	Super case-II transport

chemical potential gradient. Case-II relaxational release is the drug transport mechanism associated with stresses and state-transition in hydrophilic glassy polymers which swell in water or biological fluids. This term also includes polymer disentanglement and erosion. Table 2 describes the limits of this analysis for cylindrical shape, e.g. a tablet. The value of the exponent for case-II transport mechanism is twice that of pure Fickian diffusional mechanism.

Following a heuristic approach first developed by Alfrey et al. (1966) for the case of solvent transport in a polymer, the two phenomena controlling the release can be considered as additive. Therefore, Eq. (1) may be extended (Peppas and Sahlin, 1989)

$$\frac{M_t}{M_\alpha} = k_1 t^m + k_2 t^{2m} \tag{2}$$

where the first term of the right-hand side is the Fickian contribution, the second term being the case-II relaxational contribution. The coefficient m is the purely Fickian diffusion exponent for a device of any geometric shape which exhibits controlled release.

Eq. (2) can be rewritten as:

$$\frac{M_t}{M_\alpha} = k_1 t^m \left[1 + \frac{k_2}{k_1} t^m \right] \tag{3}$$

The percentage of drug release due to the Fickian mechanism, F, is clearly calculated as:

$$F = \frac{1}{1 + \frac{k_2}{k_1} t^m} \tag{4}$$

which leads to the ratio of relaxational over Fickian contributions as:

$$\frac{R}{F} = \frac{k_2}{k_1} t^m \tag{5}$$

Therefore, Eqs. (2) and (3) indicate that solute release from any device, irrespective of its geometric shape, can be written in terms of a Fickian and a relaxational contribution. If the Fickian contribution can be expressed as a function of t^m, then the relaxational contribution can be expressed as a function of t^{2m}. By comparison of Eqs. (1) and (2) it is concluded that $m = n$ when the relaxational mechanism is negligible.

Although the constant k in Eq. (1) is one of the measures of the drug release rate, it should not be used for comparison because there are different kinetics in different test conditions. Therefore, to characterize the drug release rate in different experimental conditions, the mean dissolution time (MDT) was calculated from dissolution data according to Mockel and Lippold (1993) using Eq. (6).

$$\mathrm{MDT} = \frac{n}{n+1} k^{-1/n} \tag{6}$$

For calculation of the release rate of the drug, the data in this study were subjected to the Higuchi equation (Higuchi, 1961):

$$Q = (2ADC_s t)^{1/2} \tag{7}$$

where Q is the percentage of drug release at time t, A is the total concentration of drug in the mini-matrix, D is the diffusion coefficient of the drug in the mini-matrix and C_s is the solubility of drug in the mini-matrix. This equation may be reduced to a simple equation as:

$$Q = at^{1/2} + c \tag{8}$$

Eq. (8), for release data dependent on the square root of time, would give a straight line release profile, where a is a $\sqrt{}$time dissolution rate constant and c is a constant. The lag period, prior to the commencement of release, is defined as $(-c/a)^2$.

3. Results and discussion

3.1. Preparation of mini-matrices

Initially, the production of mini-matrices containing $S(+)$-ibuprofen and xanthan gum or

karaya gum in a ratio of 1:1 was attempted. Both these matrices produced serious capping problems, i.e. the partial or complete separation of the top or bottom crowns of the tablet from its main body. Compaction of cooled granules (5°C) or an increase in the diameter of punches to 5.5 mm were also tried, unsuccessfully, to solve this problem. Therefore, the excipients; lactose, Encompress® and Avicel®, which are commonly used and have good compressibility properties, were added to the formulations to improve the compression characteristics.

The mini-matrices containing $S(+)$-ibuprofen, gum and excipient 1:1:1 were well formed and no capping problems were experienced.

3.2. Compression study

Compression forces in the range of 11–26 kN were suitable for the production of mini-matrices containing $S(+)$-ibuprofen, xanthan gum or karaya gum and lactose in a ratio of 1:1:1 (formulations 1A and 2A, Table 1). At compression forces ≥ 26 kN, the capping problem was amplified for both formulations. For $S(+)$-ibuprofen mini-matrices containing xanthan gum, a compression force as small as 2.3 kN could be used while for karaya gum the smallest compression force acceptable was 11.3 kN. This implied that xanthan gum had better adhesion properties than karaya gum.

Compression forces in the range 11–26 kN had little effect on crushing strength. The crushing strengths of mini-matrices containing xanthan gum varied from 25.1 to 28.0 N while those containing karaya gum varied from 23.3 to 27.6 N. Hence the crushing strengths of these two formulations were not very different.

3.3. Mini-matrices dissolution study

3.3.1. Effect of excipients on release characteristics

Xanthan gum and karaya gum were used to sustain the release of $S(+)$-ibuprofen from mini-matrices because previous studies (Sujja-areevath et al., 1996) demonstrated that these gums produced satisfactory release profiles for diclofenac sodium. The excipients were included in the formulations not only to overcome the capping problem but also to regulate the release rate of the drug. Lactose (freely water-soluble), dicalcium phosphate (Encompress®, water-insoluble) and microcrystalline cellulose (Avicel®, water-insoluble) were used in a ratio of drug: gum: excipient 1:1:1. All three excipients are commonly used as diluents in tablet formulations. The mini-matrices produced had crushing strengths in the range of 23–28 N.

The release studies of $S(+)$-ibuprofen from mini-matrices containing xanthan gum and various excipients; lactose, Encompress® or Avicel® (formulations 1A–C, Table 1) compressed at $\sim$ 20 kN and encapsulated in hard gelatin capsules were performed in 0.05 M phosphate buffer pH 7.0. The different excipients used produced differences in release profiles and the results are shown in Fig. 1. The release profile of mini-matrices containing Avicel® is higher than Encompress® and lactose, respectively. Maximum accumulated release of $S(+)$-ibuprofen at 12 h was 98% for Avicel® and 82% for Encompress® and lactose. The release mechanisms were anomalous (non-Fickian), but approached case-II transport with n values of 0.732, 0.644 and 0.881 and release rates of 3.74, 3.69 and 5.56% $min^{-1/2}$ for lactose, Encompress® and Avicel®, respectively (Table 3). There was little difference in release from the formulations containing Encompress® and lactose. Although Avicel® and Encompress® are water-insoluble excipients, their drug release profiles were different. The mini-matrices containing Avicel® exhibited a higher drug release rate than those containing Encompress® after the first 2 h. This could result from the disintegration property of Avicel®. When in contact with the dissolution medium, xanthan gum absorbs water, swells and becomes a hydrated gel. At the same time Avicel®, having disintegration properties, promoted the disintegration of the mini-matrices. The mini-matrices were therefore easier to erode, compared with Encompress®, resulting in a higher release profile. A similar result, i.e. a slightly higher dissolution rate of acetylsalicylic acid from Eudragit® S-100 matrix containing Avicel® PH101 than that containing Encompress®, was observed also (Jo-

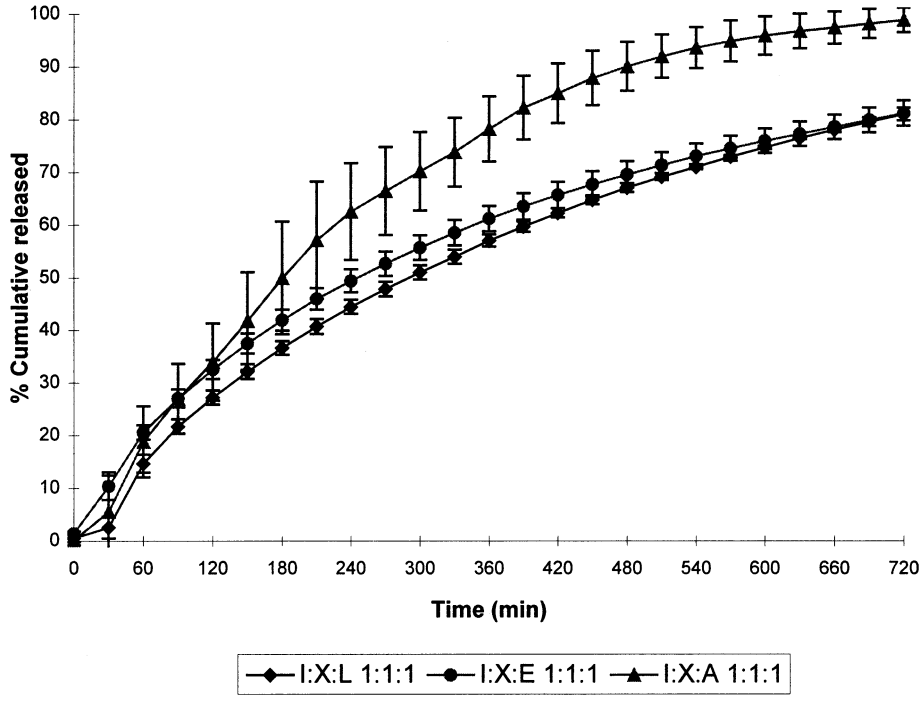

Fig. 1. Percentage of $S(+)$-ibuprofen released against time from eight mini-matrices (4.5 mm diameter) containing $S(+)$-ibuprofen (I), xanthan gum (X) and lactose (L), Encompress® (E) or Avicel® (A) enclosed in a hard gelatin capsule (mean values ± S.D.; $n = 3$).

vanovic et al., 1997). In addition, studies have been performed showing that tablets produced with Encompress® do not disintegrate readily (Rubinstein and Bodey, 1976; Koparkar et al., 1990; Fischer, 1992), so mini-matrices containing Encompress® would have less tendency to erode, compared with Avicel®, consequently showing a slower release profile.

The percentage contributions of Fickian diffusion (F) and relaxation (R) over the first 60% of

Table 3
Release parameters from the encapsulated mini-matrices using Eq. (1) to derive the release exponent (n) and the kinetic constant (k)

Mini-matrices composition [a]	Release exponent (n)	Kinetic constant (k) ($\min^{-n}) \times 10^{-3}$	Correlation coefficient (r)	Release rate (% $\min^{-1/2}$) [b]	Correlation coefficient (r)
I:X:L 1:1:1	0.732 ± 0.043	8.19 ± 2.34	0.996	3.74 ± 0.06	1.000
I:X:E 1:1:1	0.644 ± 0.012	14.53 ± 1.33	0.997	3.69 ± 0.13	1.000
I:X:A 1:1:1	0.881 ± 0.144	7.21 ± 6.27	0.997	5.56 ± 0.77	0.993
I:K:L 1:1:1	1.143 ± 0.062	1.48 ± 0.39	0.994	6.91 ± 0.69	0.998
I:K:E 1:1:1	1.248 ± 0.261	2.02 ± 2.21	0.994	7.79 ± 1.71	0.997
I:K:A 1:1:1	1.620 ± 0.181	0.30 ± 0.28	0.980	10.18 ± 0.68	0.990
I:HPMC:L 1:1:1	0.763 ± 0.030	8.88 ± 1.81	0.999	4.80 ± 0.22	0.999

[a] I, $S(+)$-ibuprofen; X, xanthan gum; L, lactose; E, Encompress®; A, Avicel®; K, karaya gum; HPMC, hydroxypropyl methylcellulose.

[b] The release rate (% $\min^{-1/2}$) was calculated from the slopes of the plots of fraction of drug released versus the square root of time (Eq. (8)) (mean values ± S.D.; $n = 3$).

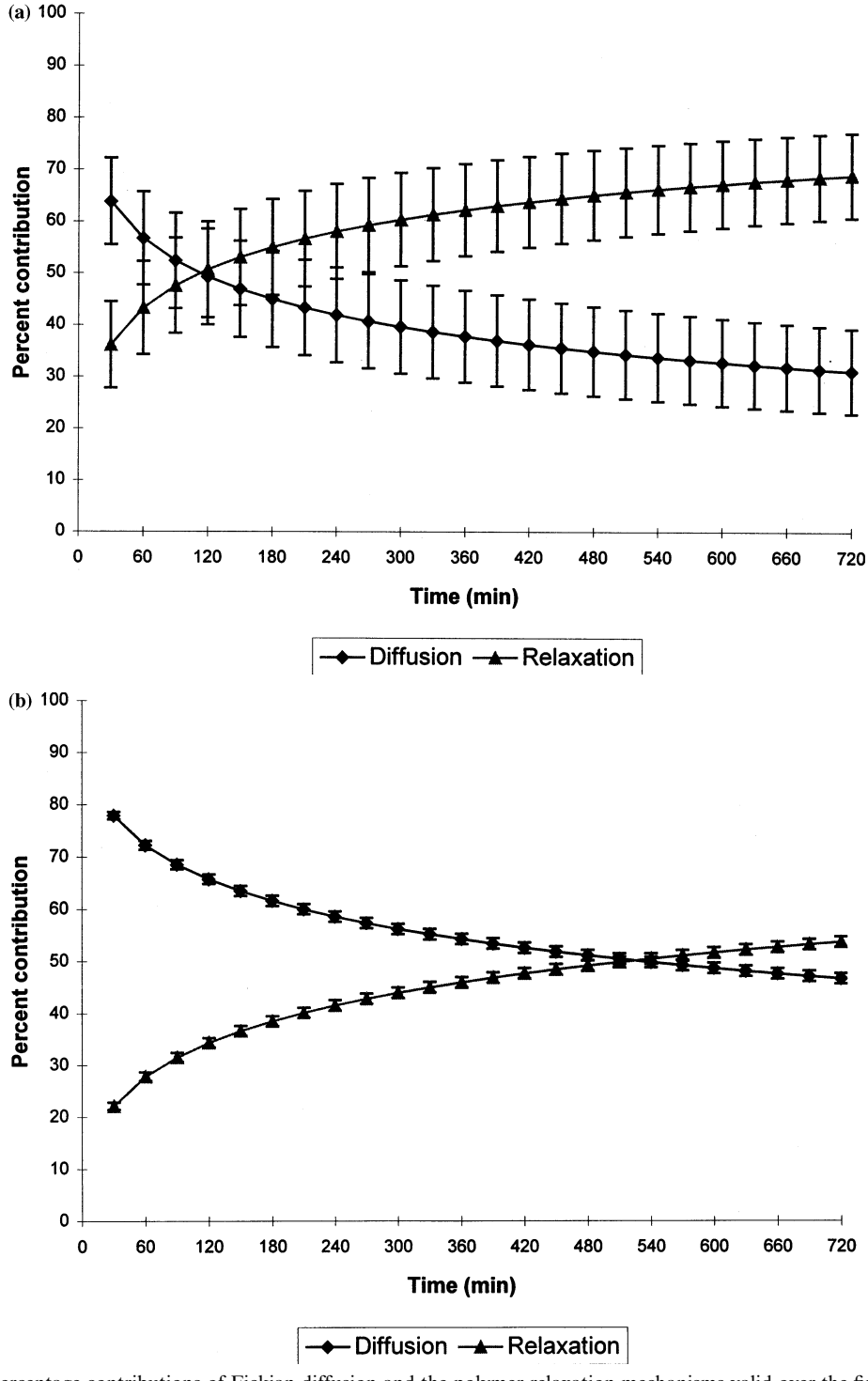

Fig. 2. (a) The percentage contributions of Fickian diffusion and the polymer relaxation mechanisms valid over the first 60% of drug release from mini-matrices containing $S(+)$-ibuprofen, xanthan gum and lactose (mean values $\pm$ S.D.; $n = 3$). (b) The percentage contributions of Fickian diffusion and the polymer relaxation mechanisms valid over the first 60% of drug release from mini-matrices containing $S(+)$-ibuprofen, xanthan gum and Encompress® (mean values $\pm$ S.D.; $n = 3$).

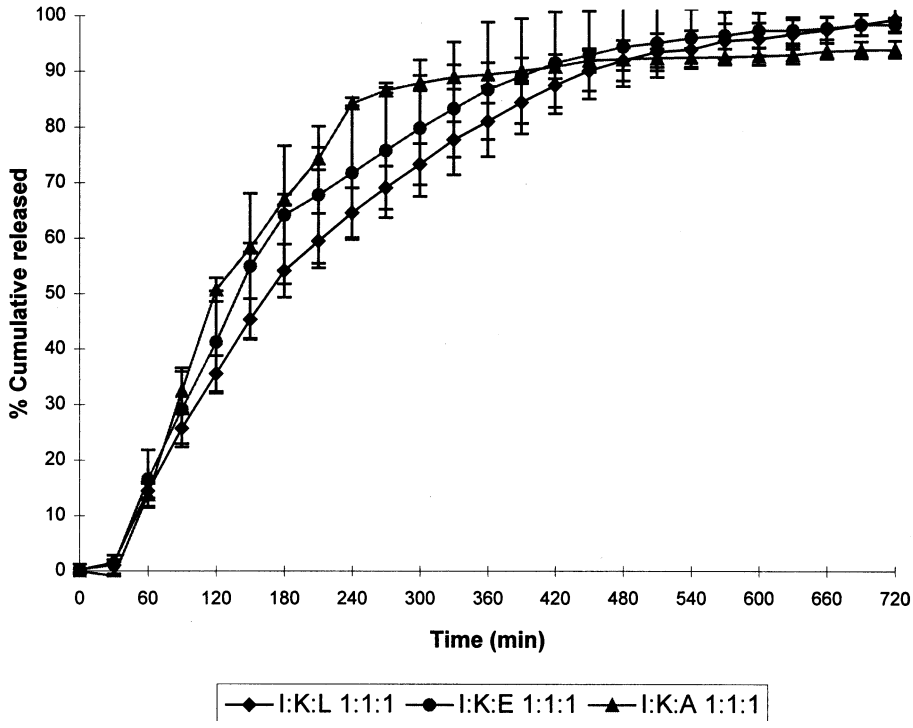

Fig. 3. Percentage of $S(+)$-ibuprofen released against time from eight mini-matrices (4.5 mm diameter) containing $S(+)$-ibuprofen (I), karaya gum (K) and lactose (L), Encompress® (E) or Avicel® (A) enclosed in a hard gelatin capsule (mean values ± S.D.; $n = 3$).

drug release from mini-matrices containing xanthan gum and lactose or Encompress® are shown graphically in Fig. 2a and b, respectively. For mini-matrices containing Encompress®, the contribution of Fickian diffusion predominated for the first 8.5 h of the dissolution period, and decreased gradually until polymer relaxation become predominant at the end (Fig. 2b). Whereas with mini-matrices containing lactose, the contribution of Fickian diffusion predominated during the first 2 h, decreasing gradually until polymer relaxation became predominant (Fig. 2a). On the other hand, with Avicel® the contribution of polymer relaxation occurs almost exclusively throughout the entire dissolution time period, and therefore the graph for this is not shown. This is also apparent from the n value of 0.881 which approaches case-II transport.

The release profiles of $S(+)$ ibuprofen mini-matrices containing karaya gum and lactose, Encompress® or Avicel® are shown in Fig. 3. The rank order of release rate is Avicel® > Encompress® > lactose, the same order as mini-matrices containing xanthan gum. The maximum accumulated drug release was 99% for lactose and Encompress®, and 94% for Avicel®. The release mechanisms are super case-II transport with n values of 1.143, 1.248 and 1.620 and release rates of 6.91, 7.79 and 10.18% $min^{-1/2}$ for lactose, Encompress® and Avicel®, respectively (Table 1).

The percentage contributions of Fickian diffusion (F) and relaxation (R) over the first 60% of drug release from mini-matrices contining karaya gum and lactose, Encompress® or Avicel® were calculated according to Eq. (2). The contribution of polymer relaxation occurs almost exclusively throughout the entire dissolution time period for all three excipients, and therefore the graphs for these are not shown. These results correlate with the high release exponents (super case-II transport) but the initial lag time leads to an increase in the calculated value of n.

3.3.2. Effect of type of gum on release characteristics

The encapsulated *S*(+)-ibuprofen mini-matrices containing HPMC and lactose in a ratio of 1:1:1 showed an intermediate release profile between *S*(+)-ibuprofen: xanthan gum: lactose 1:1:1; which is lower, and *S*(+)-ibuprofen: karaya gum: lactose 1:1:1; which is slightly higher (Fig. 4). The maximum accumulated drug release was 100% at 12 h. The release mechanism was anomalous (non-Fickian) transport with an *n* value of 0.763 and a release rate of 4.80% $min^{-1/2}$.

The percentage contributions of Fickian diffusion (*F*) and relaxation (*R*) over the first 60% of drug release is shown graphically in Fig. 5. The contribution of Fickian diffusion is relatively small whilst release due to relaxation is dominant for the entire dissolution time period.

It is noticeable that the release rates of *S*(+)-ibuprofen mini-matrices containing xanthan gum and various excipients were lower than those containing karaya gum. These results are opposite to the results from previous studies (Sujja-areevath et al., 1996) in which encapsulated mini-matrices containing diclofenac sodium: xanthan gum 1:1 release the active drug faster than those containing diclofenac sodium: karaya gum 1:1.

For diclofenac sodium: karaya gum 1:1 mini-matrices, the Fickian diffusion was dominant for the first 7 h of the dissolution period, but with *S*(+)-ibuprofen: karaya gum: excipients 1:1:1 mini-matrices, the polymer relaxation was mostly dominant for the entire dissolution time period. This means that the release mechanism of karaya gum mini-matrices containing diclofenac sodium (49.5% karaya gum) and *S*(+)-ibuprofen (32.67% karaya gum) was different. However, for *S*(+)-ibuprofen: xanthan gum: excipients (lactose or Encompress®) the release mechanism at the early period was Fickian diffusion followed by polymer

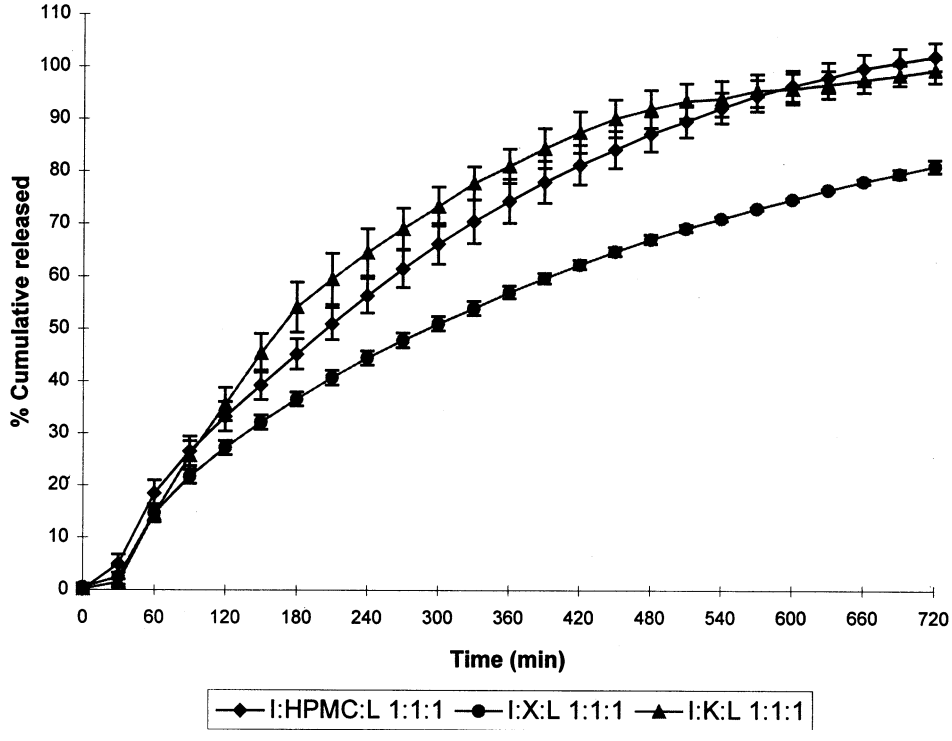

Fig. 4. Percentage of *S*(+)-ibuprofen released against time from eight mini-matrices (4.5 mm diameter) containing *S*(+)-ibuprofen (I), various gums; xanthan gum (X), karaya gum (K) or HPMC, and lactose (L) enclosed in a hard gelatin capsule (mean values ± S.D.; $n = 3$).

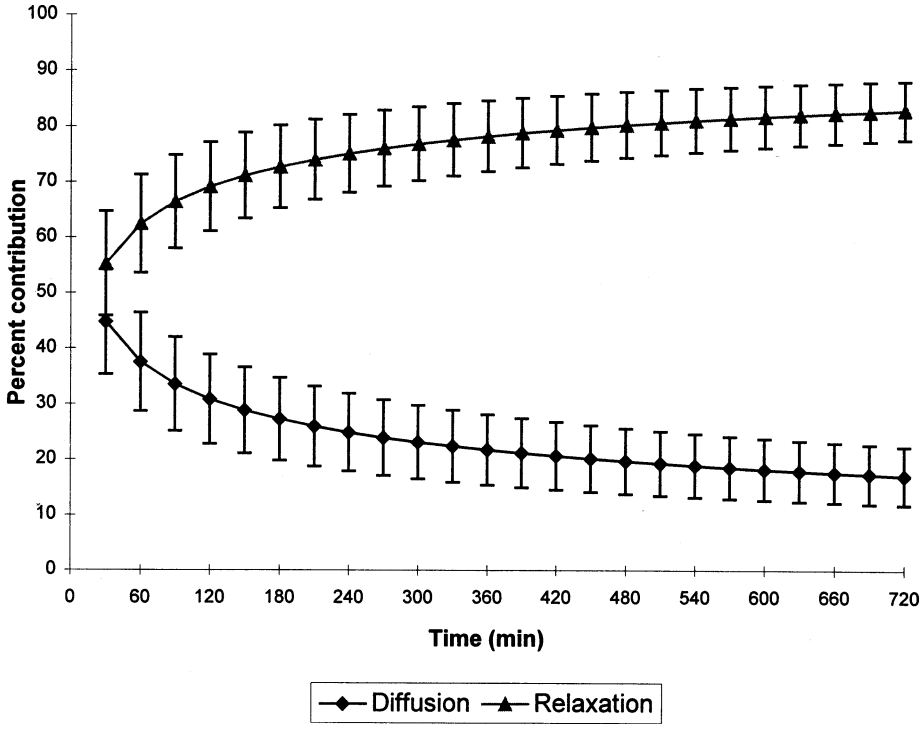

Fig. 5. The percentage contributions of Fickian diffusion and the polymer relaxation mechanisms valid over the first 60% of drug release from mini-matrices containing $S(+)$-ibuprofen, HPMC and lactose (mean values $\pm$ S.D.; $n = 3$).

relaxation, similar to the result from diclofenac sodium mini-matrices. The viscosity study (Sujja-areevath, 1997) also showed that the flow behaviour of karaya gum changed from pseudoplastic to the Herschel–Bulkley model (measured from the up-curve on the rheogram) when 50% of it was substituted by $S(+)$-ibuprofen, while the flow behaviour of xanthan gum remained pseudoplastic on substitution. These results imply that xanthan gum can tolerate higher concentrations of added substances than karaya gum. In addition, previous reports showed that 5.83% xanthan gum can sustain the release of caffeine (Talukdar and Plaizier-Vercammen, 1993) and 5% xanthan gum exhibits a release profile similar to a 15% HPMC tablet (Dhopeshwarkar and Zatz, 1993).

3.3.3. Effect of dissolution medium on release characteristics

The release profiles of encapsulated mini-matrices comprised of $S(+)$-ibuprofen, xanthan gum or HPMC, and lactose in a ratio of 1:1:1 using the pH change dissolution method are shown in Fig. 6. The release rate of $S(+)$-ibuprofen from these two formulations depends on the pH of the medium. For the first hour, in hydrochloric acid medium pH 1.5, the accumulated release was $< 1\%$ which increased slightly in citrate phosphate buffer pH 5 (second hour) but was still negligible ($< 10\%$). The release was greatly increased in phosphate buffer pH 6.5 (the next 3 h). The difference in release rate from these two formulations was noticed clearly in phosphate buffer pH 6.5 and 7.2. The release patterns were similar but the mini-matrices containing HPMC showed the higher degree of release.

In earlier work (Sujja-areevath, 1997) it was shown that the solubility of $S(+)$-ibuprofen was highly dependent on the pH of the medium used. At low pH values, the solubility of the drug was very poor (0.1 mg/ml at pH 2.0). With increasing pH, the solubility of the drug improved dramatically. Hence, it is not surprising that these dissolu-

tion studies using the pH change method demonstrated a similar trend. The drug dissolution rate increased greatly with pH over the range 1.5–7.2. It follows therefore that the pH of the dissolution medium is a critical factor in determining the dissolution rate of *S*(+)-ibuprofen.

4. Conclusion

S(+)-ibuprofen mini-matrices can be produced by the wet granulation method using xanthan gum, karaya gum or HPMC as the retarding agents. The crushing strengths used were in the range 23.3–28.0 N. Xanthan gum produced a greater sustaining effect on the release of *S*(+)-ibuprofen than karaya gum. The release rate from xanthan gum mini-matrices containing lactose or Encompress® were very similar; 3.74 and 3.69% $min^{-1/2}$, respectively, and slower than those containing Avicel®; 5.56% $min^{-1/2}$. The release mechanisms were anomalous with *n* values of 0.732, 0.644 and 0.881 for lactose, Encompress® and Avicel®, respectively. From the contribution of Fickian diffusion and relaxation, the release of *S*(+)-ibuprofen from mini-matrices containing lactose and Encompress® in the initial stages was Fickian diffusion, gradually declining and changing to polymer relaxation in the later stages of the dissolution time period. For mini-matrices containing Avicel®, polymer relaxation was dominant throughout the dissolution time period.

The release mechanism of *S*(+)-ibuprofen from karaya gum mini-matrices containing lactose, Encompress® and Avicel® was super case-II with *n* values of 1.143, 1.248 and 1.620 and release rates of 6.91, 7.79 and 10.18% $min^{-1/2}$, respectively. Polymer relaxation was dominant throughout the dissolution time period.

The release of *S*(+)-ibuprofen from *S*(+)-ibuprofen: HPMC: lactose 1:1:1 was faster than

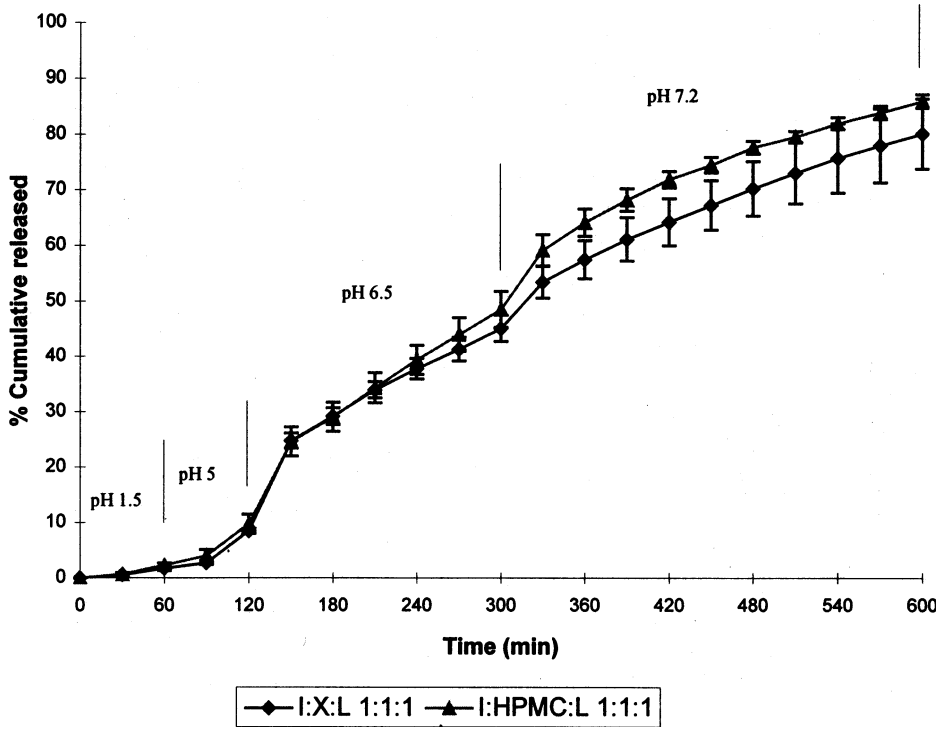

Fig. 6. Percentage of *S*(+)-ibuprofen released against time from eight mini-matrices (4.5 mm diameter) containing *S*(+)-ibuprofen (I), xanthan gum (X) or HPMC, and lactose (L) enclosed in a hard gelatin capsule using pH change method (mean values ± S.D.; $n = 3$).

xanthan gum mini-matrices but slower than karaya gum mini-matrices. The release mechanism was anomalous with an n value of 0.763 and a release rate of 4.80% $min^{-1/2}$. Again, polymer relaxation was dominant throughout the dissolution time period.

The release of $S(+)$-ibuprofen from mini-matrices containing xanthan or HPMC and lactose depended greatly on the pH of the medium. This result was consistent with the pH solubility profile of $S(+)$-ibuprofen (Sujja-areevath, 1997).

Xanthan gum and HPMC were particularly suitable with release exponents approaching zero-order (constant) release over 12-h time periods in vitro, especially when using the pH change method.

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