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Compressed xanthan and karaya gum matrices: hydration, erosion and drug release mechanisms

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Abstract

Directly compressed matrices were produced containing either xanthan gum or karaya gum as a release-controlling agent. These swellable hydrophilic natural gums were used to control the release of varying proportions of two model drugs, caffeine and diclofenac sodium, which have different solubilities in aqueous medium. Gum erosion, hydration and drug release studies were carried out using a dissolution apparatus (basket method) at two agitation speeds. Xanthan gum displayed a high degree of swelling due to water uptake and a small degree of erosion due to polymer relaxation. Neither agitation speed nor drug solubility had any significant effect on water uptake, but matrices with the lower proportion of gum produced a lesser degree of hydration. In contrast, karaya gum displayed a much lower hydration capacity and a higher rate of erosion, both markedly affected by agitation speed. Drug release from xanthan and karaya gum matrices depended on agitation speed, solubility and proportion of drug. Both xanthan and karaya gums produced near zero order drug release with the erosion mechanism playing a dominant role, especially in karaya gum matrices.

Keywords: Xanthan gum; Karaya gum; Hydration; Matrices; Drug release; Erosion

1. Introduction

The use of naturally occurring biocompatable polymeric materials has been the focus of recent research activity in the design of dosage forms for oral controlled release administration (Naggar et al., 1992; Bonferoni et al., 1993; Kristmundsdóttir et al., 1995; Sujja-areevath et al., 1996; Talukdar et al., 1996; Khullar et al., 1998; Vervoort et al., 1998). Hydrophilic gels have been shown to produce near zero order drug release kinetics (Colombo et al., 1985; Möckel and Lippold, 1993; Hussain et al., 1994). Gums from natural sources hydrate and swell on contact with water and these have been used for the preparation of single unit dosage forms (Nakano and Ogata, 1984). The powdered drug is embedded uniformly in a matrix of the hydrogel and compressed to form a tablet, a production method that is relatively simple and cheap to perform.

It has been shown that drug release from hydrophilic matrices is a complex interaction be-

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tween swelling, diffusion and erosion (Harland et al., 1988; Peppas and Sahlin, 1989; Lee and Kim, 1991; Colombo et al., 1995; Reynolds et al., 1998). The gradual penetration of water produces swelling to form a hydrated gel through which the drug has to pass by dissolution and diffusion across the ever-increasing diffusional pathway length. Swelling has been shown to follow square root of time kinetics. However, drugs contained in certain systems are released at rates approaching zero order. It is apparent, therefore, that other mechanisms, in addition to diffusion, must take place at the interface between the gel and the surrounding medium. The polymer chains will gradually disentangle from the interface. This polymer chain relaxation will increase the rate of drug release by decreasing the diffusional path length for the drug. It is important, therefore, to try to quantify the degree of surface erosion from a swollen matrix surface interfacing with the aqueous dissolution medium. By determination and adjustment of the erosion rate from the matrix surface, drug release from a matrix system can be made to approach the desired zero order release for efficient oral controlled drug delivery.

Previous work has demonstrated that naturally occurring xanthan and karaya gums are useful hydrogels for producing a constant release of drugs in vitro (Sujja-areevath et al., 1998; Cox et al., 1999). The objective of this study was to determine the degree of hydration as well as gum and drug erosion by gravimetric means. By application of various mathematical models, it was possible to quantify the relative contributions of the diffusional and erosional mechanisms to the drug release process.

2. Materials and methods

2.1. Materials

Diclofenac sodium (D), xanthan gum (X) and karaya gum (K) (from Sterculia tree) were purchased from Sigma (St. Louis, USA). The mean particle size of the gums, determined by image analysis (Microscale, Cambridge, UK), was 252 and 60 μm for xanthan gum and karaya gum, respectively. The mean particle size of the diclofenac sodium was 12 μm. The moisture content of the gums, determined by the Karl Fischer method (Mitsubishi Moisture Meter CA-20, M. Kasei Corp., Japan), was xanthan 8.32% and karaya 17.19%. Caffeine (C) (mean particle size 68 μm) was sourced from BDH Laboratory Supplies (Poole, UK). Disodium hydrogen orthophosphate and sodium dihydrogen orthophosphate were obtained from BDH Ltd.

2.2. Preparation of matrix tablets

Matrices of pure xanthan and karaya gums weighing 400 ± 5 mg were compressed (relative humidity 55%) using a Manesty F3 single punch tablet machine (Manesty Machines Ltd., Liverpool, UK) and 9.5 mm flat bevelled edge punches producing matrix tablets 4.8 mm in height with a mean crushing strength of 71 ± 5.2 N (Erweka TBH 28 Tablet Hardness Tester, FRG). Under the same conditions further tablets containing xanthan gum and diclofenac sodium (ratios of gum:drug of 3:1 and 1:1) and xanthan gum and caffeine (same gum:drug ratios) were produced. A similar set of tablets using the two drugs at the same ratios were manufactured using karaya gum.

2.3. Hydration, erosion and drug release studies

The studies were carried out using the Erweka DT6 Dissolution Bath and Drive Control (Copley Instruments, Nottingham, UK) fitted with six rotating baskets. The dissolution medium used was phosphate buffer pH 6.5 (mixed) B.P. 1993 maintained at 37 ± 0.5°C by the constant temperature water bath. Two agitation speeds, 100 ± 1 and 25 ± 0.5 rpm, were used during the experiments. Each basket was thoroughly cleaned, accurately weighed and weighed again after insertion of a matrix tablet, so that the accurate weight of each tablet could be calculated. The baskets and tablets were then rotated in the dissolution medium and at regular time intervals (usually 0.5, 1, 2, 4, 6 and 8 h) a basket was detached, blotted with absorbant tissue to remove any excess medium on the basket surface and accurately weighed on a Mettler AE50 analytical balance (Mettler Instru-

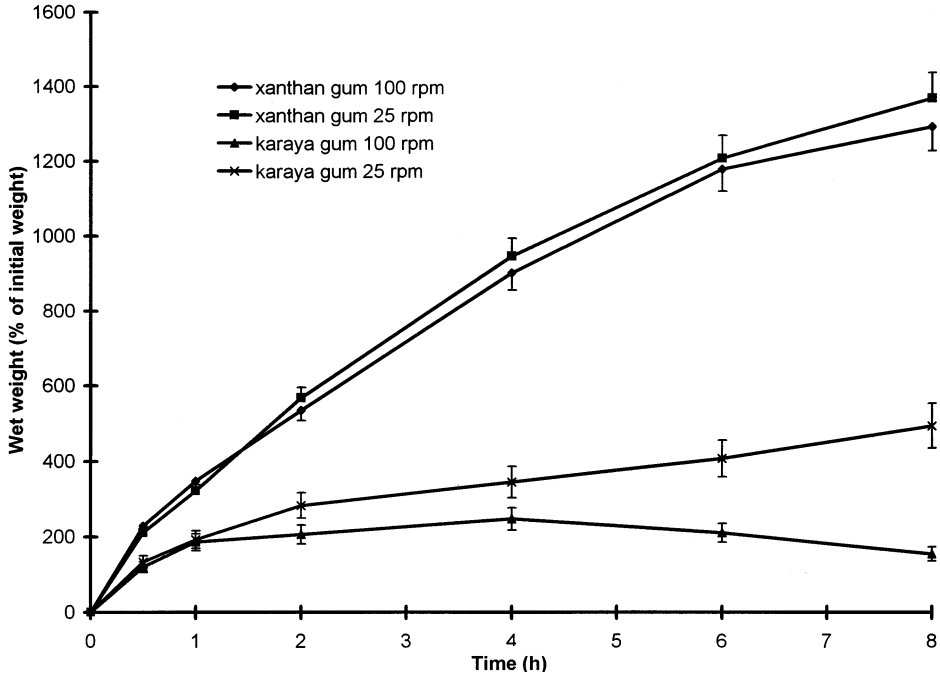

Fig. 1. Percentage increase in weight resulting from water uptake by the pure xanthan and karaya gum matrices at various time intervals (h) after contact with aqueous medium using two agitation speeds (mean values $\pm$ S.D., $n = 3$).

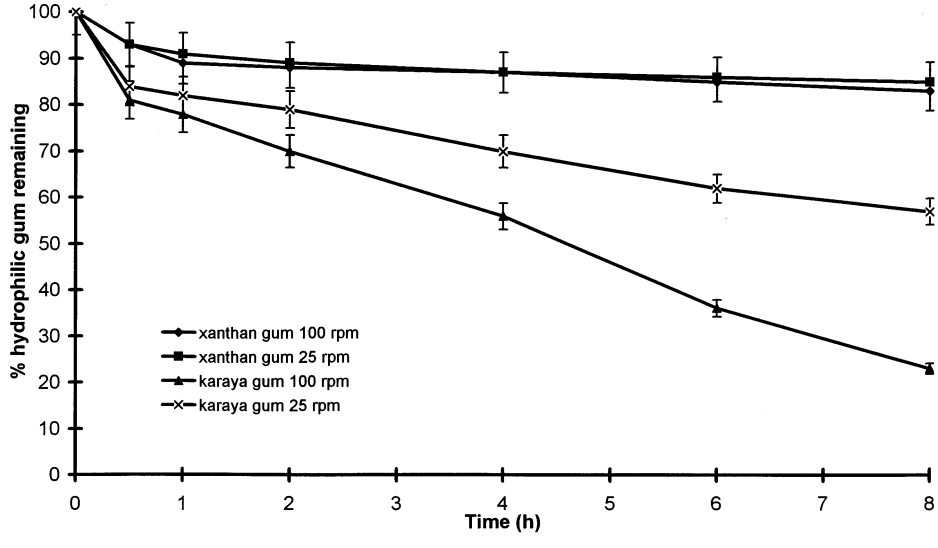

Fig. 2. Percentage of xanthan and karaya gums remaining in the pure matrices after relaxation of polymer strands in aqueous medium at various time intervals (h) using two agitation speeds (mean values $\pm$ S.D., $n = 3$).

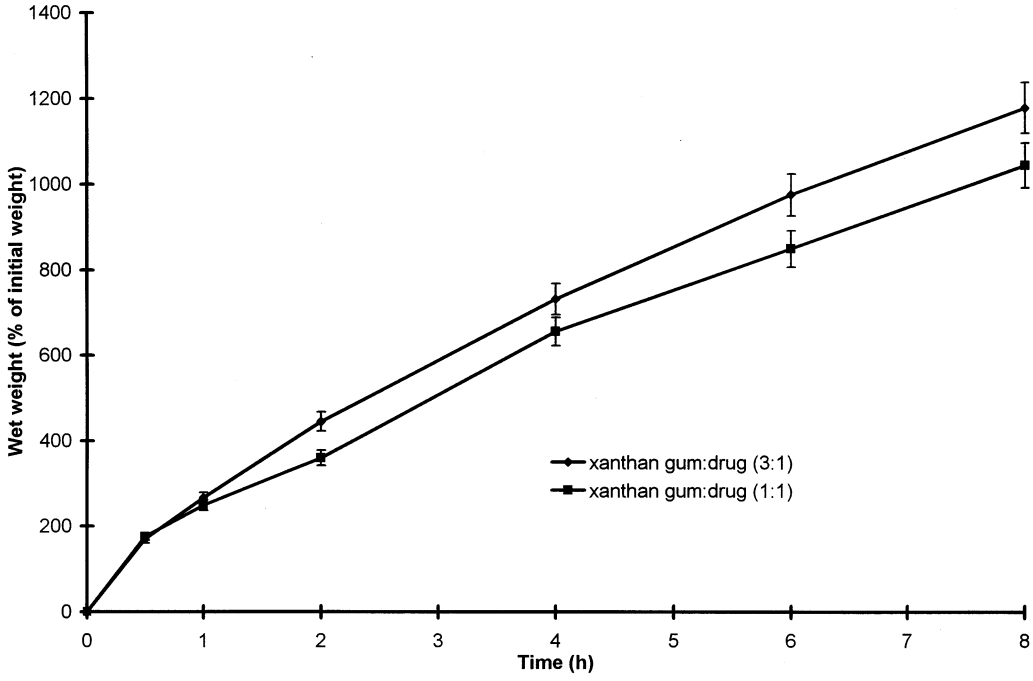

Fig. 3. Percentage increase in weight resulting from water uptake by xanthan gum/drug formulations (xanthan gum:drug, 3:1 and 1:1) at various time intervals (h) after contact with aqueous medium (mean values $\pm$S.D., $n = 3$).

ment Corp., Hightstown, NJ). After weighing, the hydrated matrices were then dried in an oven at 60°C for 18 h, cooled in a dessicator (silica gel) and the dried residue weighed. The heating–cooling–weighing process was repeated until constant weight was achieved. At the time of detachment of each basket, 5-ml samples of dissolution medium were withdrawn and an equivalent volume of medium at 37°C was added to maintain constant volume. Samples were filtered, diluted when necessary with phosphate buffer pH 6.5, mixed, and the UV absorbance of the diluted solutions measured using a Shimadzu UV-160 A recording spectrophotometer (Shimadzu Corp., Japan) at λ_{max} 275 nm for diclofenac sodium and λ_{max} 272 nm for caffeine. All studies were carried out in triplicate.

2.4. Data analysis

The drug release exponent (n), indicative of the mechanism of release, was calculated from the well-known power law expression derived by Korsmeyer et al. (1983), describing drug release from a polymeric matrix 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 and k is a constant incorporating the structural and geometrical characteristics of the release device. The values of n were obtained by linear regression analysis (values $\pm$95% confidence limits). A value of $n = 0.45$ indicates Case I (Fickian) diffusion or square root of time kinetics, $0.45 < n < 0.89$ indicates anomalous (non-Fickian) diffusion, $n = 0.89$ indicates Case II transport and $n > 0.89$ indicates Super Case II transport (Ritger and Peppas, 1987).

Drug release from delivery systems with surface erosion has also been analysed by Hopfenberg (1976), who proposed a model applicable to either a slab, cylinder or sphere showing heterogeneous

erosion

$$M_t/M_\infty = 1(1 - k_1 t)^n \quad (2)$$

where k_1 is equal to $k_0/C_0 r_0$, k_0 is the erosion rate constant, C_0 is the uniform initial concentration of drug in the matrix and r_0 is the initial radius of a sphere or cylinder, or the half-thickness for a slab. The n values are $n = 1$ for a slab, $n = 2$ for a cylinder and $n = 3$ for a sphere.

The above Hopfenberg equation assumes that drug release occurs from the primary surface area of the device only. However, when considering drug release from erodible tablets, the contribution of the flat surface ends (secondary surface area) cannot be neglected. Therefore, Katzhendler et al. (1997) derived a general model for drug release for surface-erodible matrices:

$$M_t/M_\infty = 1 - (1 - k_t C_0 a_0)^2(1 - 2k_2 t/C_0 b_0) \quad (3)$$

where k_1 and k_2 are, respectively, the radial and axial erosion rate constants and a_0 and b_0 the initial tablet radius and height. C_0 is the uniform initial concentration of the drug in the tablet matrix. The assumption is made that erosion is the rate-limiting step, with neither time-dependent diffusion processes nor matrix swelling having a significant impact on drug release.

Peppas and Sahlin (1989) have reported on the evaluation of the contributions provided by Fickian diffusion and matrix relaxation/erosion through the use of the following equation:

$$M_t/M_\infty = k_1 t^m + k_2 t^{2m} \quad (4)$$

where k_1 is the Fickian kinetic constant and k_2 is the relaxational/erosion rate constant.

Drug release data were fitted to Eq. (3) and Eq. (4) by the computer software package called CurveExpert 1.3 (SC, USA), a Windows®-based Shareware, a program designed to solve nonlinear regression problems.

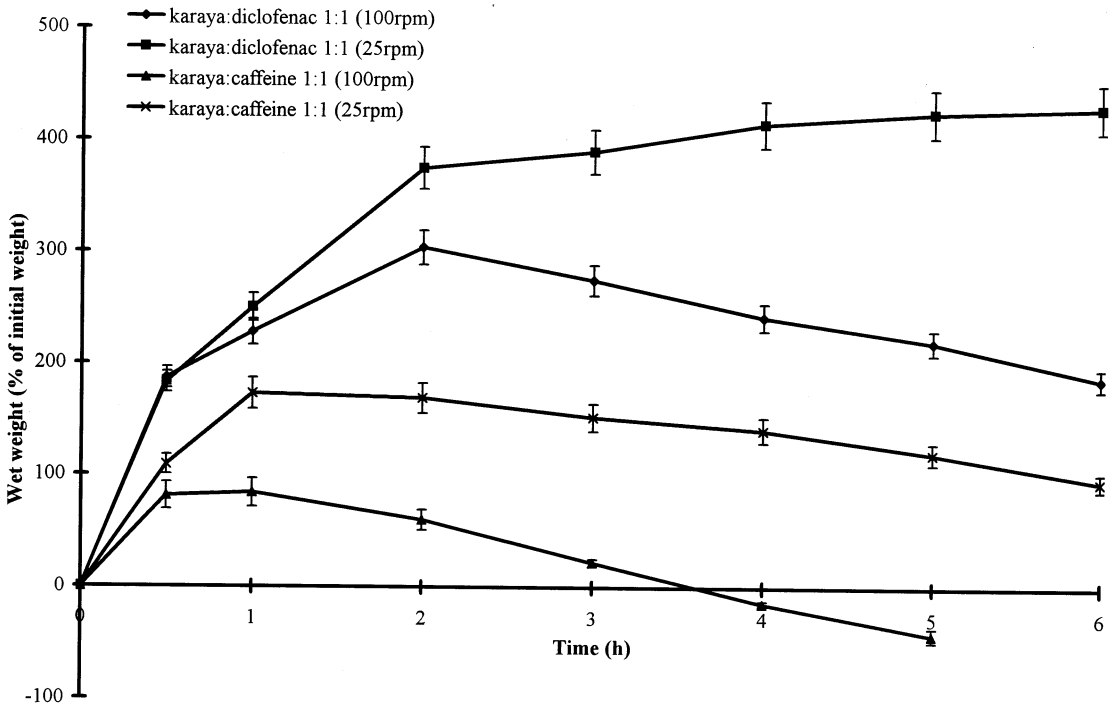

Fig. 4. Percentage variations (positive or negative) in weight resulting from submersion of karaya gum/drug formulations (karaya gum:drug, 1:1) in aqueous dissolution medium at various time intervals (h) using two agitation speeds (mean values $\pm$ S.D., $n = 3$).

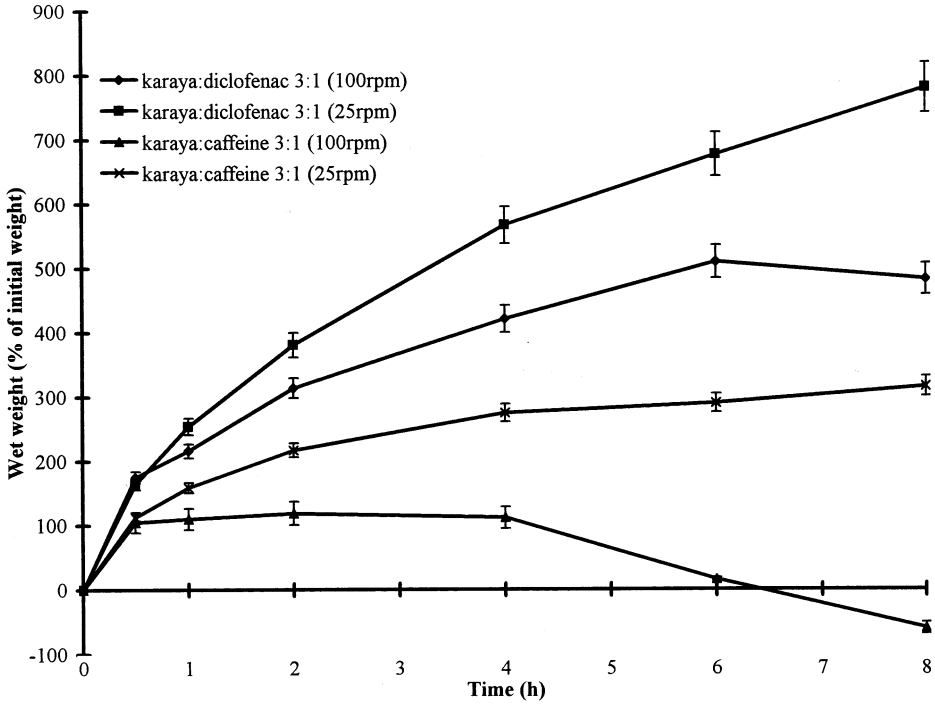

Fig. 5. Percentage variations (positive or negative) in weight resulting from submersion of karaya gum/drug formulations (karaya gum:drug, 3:1) in aqueous dissolution medium at various time intervals (h) using two agitation speeds (mean values $\pm$ S.D., $n = 3$).

3. Results and discussion

3.1. Hydration capacities and erosion

3.1.1. Pure gum matrices

The percentage increase in weight of the hydrated pure gum matrices at various time intervals up to 8 h are shown in Fig. 1. There is a strong degree of water uptake by the xanthan gum ($\approx$ 1300% weight increase after 8 h) but it is noteworthy that there is little difference in water uptake into the xanthan gum matrices at different agitation speeds ($< 10\%$ weight difference at 100 and 25 rpm after 8 h). Moreover, Fig. 2 shows that relatively few of the xanthan gum polymer strands become detached during the dissolution period, shown by the fact that $< 20\%$ of xanthan gum eroded during 8 h. Furthermore, there was a negligible difference in erosion rate at the two agitation speeds used. The large increase in weight was due to the very strong hydration capacity of xanthan gum coupled with very little simultaneous weight loss due to erosion. In contrast, karaya gum displayed a much lower increase in wet weight over the 8-h period (Fig. 1). Also, the agitation speed had a marked effect on the wet weight of the swollen material. After 8 h the gain in weight of the karaya gum matrix agitated at 100 rpm was only $\approx 154\%$, whereas at 25 rpm it was $\approx 494\%$. The rate of karaya gum erosion was also greatly influenced by agitation speed. Fig. 2 shows that only $\approx 23\%$ of the karaya gum material remained after 8 h at 100 rpm, whereas after the same time period at 25 rpm, the amount remaining was $\approx 57\%$. As erosion occurred quite readily from compressed karaya gum matrices highly influenced by agitation speed, it is clear that the weight difference with time was a measure of both the hydration and erosion processes occurring simultaneously. This is graphically demonstrated (Fig. 1) by the wet weight of the karaya gum matrix increasing initially to $\approx 250\%$ at 100 rpm after 4 h and then steadily decreasing to $\approx 154\%$ after 8 h. During the second half of

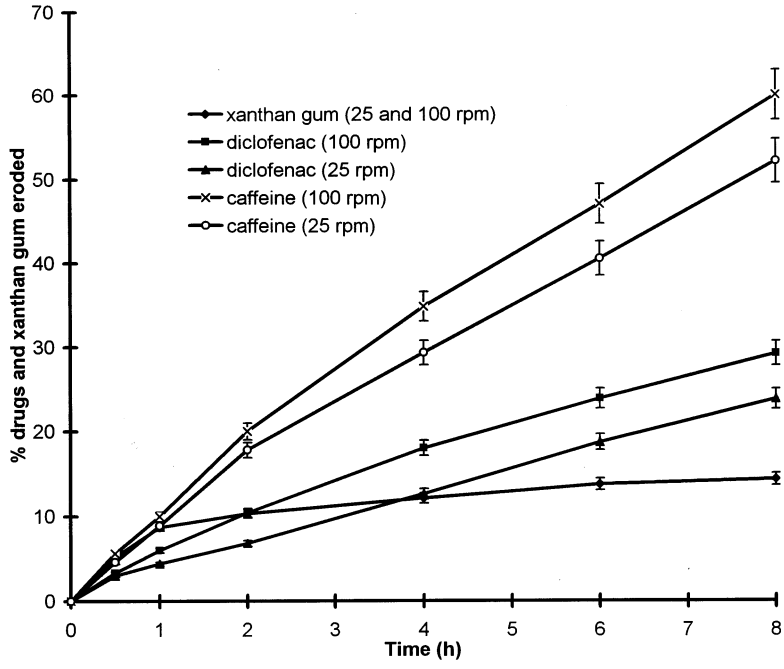

Fig. 6. Percentage of diclofenac sodium, caffeine and xanthan gum eroded into aqueous medium versus time (h) from xanthan gum/drug formulations (xanthan gum:drug, 3:1) using two agitation speeds (mean values $\pm$S.D., $n = 3$).

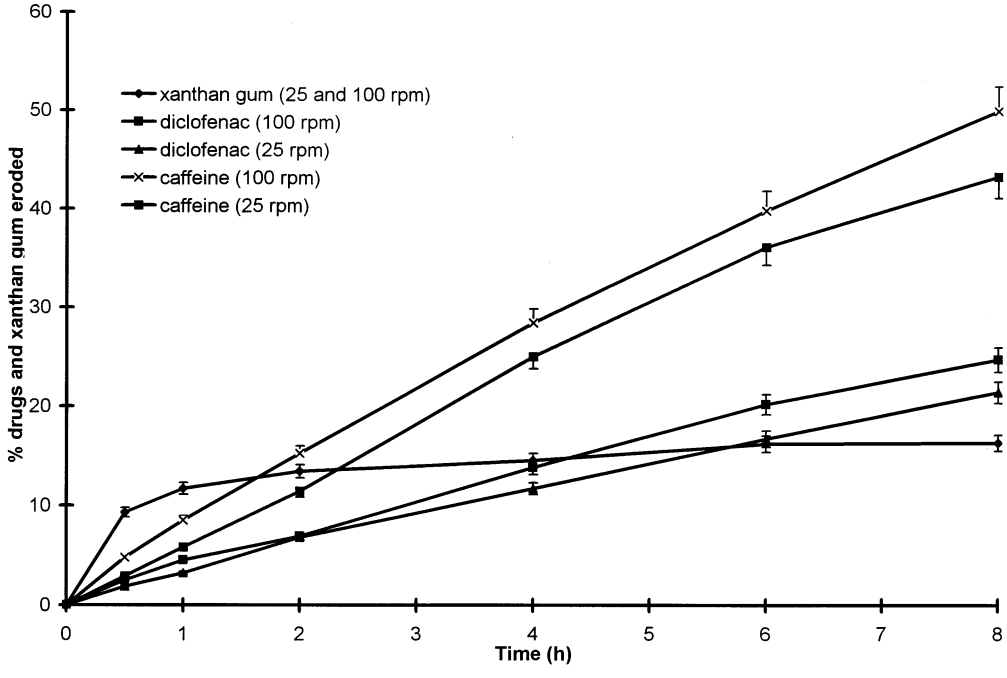

Fig. 7. Percentage of diclofenac sodium, caffeine and xanthan gum eroded into aqueous medium versus time (h) from xanthan gum/drug formulations (xanthan gum:drug, 1:1) using two agitation speeds (mean values $\pm$S.D., $n = 3$).

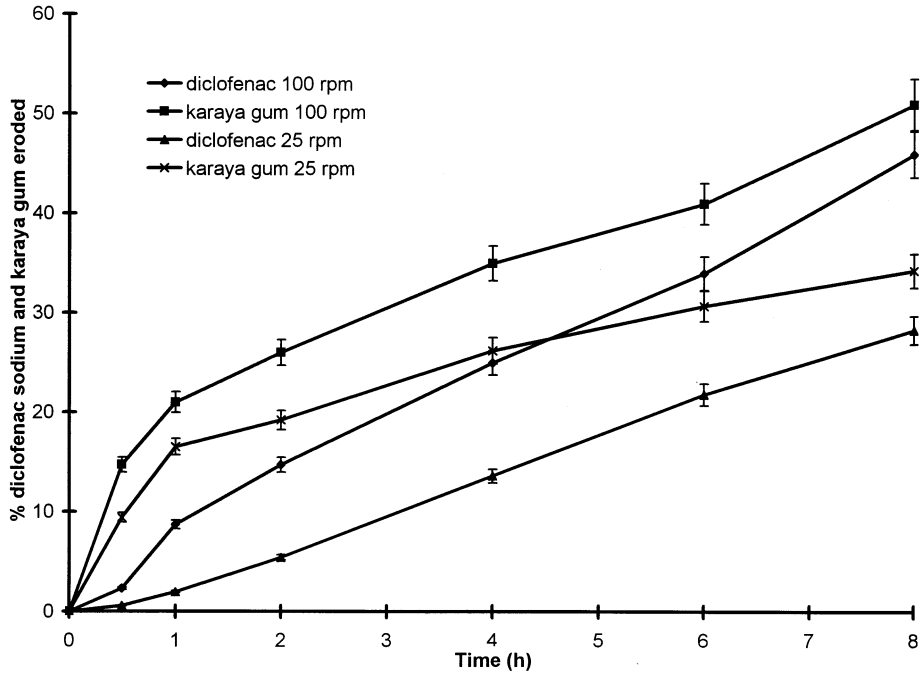

Fig. 8. Percentage of diclofenac sodium and karaya gum eroded into aqueous medium versus time (h) from karaya gum:diclofenac sodium 3:1 formulations using two agitation speeds (mean values $\pm$ S.D., $n = 3$).

the dissolution period, the erosion rate apparently exceeds the rate of water uptake with a consequent decrease in wet weight.

3.1.2. Gum/drug mixtures

In the case of xanthan gum matrices containing diclofenac sodium and caffeine separately in proportions of 3:1 and 1:1 of gum:drug respectively, there was no significant differences in weight gain (i.e. water uptake) between matrices containing the two different drugs as well as at the two different agitation speeds. The only significant differences in weight gain were shown for matrices containing different proportions of drug (see Fig. 3). Matrices containing a lower proportion of gum (1:1) showed a lower degree of weight gain with time. This is expected since the lower proportion of gum would decrease the ability of the matrix to absorb water. The dynamic balance between weight gain due to water uptake and weight loss due to gum erosion and drug dissolution is further illustrated by scrutiny of the profiles for karaya gum matrices (Figs. 4 and 5) containing diclofenac sodium and caffeine at both agitation speeds and at two levels of drug content. This is particularly significant at 1:1 gum:drug ratio levels at 100 rpm (Fig. 4). There is an initial rapid uptake of water by the dry matrices during the first 0.5–1 h, following which there is a levelling off of the wet weights due to the increasing rate of erosional release. This proceeds until the rate of erosion exceeds the rate of water uptake, with a resultant decrease in weight with time. Figs. 4 and 5 show significant differences in these profiles depending on the agitation speed as well as the proportion and the solubility of the drug (caffeine is about ten times more soluble than diclofenac sodium at pH 6.5). As expected, caffeine (the more soluble drug) was released much faster. The hydrated weight actually decreased below the initial weight of the dry matrices during the second half of the dissolution period at 100 rpm.

Profiles of xanthan gum erosion and drug release at different agitation speeds and gum:drug ratios are shown in Figs. 6 and 7. In each case there was an initial burst of xanthan gum erosion

from the dry matrices during the first hour but thereafter, the erosion of xanthan gum slowed considerably. It follows, therefore, that the hydrated xanthan gum network maintains its tight integrity with drug release by erosion and dissolution of the drug accounting for most of the weight loss during the remainder of the experimental time period. Furthermore, there is a greater burst of xanthan gum erosion in the formulation containing the lower proportion of xanthan gum (1:1 gum:drug ratio). The apparent reason for this being that the increased proportion of drug would further spatially separate the xanthan gum particles from each other. This would weaken the interparticulate adhesive forces between the dry gum particles resulting, therefore, in a greater degree of particle shedding during the first hour. Thereafter, hydration of the xanthan gum occurs when hydrogen-bonding forces maintain the integrity of the hydrophilic gum matrix during the remainder of the experimental time period.

Release profiles of diclofenac sodium and caffeine from matrices using karaya gum as the hydrophilic matrix (gum:drug ratio of 3:1) are shown in Figs. 8 and 9 respectively. In the case of tablets containing diclofenac sodium (Fig. 8), the percentage of karaya gum released was always greater than that of diclofenac sodium especially in the first half of the dissolution period. In the second half, there was a tendency of the profiles to converge suggesting that additional diclofenac sodium was being released, perhaps by enhanced erosion and diffusion. In Fig. 9, it is seen that although the percentage of karaya gum erosion is again faster initially, caffeine release speeds up greatly and in fact between 3 and 4 h actually exceeds the amount of gum erosion. The greater solubility of caffeine will account for this phenomenon. Moreover, the greater solubilty and release of caffeine from karaya matrices will reduce the integrity of the gum and accelerate the shedding of karaya gum particles into solution. Also of significance was the accelerating effect

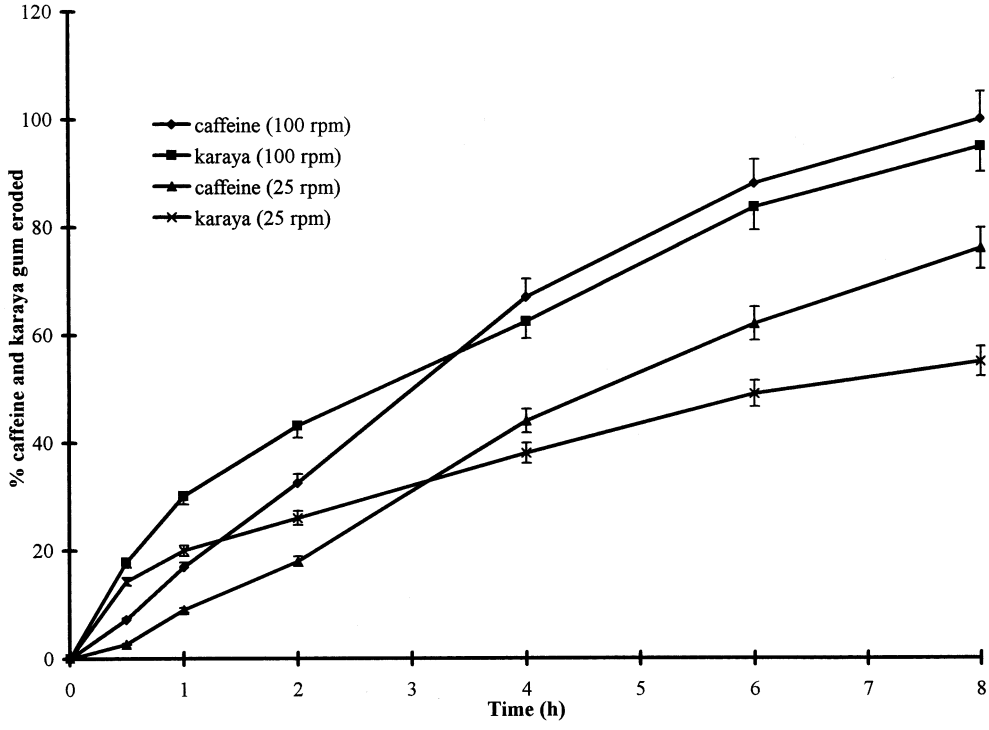

Fig. 9. Percentage of caffeine and karaya gum eroded into aqueous medium versus time (h) from karaya gum:caffeine 3:1 formulations using two agitation speeds (mean values $\pm$S.D., $n = 3$).

Table 1
Release parameters from hydrophilic gum matrices containing diclofenac sodium, caffeine, xanthan gum and karaya gum[a]

Matrix composition*	Agitation speed (rpm)	Drug release exponent (n)	Correlation coefficient (r)	Karaya gum† erosion exponent (n)	Correlation coefficient (r)	Drug release rate (% h^{-1})	Correlation coefficient (r)	Gum†† erosion rate (% h^{-1})	Correlation coefficient (r)
X:D 3:1	100	0.786 ($\pm$0.031)	0.999	–	–	3.302 ($\pm$0.073)	0.996	0.795 ($\pm$0.059)	0.975
	25	0.759 ($\pm$0.082)	0.995	–	–	2.821 ($\pm$0.058)	0.999	–	–
X:D 1:1	100	0.833 ($\pm$0.055)	0.998	–	–	2.984 ($\pm$0.067)	0.997	0.649 ($\pm$0.078)	0.955
	25	0.885 ($\pm$0.064)	0.999	–	–	2.556 ($\pm$0.023)	0.998	–	–
X:C 3:1	100	0.859 ($\pm$0.052)	0.999	–	–	7.001 ($\pm$0.121)	0.997	–	–
	25	0.866 ($\pm$0.029)	0.998	–	–	6.018 ($\pm$0.158)	0.998	–	–
X:C 1:1	100	0.852 ($\pm$0.040)	0.999	–	–	5.943 ($\pm$0.223)	0.998	–	–
	25	0.998 ($\pm$0.053)	0.999	–	–	5.503 ($\pm$0.198)	0.994	–	–
K:D 3:1	100	0.995 ($\pm$0.068)	0.980	0.423 ($\pm$0.025)	0.995	5.037 ($\pm$0.243)	0.999	4.017 ($\pm$0.212)	0.997
	25	1.064 ($\pm$0.095)	0.997	0.437 ($\pm$0.047)	0.984	3.993 ($\pm$0.162)	0.999	2.912 ($\pm$0.174)	0.992
K:D 1:1	100	1.053 ($\pm$0.019)	0.995	0.540 ($\pm$0.084)	0.997	13.008 ($\pm$0.875)	0.997	10.266 ($\pm$0.651)	0.994
	25	1.089 ($\pm$0.020)	0.996	0.518 ($\pm$0.072)	0.998	9.020 ($\pm$0.553)	0.997	7.049 ($\pm$0.546)	0.987
K:C 3:1	100	0.956 ($\pm$0.069)	0.995	0.593 ($\pm$0.086)	0.998	14.466 ($\pm$1.128)	0.994	10.515 ($\pm$0.623)	0.999
	25	1.049 ($\pm$0.118)	0.991	0.489 ($\pm$0.059)	0.998	10.898 ($\pm$0.870)	0.997	5.814 ($\pm$0.481)	0.999
K:C 1:1	100	0.910 ($\pm$0.073)	0.980	0.538 ($\pm$0.079)	0.997	19.860 ($\pm$2.136)	0.995	16.190 ($\pm$1.166)	0.992
	25	1.141 ($\pm$0.064)	0.996	0.537 ($\pm$0.069)	0.994	12.140 ($\pm$0.894)	0.994	9.654 ($\pm$0.752)	0.996

[a] The release exponents were derived using Eq. (1) and the release rates (% h^{-1}) from the linear regression slopes of the release profiles (mean $\pm$ S.D., $n = 3$).
* X, xanthan gum; D, diclofenac sodium; K, karaya gum; C, caffeine.
† As the amount of xanthan gum eroded was <20% in each case, calculation of an erosion exponent for this gum was not appropriate.
†† Differences in xanthan gum erosion rates using both drugs at the two agitation speeds were insignificant.

Table 2
Drug release kinetic data from xanthan gum (X) formulations derived using various mathematical models (Eq. (2), Eq. (3) and Eq. (4)) (D, diclofenac sodium; C, caffeine)[a]

Model $M_t/M_\infty =$	Matrix composition	Agitation speed (rpm)	k_1	k_2	r	S
$1-(1-k_1t)^2$	X:D 3:1	100	0.0213	–	0.9910	0.0149
		25	0.0162	–	0.9966	0.0073
	X:C 3:1	100	0.0466	–	0.9987	0.0116
		25	0.0391	–	0.9979	0.0127
	X:D 3:1	100	0.0172	–	0.9973	0.0069
		25	0.0146	–	0.9980	0.0052
	X:C 1:1	100	0.0374	–	0.9991	0.0082
		25	0.0320	–	0.9984	0.0096
$1-(1-k_1t/C_0a_0)^2(1-2k_2t/C_0b_0)$	X:D 3:1	100	0.0186	0.0091	0.9922	0.0150
		25	0.0136	0.0075	0.9969	0.0075
	X:C 3:1	100	0.0409	0.0218	0.9993	0.0090
		25	0.0342	0.0149	0.9986	0.0112
	X:D 1:1	100	0.0314	0.0134	0.9977	0.0069
		25	0.0260	0.0117	0.9983	0.0051
	X:C 1:1	100	0.0686	0.0308	0.9996	0.0060
		25	0.0554	0.0290	0.9986	0.0098
$k_1t^m+k_2t^{2m}$	X:D 3:1	100	0.0215	0.0408	0.9994	0.0042
		25	0.0028	0.0384	0.9989	0.0045
	X:C 3:1	100	0.0138	0.0951	0.9996	0.0072
		25	0.0118	0.0822	0.9995	0.0068
	X:D 1:1	100	0.0011	0.0418	0.9991	0.0044
		25	0.0001	0.0385	0.9997	0.0020
	X:C 1:1	100	0.0199	0.1228	0.9999	0.0034
		25	0.0041	0.0825	0.9980	0.0116

[a] r, correlation coefficient; S, standard error of the estimate $= \sqrt{(\Sigma_{i=1}^{n_{\text{points}}}(y_i-f_i(x_i))^2)/(n_{\text{points}}-n_{\text{param}})}$, where y_i and x_i denote the experimental and calculated fractions of drug released respectively, n_{param} is the number of parameters in the particular model and n_{points} is the number of data points.

that agitation speed has on both karaya gum and drug release in all cases. A similar pattern of drug and gum release from matrices containing karaya gum:drug in the ratio of 1:1 was obtained. The profiles are not shown for the sake of brevity. In contrast to matrices containing xanthan gum, karaya gum formulations containing a greater proportion of drug (K:drug 1:1) showed much higher rates of drug release and gum erosion.

3.2. Drug release kinetics

It is important to note that drug release approaching zero order kinetics was achieved during the dissolution period of 8 h. The release exponents (n values) using Eq. (1) and release rates are given in Table 1. Scrutiny of Table 1 shows that for xanthan gum matrices containing the two drugs, the drug release exponents (n values) ranged from 0.759 ($\pm$ 0.082) (X:D 3:1 25 rpm) to 0.998 ($\pm$ 0.058) (X:C 1:1 25 rpm). The percentage of drug released per hour was calculated from the slopes of the lines obtained by linear regression of the percentage drug release versus time data. It is clear that a slower agitation speed (25 rpm) produced a decreased drug release rate, but without significantly influencing the xanthan gum erosion rate. Moreover, caffeine (the more soluble drug) was released at a much greater rate than diclofenac sodium (poorly soluble at pH 6.5). A further characteristic of the xanthan gum matrices was that when the proportion of drug was increased (X:drug 1:1 formulations), the rate of drug release decreased, even though the actual amount of drug

released was higher. Due to the much greater water solubility of caffeine at pH 6.5, caffeine release takes place by rapid dissolution of the drug from the outer surface of the gel exposed to the medium, as well as by diffusion of the dissolved drug through the xanthan gum gel. This process is enhanced by the creation of channels and pores by the vacating drug particles. On the other hand, diclofenac sodium is less soluble and therefore, the release of this drug would be much slower. Initially (0–1 h) there would be 'burst' erosional release of diclofenac sodium from the outer surfaces of the pre-hydrated matrix followed by a slower rate of erosional release and some drug diffusion through the swollen gel.

The drug release exponents for karaya gum matrices (Table 1) display zero-order (Case II) to Super Case II release kinetics (ranging from 0.910 to 1.141). Table 1 also shows both the drug release rate and the karaya gum erosion rate from karaya gum formulations containing diclofenac sodium and caffeine. These values were, as in the case of the xanthan gum formulations, calculated from the slopes of the linear regression lines of the percentage release against time (h) profiles. As a result of the normal tendency for 'burst' release to occur, the first point at 0.5 h was omitted in calculating these release and erosion rates.

3.3. Evaluation of drug release mechanism using various kinetic models

The Hopfenberg equation (Eq. (2)) assumes that the surface erosion process is the rate-limiting

Table 3
Drug release kinetic data from karaya gum (K) formulations derived using various mathematical models (Eq. (2), Eq. (3) and Eq. (4)) (D, diclofenac sodium; C, caffeine)[a]

Model $M_t/M_\infty =$	Matrix composition	Agitation speed (rpm)	k_1	k_2	r	S
$1-(1-k_1t)^2$	K:D 3:1	100	0.0330	–	0.9970	0.0134
		25	0.0186	–	0.9943	0.0118
	K:C 3:1	100	0.1039	–	0.9977	0.0274
		25	0.0619	–	0.9959	0.0274
	K:D 1:1	100	0.0729	–	0.9904	0.0375
		25	0.0405	–	0.9780	0.0363
	K:C 1:1	100	0.1786	–	0.9983	0.0237
		25	0.0752	–	0.9962	0.0238
$1-(1-k_1t/C_0a_0)^2(1-2k_2t/C_0b_0)$	K:D 3:1	100	0.0888	0.0237	0.9973	0.0136
		25	0.0293	0.0143	0.9977	0.0080
	K:C 3:1	100	0.0961	0.0441	0.9984	0.0244
		25	0.0823	0.0332	0.9980	0.0205
	K:D 1:1	100	0.5305	0.1366	0.9984	0.0168
		25	0.1268	0.0595	0.9915	0.0244
	K:C 1:1	100	0.6125	0.0638	0.9986	0.0235
		25	0.3746	0.0714	0.9980	0.0184
$k_1t^m+k_2t^{2m}$	K:D 3:1	100	0.0504	0.1597	0.9980	0.0116
		25	0.0464	0.0767	0.9995	0.0037
	K:C 3:1	100	0.0632	0.2840	0.9942	0.0471
		25	0.0290	0.1657	0.9976	0.0227
	K:D 1:1	100	0.1280	0.4417	0.9987	0.0148
		25	0.1147	0.4161	0.9974	0.0135
	K:C 1:1	100	0.1331	0.3176	0.9919	0.0565
		25	0.0651	0.2002	0.9977	0.0197

[a] r, Correlation coefficient; S, standard error of the estimate $= \sqrt{(\Sigma_{i=1}^{n_{\text{points}}}(y_i-f_i(x_i))^2)/(n_{\text{points}}-n_{\text{param}})}$, where y_i and x_i denote the experimental and calculated fractions of drug released respectively, n_{param} is the number of parameters in the particular model and n_{points} is the number of data points.

step and ignores the contribution of the secondary surface area (flat surface ends) to the erosion process. The only implication of applying the dissolution data to the Hopfenberg equation is that it is seen (Tables 2 and 3) that the erosion rate constant (k_1) is influenced by the agitation speed. In each case — irrespective of the gum type, nature of the incorporated drug and the gum:drug ratio — an agitation speed of 100 rpm produced a greater k_1 value compared with 25 rpm. This simply means that the greater the agitation speed, the greater the erosion rate.

In the equation derived by Katzhendler et al., 1997 (Eq. (3)), which is an extension of the Hopfenberg model, account is taken of the different radial (k_1) and vertical (k_2) erosion rate constants of the tablets. This means that the contribution of the flat ends (secondary surface area) and the lateral surfaces (primary surface area) of the cylindrical tablets are considered. The application of this equation shows that radial erosion rates (k_1 values) are always greater than vertical erosion rates (k_2 values). In the case of the X:drug formulations $k_1 \approx 2k_2$, whereas with K:drug formulations $k_1 > 2k_2$ in some cases. This implies that there are different gel properties in the radial and vertical directions and that erosional drug release occurs at a higher rate from the two flat ends compared with the lateral surfaces of these matrices. It is also demonstrated from the application of this model derived by Katzhendler et al. that a decrease in agitation speed from 100 to 25 rpm resulted in a decrease in both the radial (k_1) and vertical (k_2) erosion rate constants. This is consistent with the results obtained from the application of the Hopfenberg equation discussed earlier.

The Peppas and Sahlin equation (Eq. (4)) can be applied irrespective of the dosage form geometry. The first term of the right hand side of the equation is the Fickian contribution, while the second term is the Case II relaxational contribution. The coefficient m is the purely Fickian diffusion exponent for the device. For matrices of these dimensions, the value for m was 0.43 calculated from the aspect ratio. The k_1 and k_2 values in Tables 2 and 3 show that in every case k_2 values are considerably greater than k_1 values, implying that the relaxational contribution is the major factor contributing to drug release.

In conclusion, each gum demonstrated different abilities to hydrate and erode on contact with water. Both gums were capable of producing near zero order drug release by erosion and diffusion mechanisms, although the contribution of these mechanisms varied considerably depending on gum type, drug solubility, drug proportion and agitation speed. The erosion mechanism appeared to play a dominant role in drug release.

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