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Release characteristics of diclofenac sodium from encapsulated natural gum mini-matrix formulations

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Abstract

In attempts to design an oral sustained release multiple-unit dosage form for diclofenac sodium (D), we evaluated the use of four natural hydrophilic gums as mini-matrix formulations enclosed in a hard gelatin capsule. Carrageenan (C), locust bean (LB), karaya (K) and xanthan gums (X) were used to produce mini-matrices (3, 4.5 and 5.5 mm in diameter) containing a gum and D, and also with other release-regulating excipients in different proportions, namely lactose (L), Encompress® (E), cellulose acetate phthalate (CAP) and Veegum F® (V). The release profiles from several encapsulated mini-matrices in buffered dissolution medium (pH 7.0) showed that sustained release of D up to 77% of drug content was achieved from mini-matrices containing LB, X and K, while C did not produce sufficient sustained release. The calculated release exponents (n values) indicated that release behaviour was anomalous (non-Fickian). Polymer swelling and relaxation were both involved in the release process. For X, the drug release rate declined linearly with progressive increase in gum content but without changing the release behaviour. Maximum release from individual mini-matrices was $> 90\%$ and approaching zero-order release kinetics ($n \rightarrow 1$). This was due to the larger surface area to volume ratio which provided an optimum balance between the diffusion and dissolution mechanisms. Solubility differences between the excipients did not affect the release rate, but increasing proportions of each excipient produced a faster release rate with the release mechanism changing from anomalous to Case II and then to Super Case II transport. The amount of gum present appeared to play the dominant role in determining the drug release rate.

Keywords: Diclofenac sodium; Mini-matrix; Dissolution; Xanthan gum; Carrageenan gum; Karaya gum; Locust bean gum; Sustained release

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1. Introduction

Hydrophilic matrix tablets have been used extensively to produce sustained drug delivery by the gastro-intestinal (GI) route (Huber and Christenson, 1968; Lapidus and Lordi, 1968; Nakano and Ogata, 1984; Möckel and Lippold, 1993). Such matrix formulations often contain hydroxypropylmethylcelluloses (HPMC), although other polymeric materials have also been evaluated (Ford et al., 1985; Naggar et al., 1992; DiLuccio et al., 1994; Katikaneni et al., 1995). The mechanisms of drug release have also been well reported and reviewed (Higuchi, 1962; Higuchi, 1963; Korsmeyer et al., 1983; Ritger and Peppas, 1987; Hogan, 1989; Lee and Kim, 1991) and generally the release kinetics can be best described by a linear relationship between % cumulative release and $\sqrt{}$time. The operating principle controlling drug release from hydrogel matrix tablets on exposure to aqueous fluids is also well known and has been shown to be a complex interaction between swelling, diffusion and erosion (Bonferoni et al., 1993; Wan et al., 1993; Bettini et al., 1994; Colombo et al., 1995).

In our study, four natural hydrophilic gums were evaluated in mini-matrix formulations. Carrageenan consists of sulphated linear polysaccharides of D-galactose and 3,6-anhydro-D-galactose. Locust bean gum is a linear chain of β-D-mannopyranosyl units with non-uniformly spaced side branches. Xanthan gum contains D-glucose and D-mannose units with D-glucuronic acid, and is prepared as the sodium, potassium and calcium salt. Karaya gum (from Sterculia tree) is a partially acetylated polymer of galactose, rhamnose and glucuronic acid. Matrix tablets are normally single-unit dosage forms (SUDFs), but multiple-unit dosage forms (MUDFs) have distinct advantages over SUDFs (Beckett, 1981; Bechgaard, 1982). MUDFs are usually comprised of coated pellets, beads, granules or mini-tablets enclosed in a hard gelatin capsule. Technological processes in production make MUDFs more expensive than SUDFs. Therefore, mini-matrices were produced to combine the physiological advantages of MUDFs with the economic advantages of SUDFs. These mini-matrices were encapsulated in hard gelatin capsules and contained a model drug, diclofenac sodium, together with the hydrophilic gums and other release-regulating excipients. The in vitro drug release profiles and the kinetics of release from various gum mini-matrix formulations are reported.

2. Materials and methods

2.1. Materials

Diclofenac sodium (D) powder was purchased from Sigma Chemical Company (St Louis, USA). Carrageenan (C), karaya (K), locust bean (LB) and xanthan (X) gums were also purchased from the same source. Spray-dried lactose (Zeparox®) was obtained from Dairy Crest (Surrey, UK). Dicalcium phosphate dihydrate (Encompress®) was supplied by Forum Chemicals Ltd. (Surrey, UK). Cellulose acetate phthalate (CAP) was obtained from Eastman (Newcastle, UK). Magnesium aluminium silicate (Veegum F®) was supplied by R.T. Vanderbilt Co. Inc. (Norwalk, USA). Magnesium stearate, sodium hydroxide and potassium dihydrogen orthophosphate were all received from BDH Ltd. (Poole, UK). All other materials were of analytical reagent grade.

2.2. Rationale for selection of certain excipients

Lactose (freely water-soluble), dicalcium phosphate dihydrate (Encompress®) (water-insoluble), cellulose acetate phthalate (CAP; soluble in USP buffer solutions ≥ 6.2) and magnesium aluminium silicate (Veegum F®; practically insoluble in water, but swells to form a colloidal dispersion) were used as excipients in various proportions. Lactose and Encompress® are commonly used as diluents in tablet formulations. Having opposite solubility characteristics, it is reasonable to expect that lactose and Encompress® would exhibit significant differences in drug release from hydrated gum matrices. It has been reported that lactose produced increased release rates of various drugs from polymeric matrices (Marín Boscá et al., 1995; Talukdar and Kinget, 1995). Lactose diffuses outwards through the gel layer, increasing the porosity and decreasing the tortuosity of the diffusion path of drug. On the other hand, En-

Table 1
Composition (%) of the mini-matrices containing diclofenac sodium and four hydrophilic gums

	Formulation						
	1[a]	2[a]	3[a]	4[a]	5[a]	6[b]	7[c]
Diclofenac sodium	49.5	49.5	49.5	49.5	66	39.6	33
Xanthan	49.5	—	—	—	33	59.4	66
Carrageenan	—	49.5	—	—	—	—	—
Karaya	—	—	49.5	—	—	—	—
Locust bean	—	—	—	49.5	—	—	—
Magnesium stearate	1	1	1	1	1	1	1

Weight of each mini-matrix: [a]30.2 ± 1.1 mg; [b]50.1 ± 1.5 mg; [c]60.3 ± 2.2 mg

compress® forms a porous, insoluble and non-swellable matrix which has been used to control the release of some water-soluble drugs (Mulye and Turco, 1994). In our work, CAP was blended with gum in order to maintain the integrity of the mini-matrix in the acid contents of the stomach. On reaching the intestine (pH > 6), the CAP would dissolve and then possibly act in a similar manner to lactose in regulating the drug release rate. Furthermore, it has been reported that the viscosity of aqueous xanthan gum solutions is greatly increased, or gelation occurs, by combination with Veegum F® due to synergistic effects (Kovacs, 1973). Veegum F® was therefore combined with xanthan gum to investigate whether such synergism would produce any significant effect on drug release from the solid mini-matrices.

2.3. Preparation of matrix tablets

All materials were passed through a mesh sieve with aperture of 250 μm before use. Matrix tablets were prepared by the wet granulation method. The composition of the formulations are presented in Tables 1 and 2. All materials, with the exception of magnesium stearate, were thoroughly mixed in a tumbling mixer for 5 min and then wetted in a mortar with 50% v/v ethanol (except for formula 3 which was wetted with 70% v/v ethanol). The wet mass was then passed through a 500 μm mesh sieve and dried at a temperature not greater than 60°C for 12 h (except for formula 3 which was dried at room temperature). The dried granules were then re-creened through a 300 μm mesh sieve, lubricated with magnesium stearate 1% w/w and compressed into flat-faced mini-matrices of diameters 3, 4.5 and 5.5 mm weighing 20, 30 and 40 mg (except as indicated in Table 1), and containing 10, 15 and 20 mg of D respectively. An instrumented Manesty F3 single punch tablet machine (Manesty Machines Ltd., Liverpool, England) was used to compress the mini-matrices using a compression force of 21.2 ± 0.6 kN and having an average crushing strength of 22.3 ± 3.6 N (Erweka TBH 28 Tablet Hardness Tester, FRG). A sufficient number of mini-matrices containing a dose of either 90 or 100 mg of D were encapsulated in size 1 hard gelatin capsules to produce a MUDF.

2.4. In vitro dissolution studies

The USP XXIII basket method (Copley Dissolution System and Drive Control, Copley Instruments, Nottingham, England) was used with a constant temperature water bath at 37 ± 0.5°C. The dissolution media used were 0.1 M dilute HCl (pH 1.5) and 0.05 M phosphate buffer (pH 7.0). The speed of rotation was 100 ± 1 rev./min. The dissolution apparatus was connected to a flow-through ultraviolet (UV) spectrophotometer (Ultrospec II, LKB Biochrom Ltd., England) via a peristaltic pump. The absorbance was measured automatically at 275 nm in a 10 mm cell at 30 min time intervals over a 12 h period. Replicate studies were performed, the cumulative percentage of D calculated (± SD) and plotted against time.

Table 2
Composition (%) of the mini-matrices (4.5 mm diameter) containing diclofenac sodium, xanthan gum and various excipients

	Formulation				
	8A-D*	9A-D*	10A-D*	11A-D*	12A-D*
Diclofenac sodium	49.5	49.5	49.5	49.5	49.5
Xanthan	41.3	33	24.75	16.5	8.2
Excipients (lactose, Encompress®, CAP and Veegum F®)	8.2	16.5	24.75	33	41.3
Magnesium stearate	1	1	1	1	1

*A, B, C and D series for each formulation number contain lactose, Encompress®, CAP and Veegum F® respectively.

2.5. Data analysis

Korsmeyer et al. (1983) derived a simple relationship (1) which describes drug release from a polymeric system

$$\frac{M_t}{M_\infty} = k.t^n \quad (1)$$

where M_t/M_∞ is the fraction of drug released, t is the release time, k is a constant incorporating structural and geometric characteristics of the release device and n is the release exponent indicative of the mechanism of release. Values for n and k for each matrix formulation were obtained by plotting the logarithm of the fractional release against the logarithm of time. The slope of the line is n while log k is the intercept. The drug release data were plotted using values of M_t/M_∞ within the range of 0.10–0.60, and the values of n and k calculated by regression analysis (values ± 95% confidence limits). The n and k values were calculated from plots of M_t/M_∞ within the range of 0.10–0.60 because, in the initial stages (< 0.10), the drug release rate is usually very rapid, and above 0.60 it tends to slow down with time.

3. Results and discussion

3.1. Type of gum

The four natural hydrophilic gums used showed greatly different in vitro dissolution profiles for diclofenac sodium from the encapsulated mini-matrices using a buffered dissolution medium (pH 7.0) and at drug:gum ratios of 1:1. The studies were carried out using hard gelatin capsules each containing six mini-matrices (4.5 mm diameter, 30.2 ± 1.1 mg weight) of each gum formulation (formulations 1–4 of Table 1). As seen in Fig. 1, the mean times for 50% release ($t_{50\%}$ values) are 0.5, 2.75, 5.25 and 10.5 h for carrageenan, locust bean, xanthan and karaya gums respectively. The Type 1 carrageenan gum used, which contains predominantly κ- and lesser amounts of λ-carrageenan, does not produce sufficient sustained release of diclofenac sodium in spite of the fact that κ-carrageenan is reported (suppliers' literature) to form rather rigid gels. On the other hand, locust bean, xanthan and karaya gums do show variable degrees of sustained release. The maximum amount of accumulated drug released is

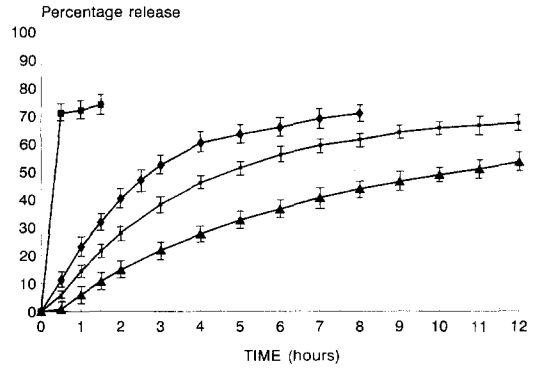

Fig. 1. Percentage of diclofenac sodium released against time (h) from 6 mini-matrices (4.5 mm diameter) comprised of various hydrophilic gums enclosed in a hard gelatin capsule (mean values ± SD, n = 3). (■), diclofenac sodium:xanthan gum 1:1; (▲), diclofenac sodium:karaya gum 1:1; (◆), diclofenac sodium:locust bean gum 1:1; (■), diclofenac sodium:carrageenan gum 1:1.

Table 3
Release parameters from the encapsulated mini-matrices using Equation 1 (mean ± S.D., $n = 3$)

Capsule contents			Release exponent (n)	Kinetic constant (k) (min^{-n}) × 10^{-3}	Correlation coefficient (r)
Mini-matrices Composition*	Diameter (mm)	Number per capsule			
D:X 2:1	5.5	5	0.917 ± 0.102	4.538 ± 2.371	0.994
D:X 2:2	5.5	5	0.740 ± 0.095	9.315 ± 4.396	0.970
D:X 2:3	5.5	5	0.719 ± 0.040	8.012 ± 0.598	0.978
D:X 2:4	5.5	5	0.719 ± 0.013	4.393 ± 0.407	0.994
D:X 1:1	4.5	6	0.703 ± 0.014	9.268 ± 1.329	0.988
D:LB 1:1	4.5	6	0.777 ± 0.080	10.213 ± 3.845	0.994
D:K 1:1	4.5	6	0.731 ± 0.008	4.704 ± 0.506	0.991
D:X 1:1	3.0	1	0.910 ± 0.068	5.755 ± 2.375	0.997
D:X 1:1	4.5	1	0.870 ± 0.053	5.917 ± 1.133	0.996
D:X 1:1	5.5	1	0.825 ± 0.022	7.344 ± 1.066	0.998

*D, Diclofenac sodium; X, Xanthan gum; LB, Locust bean gum; K, karaya gum.

about 75% for carrageenan and locust bean gums, whereas for xanthan and karaya gums the maximum amount released after 12 h was 66% and 54%, respectively. However, in the case of the latter two gums the drug was still being released slowly from the hydrated matrices after 12 h. After 24 h, this cumulative amount released had risen to 77% and 71% respectively. When dissolution was carried out in dilute HCl (pH 1.5), the amount released was almost negligible (< 1% after 6 h). A pH solubility profile carried out on diclofenac sodium showed that diclofenac sodium was practically insoluble in dilute HCl at pH 1.5 (3.8 mg l^{-1}), and at pH 5 the drug was still practically insoluble (43.8 mg l^{-1}). Since the solubility of the drug in the acid gastric fluid would be so poor, it is doubtful whether there is a need to enteric coat oral sustained release dosage forms of diclofenac sodium (which are based on the matrix principle) to protect the gastric membrane from its irritant effects.

The values for release exponent n and kinetic constant k together with the correlation coefficient (r) for each gum are given in Table 3. A value of $n = 0.45$ indicates square root of time kinetics (Case I or Fickian diffusion), $n = 0.89$ indicates Case II transport, $0.45 < n < 0.89$ indicates anomalous (non-Fickian) diffusion and $n > 0.89$ for Super Case II transport (Ritger and Peppas, 1987). The release behaviour of each of the three gums displaying sustained release was clearly anomalous (non-Fickian) with values of $n = 0.703$, 0.731 and 0.777 for xanthan, karaya and locust bean gums respectively. This suggests that these gums (particularly locust bean) are in moving boundary conditions, since the swelling and dissolution of the gum continuously modify the effective diffusivity of the drug.

3.2. Different drug:gum ratios

Xanthan gum was selected for this study because 50% of the drug was released after almost 50% of the dissolution time period. Drug/xanthan gum ratios of 2:1, 2:2, 2:3 and 2:4 were used with compositions as shown in Table 1 (formulations 5, 1, 6 and 7, respectively). Each mini-matrix contained 20 mg of D and therefore a slightly larger mini-matrix (5.5 mm diameter) was produced to accommodate the increased amount of gum. Fig. 2 clearly shows that the drug release rate is greatly influenced by the diclofenac sodium:xanthan gum ratio of the matrix. As the proportion of xanthan gum increases, there is a

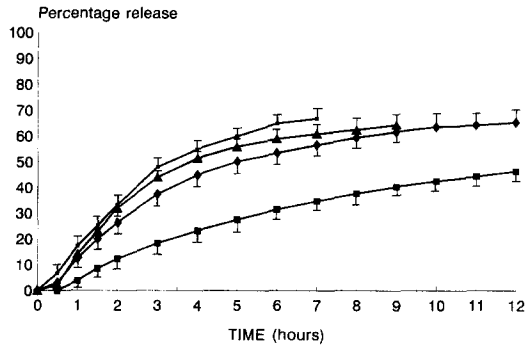

Fig. 2. Percentage of diclofenac sodium released against time (h) from 5 mini-matrices (5.5 mm diameter) comprised of diclofenac sodium and xanthan gum in various proportions enclosed in a hard gelatin capsule (mean values ± SD, n = 3). (■), diclofenac sodium:xanthan gum 2:1; (▲), diclofenac sodium:xanthan gum 2:2; (◆), diclofenac sodium:xanthan gum 2:3; (■), diclofenac sodium:xanthan gum 2:4.

progressive decline in the release rate. This can also be shown by plotting the release rates (% $\text{min}^{-\frac{1}{2}}$) for diclofenac sodium against the percentage of xanthan gum in each capsule (Fig. 3). This curve could be used to allow predictions of the release rate to be made for diclofenac sodium:xanthan gum ratios not experimentally determined, provided that no drug/gum interactions are encountered which will complicate the calculations. Values for n and k (± SD; n = 3) are shown in Table 3 and these also show anomalous (non-Fickian) release behaviour for drug/

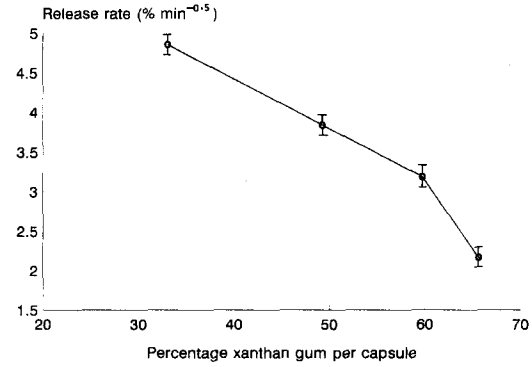

Fig. 3. Relationship between release rate of diclofenac sodium (% $\text{min}^{-0.5}$) and the percentage of xanthan gum contained in each capsule. (mean values ± SD, n = 3).

xanthan gum ratios of 2:2, 2:3 and 2:4. Although the drug release rate decreased with increasing gum content, the mechanism of release nevertheless remained the same. However, for drug/gum ratio of 2:1, the n value → 1 (Case II transport). This would be due to the greater drug concentration which would enhance the dissolution mechanism and compensate for the decrease in release due to gum swelling.

3.3. Volume of matrix

An increase in matrix volume could account for the slower drug release with increasing proportions of gum whilst keeping the drug content constant. In order to establish the effect of matrix volume on drug release rate, mini-matrices of diameters 3 mm, 4.5 mm, and 5.5 mm were produced with the same composition (drug:xanthan gum ratio 1:1). The calculated volumes of the 3, 4.5 and 5.5 mm mini-matrices were 15.1, 22.35 and 31.14 mm^3 respectively. Dissolution studies were carried out on a single mini-matrix of each volume and the profiles show that more than 90% of drug was released (Fig. 4). There was < 10% difference in the average cumulative release between the smallest and largest volume matrices after 10 h. Compared with the substantial differences in volume, the differences in cumulative release are relatively small and provides evidence that gum concentration is the main retarding factor. The release exponents (n values) calculated from a plot of log M_t/log M_∞ ($M_t/M_\infty \geq 0.10 \leq 0.60$) versus log t of the individual mini-matrices were 0.910, 0.870 and 0.825 for the 3, 4.5 and 5.5 mm diameters respectively (Table 3). Phenomenologically, therefore, the single mini-matrices behave as near zero-order release systems (Case II transport) regardless of the specific molecular mechanisms of drug transport. The larger surface area to volume ratio of the individual mini-matrices provides a suitable balance between swelling and dissolution of the matrix to achieve Case II transport. As noted earlier, the maximum release after 12 h from five or six encapsulated mini-matrices contained in the dissolution basket was lower (± 70%) than that from individual mini-matrices (> 90%). This is proba-

Table 4
Release parameters from encapsulated mini-matrices (4.5 mm diameter) containing diclofenac sodium, xanthan gum and four different excipients using Equation 1

Composition Drug:gum:excipient	D:X:L*		D:X:E*		D:X:CAP*		D:X:V*	
	Release exponent (n)	Correlation coefficient (r)	Release exponent (n)	Correlation coefficient (r)	Release exponent (n)	Correlation coefficient (r)	Release exponent (n)	Correlation coefficient (r)
3:3:0	0.703 ± 0.014	0.988	0.703 ± 0.014	0.988	0.703 ± 0.014	0.988	0.703 ± 0.014	0.988
3:2.5:0.5	0.695 ± 0.042	0.983	0.727 ± 0.036	0.980	0.745 ± 0.081	0.976	0.816 ± 0.033	0.989
3:2:1	0.727 ± 0.040	0.991	0.795 ± 0.031	0.995	0.839 ± 0.052	0.940	0.861 ± 0.054	0.991
3:1.5:1.5	0.985 ± 0.122	0.991	0.887 ± 0.085	0.998	1.199 ± 0.108	0.991	0.930 ± 0.062	0.989
3:1:2	1.123 ± 0.187	0.989	1.122 ± 0.147	0.978	1.181 ± 0.080	0.979	1.016 ± 0.106	0.990

(Mean ± S.D., $n = 3$)
*D, diclofenac sodium; X, xanthan gum; L, spray-dried lactose; E, Emcompress® (dicalcium phosphate dihydrate); CAP, cellulose acetate phthalate; V, Veegum F® (magnesium aluminium silicate).

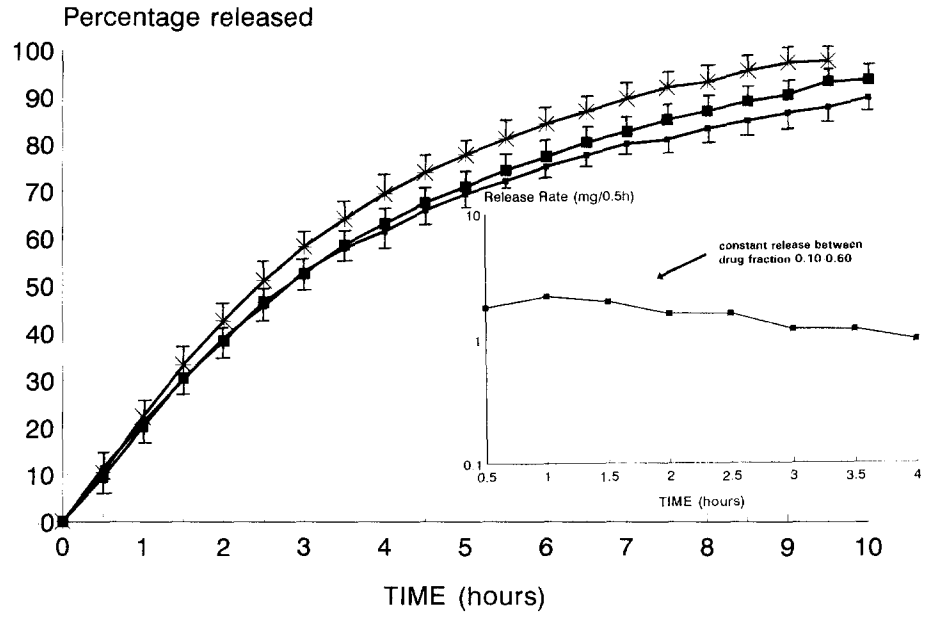

Fig. 4. Percentage of diclofenac sodium released against time (h) from single mini-matrices of varying diameter containing diclofenac sodium and xanthan gum 1:1 (mean values ± SD, $n = 3$). (▪), 5.5 mm diameter; (■), 4.5 mm diameter; (*), 3 mm diameter. The inset shows the constancy of the release rate (mg/0.5 h) versus time (h) using a 4.5 mm diameter mini-matrix over the fractional release range of 0.10 to 0.60.

bly due to the fact that in the former case the mini-matrices are confined to the area of the base of the basket (± 3.14 cm^2). They tend to aggregate, forming a gel-like mass which is much larger in volume than an individual mini-matrix. Therefore, complete release of the drug from the centre of the collective gel is very slow. The surface area to volume ratio is smaller and dissolution is suppressed. The main release mechanism through this larger swollen gel is diffusion, while dissolution is reduced. Hence, the release mechanism tends towards Case I (Fickian) transport.

3.4. Drug:gum mixtures including excipients

Various workers have demonstrated the effect that excipients have on drug release from HPMC matrices (Ford et al., 1987; Feely and Davis, 1988a; Feely and Davis, 1988b; Xu and Sunada, 1995). Our work investigated the effect of various excipients on diclofenac sodium release from xanthan gum mini-matrices. The dissolution studies were carried out on formulations 8–12 (Table 2) and consisted of six mini-matrices (4.5 mm diameter, 30.2 ± 1.1 mg weight) enclosed in a hard gelatin capsule.

In spite of the widely varying physico-chemical characteristics of the excipients, the drug dissolution profiles displayed similar tendencies. The drug release rate increased with increasing proportions of excipient (corresponding decrease in xanthan gum content) irrespective of the solubility characteristics of the excipient. A typical profile (using Veegum F®) is illustrated in Fig. 5. For simplicity, the profiles of the other excipients are not shown, but the values for n ($P < 0.05$) of these evaluations are shown in Table 4. The release exponent for the formulations containing drug, xanthan gum and excipient in the ratio 3:0.5:2.5 respectively are not shown because there were insufficient data points on the release profiles between 10% and 60% release to provide accurate values. The tabulated data show that values of $n \rightarrow 1.0$ and > 1.0 when the excipient content $\geq$ the xanthan gum content. This implies that the release mechanism changes from anomalous (non-

Fickian) diffusion ($0.45 < n < 0.89$) to Case II transport (zero-order) ($n = 0.89$) to Super Case II transport ($n > 0.89$). It is evident that dissolution or erosion of the excipient would account for the increasing values of n as the excipient content increased. The $t_{50\%}$ values for mini-matrices containing Veegum F®/xanthan gum and CAP/xanthan gum mixtures were on average 10%–15% longer than those containing lactose and Encompress® as excipients. These relatively small differences in $t_{50\%}$ values suggest that the nature of the excipient used appeared to play a minor role in regulating release, while the xanthan gum content was the dominating factor. A lower gum content would result in reduced swelling with corresponding decrease in diffusional path length. Moreover, the excipients would enhance either the dissolution or erosion mechanism, depending on the solubility of the excipient, which compensates for the slowing diffusion rate through the gradually increasing gel layer by creating greater porosity for the drug pathway. A plot of release rate (% $\text{min}^{-\frac{1}{2}}$) versus the percentage of Veegum F® contained in the mini-matrices is shown in Fig. 6. It is seen from this graph that there is a linear increase in release rate with percentage increase in Veegum F® until about 33%. Higher percentages of Veegum F® result in a sudden marked increase in release rate. This plot can be used to predict release rates for amounts of excipient not experimentally determined. From these results there is no evidence to show that the synergistic viscosity effects between Veegum F® and xanthan gum had any noticeable affect on the rate of drug release from solid mini-matrices.

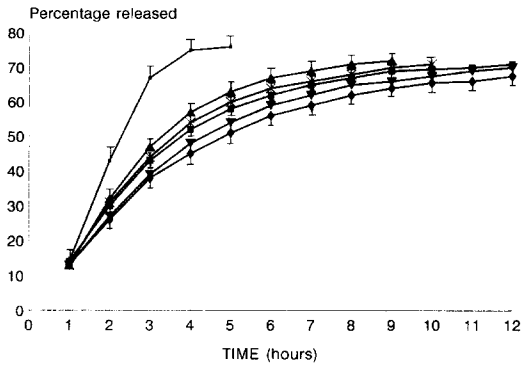

Fig. 5. Percentage of diclofenac sodium released against time (h) from 6 mini-matrices comprised of diclofenac sodium, xanthan gum and Veegum F® enclosed in a hard gelatin capsule (mean values ± SD, $n = 3$). Each mini-matrix contains 15 mg of diclofenac sodium (D) and variable ratios of xanthan gum (X) and Veegum F®(V). (■), D:X:V, 3:0.5:2.5; (▲), D:X:V, 3:1:2; (*), D:X:V, 3:1.5:1.5; (■), D:X:V, 3:2:1; (▼), D:X:V, 3:2.5:0.5; (◆), D:X:V, 3:3:0.

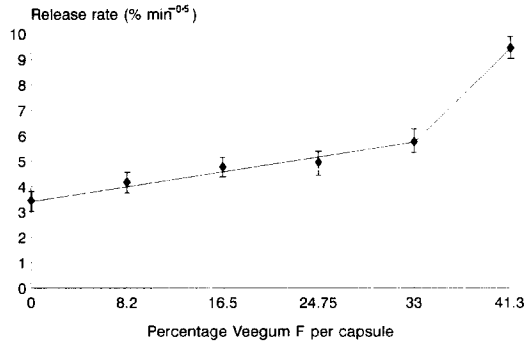

Fig. 6. Relationship between release rate of diclofenac sodium (% $\text{min}^{-0.5}$) and the percentage of Veegum F® contained in each capsule (mean values ± SD, $n = 3$).

4. Conclusion

Sustained release of diclofenac sodium was achieved from several mini-matrices enclosed in a hard gelatin capsule containing locust bean, xanthan and karaya gums. The release behaviour was anomalous (non-Fickian), indicating that polymer swelling and relaxation were both involved in the release process. The amount of xanthan gum present determined the rate of drug release. Individual mini-matrices showed higher cumulative release amounts with release exponent values approaching zero-order kinetics. The surface area to volume ratio of the mini-matrices should be such as to provide an optimum balance between swelling and dissolution. Increasing proportions of excipient produced a faster release rate, changing the release behaviour from anomalous to Case II and to Super Case II transport. Xanthan gum content appears to play the dominant role in determining drug release rate. Swelling and ero-

sion experiments are currently in progress to investigate the affects of gel formation and dissolution on drug release.

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