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Xanthan and galactomannan (from *M. scabrella*) matrix tablets for oral controlled delivery of theophylline

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Abstract

Directly compressed theophylline tablets, containing commercial xanthan (X) (Keltrol®) and a highly hydrophilic galactomannan (G) from the seeds of *Mimosa scabrella* (a brazilian leguminous tree called bracatinga) as release-controlling agents, were obtained. Gums were used at 4, 8, 12.5 and 25% (w/w), either alone or in mixture (X:G 1:1). During galactomannan extraction process, the biopolymer was dried in a scale up, by vacuum oven (VO) or spray dryer (SD). The in vitro drug release was evaluated at different time intervals during 8 h using apparatus 1 (USP 26) at 100 rpm. The pH of the dissolution medium (1.4) was changed to 4.0 and 6.8 after 2 and 3 h, respectively. Tablets containing G(SD) resulted in more uniform drug release than G(VO) ones, due to their smaller particle size. The drug release decreased with the increase of polymer concentration and all formulations at 25% w/w of gums showed excessive sustained release effect. The matrices made with alone X showed higher drug retention for all concentrations, compared with G matrices that released the drug too fast. The XG matrices were able to produce near zero-order drug release. The XG(SD) 8% tablets provided the required release rate (about 90% at the end of 8 h), with zero-order release kinetics. Tablets containing G(VO) in low concentration showed a complete erosion, while the others demonstrated fast hydration and swelling in contact with the dissolution medium. The release mechanism was a combination of difusion and relaxation. The relative importance of these two processes varied with matrix composition. The XG(SD) 8% matrix showed higher contribution of polymer relaxation.

Keywords: Xanthan; Galactomannan; Hydrophilic matrices; Theophylline

1. Introduction

The use of biopolymeric matrix devices to control the release of a variety of therapeutic agents has

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become important in the development of modified release dosage forms (Bhardwaj et al., 2000; Billa and Yuen, 2000; Munday and Cox, 2000; Talukdar et al., 1998).

Xanthan (X) is a commercial hydrophilic polymer, secreted from *Xanthomonas campestris* (Nürnberg and Retting, 1974). In earlier studies, the performance of xanthan gum as a potential excipient for oral controlled release tablet dosage forms was thoroughly evaluated and characterized by in vitro tests (Cox et al., 1999; Munday and Cox, 2000; Sujja-areevath et al., 1998; Talukdar and Kinget, 1997; Talukdar et al., 1998). Hydrophilic gels have been shown to produce near zero-order drug release kinetics (Colombo et al., 1985; Mockel and Lippold, 1993). Sujja-areevath et al. (1998) observed that Fickian diffusion was dominant during the first half of the dissolution period of Diclofenac Sodium mini-matrices with xanthan gum of different ratios, while erosion predominates during the latter half, facilitating an approach toward zero-order release. Xanthan solutions have high intrinsic viscosity and a pronounced pseudoplastic flow at relatively low concentrations. Although xanthan solutions exhibit weak gel-like properties at low shear rates, which makes it suitable as a suspending agent, it does not form true gels at any concentration or temperature (Milane and Wang, 1990).

Seed galactomannans have a typical chemical structure, with a (1 → 4) linked β-D-mannopyranosyl (Man) backbone substituted in varying degrees at O-6 with single unit α-D-galactopyranosyl (Gal) residues (Dea and Morrison, 1975). In simple aqueous systems, they are effective thickeners, a property that is essentially controlled by molecular size, and when associate with other polysaccharides such as xanthan, they can produce gel (Morris et al., 1977). The level and distribution of galactose plays an important role in gel formation (Bresolin et al., 1997, 1999). Commercially galactomannans of guar gum (*Cyamopsis tetragonolobus* L. Taub, Man:Gal 2:1), locust bean gum (*Ceratonia siliqua*, Man:Gal 2:1) and tara (*Caesalpinea spinosa*, Man:Gal 3:1) are used (Maier et al., 1993).

Guar gum at high concentrations, on exposure to dissolution fluids, gets hydrated and forms a viscous gel layer that slows down further seeping-in of dissolution fluids towards the core of the matrix tablet (Krishnaiah et al., 1998). This polymer has been studied as a controlled release agent (Baveja et al., 1991; Dürig and Fassihi, 2002; Khullar et al., 1998; Krishnaiah et al., 2002; Nürnberg and Retting, 1974) and as a carrier for colon-specific drug delivery based on degradation of polygalactomannnans by colonic bacterial enzymes (Krishnaiah et al., 1999). Recently, Üner and Altinkurt (2004) evaluated honey locust gum (HLG), the galactomannan from the seeds of *Gleditsia triacanthos* (with a Man:Gal ratio about 3:1), as a hydrophillic matrix in theophylline tablets and showed no significant difference between commercial sustained release tablet and 10% HLG tablet.

Between the galactomannans of native Brazilian species under investigation (Ganter et al., 1993, 1995), there is the *Mimosa scabrella* Bentham, known as bracatinga, of the *Mimosaceae* family. Its seeds provided 20–30% of galactomannan (G) with a Man:Gal ratio of 1.1:1 (Ganter et al., 1992).

A drug delivery tablet system of xanthan and locust bean gum, commercially known as TIMERx®, was developed by Penwest Pharmaceuticals Company (Baichwall and Neville, 2002). The system is based on the synergistic interaction of heteropolysaccharides (1:1 at 50% concentration), which in the presence of dextrose (50%), form a strong binder gel in water. The in vitro and in vivo controlled release potential of this system has been demonstrated (Staniforth and Baichwall, 1993; McCall and Baichwall, 1994).

In this context, reports from our laboratory using X:G (*M. scabrella*) (2:1) gel and diclofenac sodium tablets and capsules (16:1 gum:drug ratio), prepared by the wet granulation technique, showed a very slow drug delivery (78.6 and 35.1% of drug after 24 h for capsules and tablets, respectively), probably due to excessive polymer amount and previous gel formation during the granulation process. Analysis of release data indicates a rather zero-order drug release, with the erosion mechanism playing a dominant role (Ughini et al., 2004).

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 drug release mechanisms from theophylline tablets produced with commercial xanthan (X) and the highly hydrophilic galactomannan (G) from the seeds of *M. scabrella* Bentham. Different concentrations of gums, alone (X or G) or in physical mixture (XG 1:1), were tested to evaluate their performance as release-controlling agents.

2. Materials and methods

2.1. Materials

Theophylline (97–102% assay) was purchased from All Chemistry (China, batch S991209). Lactose monohydrate was purchased from Gerbrás (Germany, batch 1073) and xanthan gum was purchased from Kelko (Merck), both being of Pharmacopoeia quality (USP 26 2003). *M. scabrella* Bentham, Argentina variety, seeds were obtained from EMATER (Empresa Paranaense de Assistência Técnica e Extensão Rural, Bocaiúva do Sul-PR, Brazil).

2.2. Extraction and analysis of galactomannan

The milled seeds of *M. scabrella* were boiled in water for 10 min for enzymatic inactivation. The galactomannan was obtained by water extraction during 4 h under mechanical stirring at 30 °C. The dispersion was filtered through phytoplancton cloth (nylon membrane with 25 μm pores) and the filtrate was precipitated with ethanol 50% (v/v). The precipitate was washed in a gradient of ethanol (70–100%, v/v) and dried by vacuum oven (VO) (model MA 030, Marconi) at 30 °C or in spray dryer (SD) (model SD 05, Lab Plant). The spray dryer system consists of an apparatus with an inlet temperature of 160 °C and an outlet temperature of 85 °C, pump speed of 600 mL/h, compression of 1.5 bar and air flow of 40 m^3/h.

The Man:Gal ratio (M:G) was confirmed by gas liquid chromatography (GLC), as described previously (Ganter et al., 1992), using a SII HP Gas chromatograph (model 5890) at 220 °C (free induction decay and injector temperature, 250 °C) with DB-225 capillary column (0.25 mm i.d. × 30 m) and nitrogen as carrier gas.

The intrinsic viscosity $[\eta]_{25}$ was determined by means of a capillary viscosimeter (Cannon Fenske, n. 50) in the Newtonian regimen (Ganter et al., 1992).

Particle size analysis of powders (both galactomannan and xanthan) was carried out on a vibratory sieve shaker (Retsch Vibro, Haan, Germany) using 500, 355, 250, 180, 125, 90, 63, 45, 38 μm calibrated sieves (Cisa, Barcelona, Spain).

The loss on drying was determined using an infrared moisture analyzer (model LJ16, Mettler Toledo, Greifensee, Switzerland) until constant weight.

2.3. Preparation and analysis of tablets

Matrix granules of theophylline and lactose were prepared by the wet granulation method. The different quantities of lactose (Table 1) were mixed with theophylline and wet with ethanol 70%. The wet mass was passed through a mesh (<850 μm) and dried at 25 °C for 2 h. The dried granules were sieved (<500 μm) for further incorporation of polymers. The X and G (SD or VO), alone or in mixture (1:1), were diluted with previous formulations (drug + lactose granules) to a ratio of 8, 12.5 and 25% of each polymer and blended in a V mixer (model MA20, Marconi®, São Paulo, Brazil) for 20 min.

The final powder mixtures were found to have poor flow properties, with a Carr Index of 24–46. Values below 15 can indicate an excellent flow, however, powders with values above 20–30 will present a weakened flow (The Pharmaceutical Codex, 1994).

Flat-faced tablets of 200 mg weight, 6 mm diameter and average hardness >45 N were compressed using a rotative tabletting machine (model 2000 10 PSC, Lawes, São Paulo, Brazil), at a speed of 5 rpm. The hardness and friability of tablets were measured in a Hardness Tester (model TBH 20, Erweka, Heusenstamm, Germany) and friabilometer (model TA 20, Erweka, Heusenstamm, Germany), respectively. The drug content uniformity of batches (10 units tablets) was analysed in a spectrophotometer (model UVPC 1601, Shimadzu, Tokyo, Japan), in a 1 cm quartz cell, at 268 nm (USP 26 2003). Each one of 10 tablets was transferred to a 100 mL volumetric flask and dissolved with pH 1.4 buffer. The solution was sonicated for 2 h to ensure complete solubility of the drug, filtered, diluted to volume with the same solvent and the absorbance was read using the solvent as blank.

2.4. Water uptake and erosion determination

Measurement of hydration and erosion rates of XG(SD) 8% were carried out, after the immersion of the tablets in the test medium (Efentakis and Loutlis, 2001), to relate the observed phenomena of drug release with the rates of polymer hydration. Weighed tablets were placed in the baskets of the dissolution apparatus rotating at 50 rpm, with the dissolution medium of phosphate buffer pH 6.8 at 37 ± 0.5 °C. After 0.5, 1, 2, 3, 4, 5, 6 and 7 h, each dissolution basket con-

Table 1
Composition (%) and analysis of theophylline (100 mg) tablets (200 mg)

Formulations	Lactose (mg)	Xanthan (mg)	Galactomannan (mg)	Hardness (N) ± S.D.	Friability (%)	% Assay (R.S.D.)
XG(SD) 8%	84	8	8	111.7 ± 28.9	0.3	95.8 (0.8)
XG(VO) 8%	84	8	8	98.1 ± 16.6	0.2	97.4 (1.3)
XG(SD) 12.5%	75	12.5	12.5	143.1 ± 22.8	0.1	95.6 (1.6)
XG(VO) 12.5%	75	12.5	12.5	148.0 ± 13.1	0.2	94.5 (1.6)
XG(SD) 25%	50	25	25	127.7 ± 40.6	0.3	95.5 (1.8)
XG(VO) 25%	50	25	25	132.2 ± 30.6	0.2	93.6 (1.8)
X 4%	92	8	–	45.8 ± 6.3	Capping	100.4 (1.4)
X 8%	84	16	–	123.4 ± 23.4	0.2	96.2 (0.9)
X 12.5%	75	25	–	127.9 ± 17.5	0.1	94.9 (1.7)
X 25%	50	50	–	158.1 ± 25.5	0.1	93.6 (1.1)
G(SD) 8%	84	–	16	79.1 ± 23.4	Capping	99.2 (1.7)
G(SD) 12.5%	75	–	25	110.3 ± 43.3	Capping	97.5 (1.0)
G(SD) 25%	50	–	50	79.3 ± 52.6	Capping	94.6 (2.5)
Control[a]	75	12.5	12.5	115.2 ± 18.9	0.2	–

[a] Absence of theophylline; S.D. = standard deviation; R.S.D. = relative standard deviation; values of hardness and friability are mean of 10 determinations.

taining the sample was withdrawn, blotted to remove excess water and weighed on a analytical balance (model AG 204, Mettler-Toledo, Greifensee, Switzerland). The wet samples (basket + sample) were then dried in an oven at 110–120 °C for 24 h time period, allowed to cool in a desicator and finally weighed until constant weight was achieved (final dry weight). The experiment was performed in triplicate for each time point and fresh samples were used for each individual time point.

The increase in weight due to absorbed liquid (Q) was estimated at each time point from the following equation:

$$Q = \frac{100\ (W_w - W_f)}{W_f} \quad (1)$$

where W_w is the mass of the hydrated sample before drying and W_f the final weight of the same dried and partially eroded sample. The percentage erosion (E) was estimated from the following equation:

$$E = \frac{100(W_i - W_f)}{W_f} \quad (2)$$

where W_i is the initial dry sample weight.

2.5. In vitro analysis

The dissolution test was carried out using apparatus 1 USP (model DT 80, Erweka, Heusenstamm, Germany) at 100 rpm. In order to reproduce digestive physiological phases, 900 mL of dissolution medium with different pH environments at 37 ± 0.5 °C was performed. The dissolution medium consists of a mixture of 50 mM hydrochloric acid, 50 mM glacial acetic acid and 50 mM phosphoric acid (pH 1.4). After 1 h, the pH was increased to 4.0 and, 2 h later, to pH 6.8, both by the addition of drops of 20 M sodium hydroxide (Webster, 1999). At suitable intervals, samples were withdrawn, filtered, neutralized at pH 6.8, diluted when necessary with buffer pH 6.8 and analyzed spectrophotometrically (model UVPC 1601, Shimadzu, Tokyo, Japan) at 268 nm. Studies were performed in triplicate and the mean cumulative percentage of drug calculated (±S.D.) and plotted against time. During the drug release studies, all the formulations were observed for physical integrity at different time.

2.6. Drug release kinetics

Data from the in vitro drug release were analyzed by different equations and kinetic models in order to evaluate the release mechanism of theophylline from the matrices. The software SPSS version 10.0 were used. The kinetic models used were:

(a) Korsmeyer and Peppas model (Korsmeyer and Peppas, 1981):

$$\frac{M_t}{M_\infty} = kt^n \quad (3)$$

where M_t/M_∞ is the fraction of drug release at time t (first 60%), k is a constant incorporating the properties of the macromolecular polymeric system and the drug. The n is an exponent used to characterize the transport mechanism. For example, $n = 0.45$ for Case I or Fickian diffusion, $0.45 < n < 0.89$ for anomalous behaviour or non-Fickian transport, $n = 0.89$ for Case II transport, and $n > 0.89$ for Super Case II transport (Ritger and Peppas, 1987). Fickian diffusional release occurs by the usual molecular diffusion of the drug due to a 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 (Peppas and Sahlin, 1989).

(b) Peppas and Sahlin equation (Peppas and Sahlin, 1989):

$$\frac{M_t}{M_\infty} = k_1 t^m + k_2 t^{2m} \tag{4}$$

where the first term on the right side represents the contribution of Fickian diffusion and the second term represents the contribution of Case II transport. The coefficient m is purely the exponent for Fickian diffusion for any geometric form. The Eq. (4) can be rewritten as:

$$\frac{M_t}{M_\infty} = k_1 t^m \left[1 + \frac{k_2}{k_1} t^m\right] \tag{5}$$

The drug percentage due to Fickian diffusion mechanism (F), is clearly calculated as:

$$F = \frac{1}{1 + k_2/k_1 t^m} \tag{6}$$

which leads to the ratio of relaxation/erosion (R) over Fickian contribution as:

$$\frac{R}{F} = \frac{k_2}{k_1} t^m \tag{7}$$

The determination coefficient was used to test the applicability of the release models.

3. Results and discussion

3.1. Analysis of galactomannans

The galactomannans from *M. scabrella* dried by vacuum oven (VO) or spray dryer (SD) were analyzed and the results are shown in Table 2.

Both galactomannans showed similar properties than previously reported (Ganter et al., 1992). However, the average size of G(VO) was greater than G(SD). The last one showed a more white-off and uniform aspect.

3.2. Analysis of theophylline matrices

Tablets were obtained individually with 200 mg weight, 6 mm diameter and 5 mm height and were subjected to quality control tests such as hardness, friability and drug content (Table 1). They were off-white color, with homogeneous aspect for XG(SD) tablets and with dark points for XG(VO) tablets, due to the greater particle size of G(VO) granules. The formulations had acceptable for content uniformity, since the amount of the active ingredient in each of the 10 units tested was within the range of 90.4–100.5% and the relative standard deviations (R.S.D.) were less than 6.0%, indicating uniform mixing of gums, lactose and drug. The mean values for hardness were over 45N and all formulations presented a friability less than 0.5%, except the G(SD) alone matrices and the X 4% tablets, which showed capping during the friability determination.

3.3. In vitro drug release

On contact with an aqueous medium, the hydrophilic polymer matrix gradually begins to hydrate

Table 2
Properties of galactomannans dried by vacuum oven (G(VO)) or spray dryer (G(SD))

Properties	G(VO)	G(SD)
M:G ratio[a]	1.3:1	1.3:1
Loss on drying (%)[b]	9.0	7.1
$[\eta]_{25}$ (mL/g)[c]	498.0	366.7
Average size (S.D.) (μm)[d]	228 (115)	173 (84)

[a] By GLC.
[b] By infrared moisture analyser.
[c] By capillary viscosimeter.
[d] By sieving.

from the periphery towards the centre, forming a gelatinous swollen mass, which controls the diffusion of drug molecules through the polymeric material into the aqueous medium. Penetration by the solvent produces a clearly defined front (solvent penetration front) at the interface between the dry and hydrated polymer. The hydrated gel layer thickness determines the diffusional path length of the drug.

The in vitro drug release profiles of theophylline (100 mg) from tablets containing the mixture XG(SD) and XG(VO) at 1:1 (X:G) in different gum proportions (Table 1), are shown in Fig. 1a and b, respectively. After 1 h, the initial pH of 1.4 was changed to 4.0 and, after 2 h to 6.8.

It is known that drug release rate is dependent on the equilibrium solubility of the drug, which, in turn, is dependent upon the pH of its solution, however, theophylline dissolves in acid and basic medium (The Merck Index, 2001). As other authors (Serajuddin and Jarowski, 1985) have demonstrated, the solubility of theophylline remained almost constant between pH 2 and 7.5.

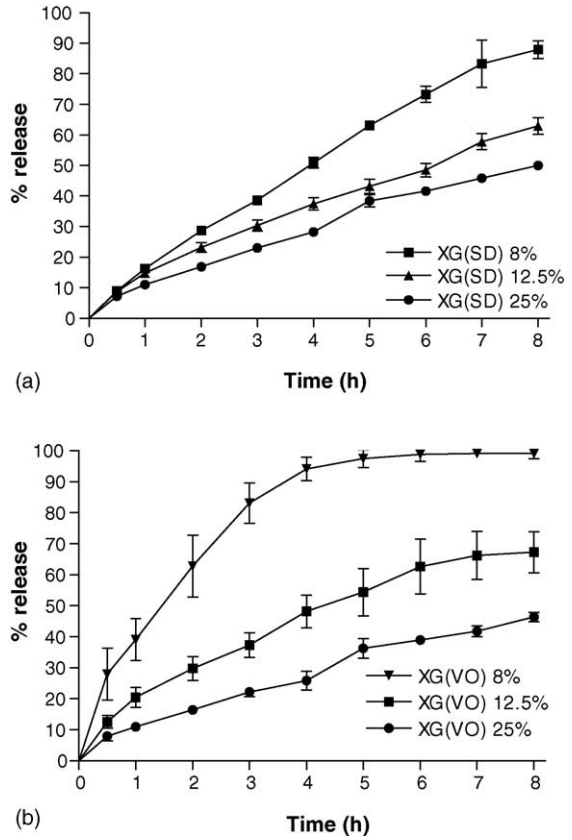

Fig. 1. In vitro release profiles of theophylline from tablets containing XG (1:1) mixture in different concentrations (8–25%), with galactomannan obtained by spray dryer (a) or vacuum oven (b). Each data point represents the mean of three experiments and the bar represents the standard deviation from the mean.

In both systems, the drug release rate decreased when the proportion of gums increased, as observed by other authors who used xanthan alone as a matrix forming material (Talukdar and Plaizier-Vercammen, 1993; Billa and Yuen, 2000). It was reasoned that, as the amount of gum in the matrix increased, there would be a greater degree of gum hydration with simultaneous swelling. This would result in a corresponding lengthening of the drug diffusion pathway and reduction in drug release rate. Drug release was generally linear for most of the formulations, specially XG(SD) matrices. Such linear drug release from hydrophilic matrices has been attributed to synchronization between swelling and erosion of the polymer in maintaining a constant gel layer (Lee and Peppas, 1987). Since theophylline is soluble in the pH range tested its release from the hydrogel matrix is controlled by the swelling of the matrix and the dissolution/erosion in the periphery of the matrix. Galactomannans are non-ionic polysaccharides and their hydration process is independent of pH. However, Billa and Yuen (2000) related that hydration rates of xanthan gum matrix, an ionic polymer, has been slower at lower pH values. During the test, all the formulations swelled and the outer layer of most of the tablets appeared to be hydrated after being placed in dissolution medium, with a progressive increase in the size of this hydrated layer, specially visualized for matrices containing xanthan, followed by a gradual loss of integrity, resulting from the hydrodynamic stress induced by the dissolution apparatus (Ueberreiter, 1967). Thereafter, it remained more or less unchanged until the final stages of dissolution test, when the inner dry core became wetted. The XG(VO) tablets showed a higher tendency to loss of integrity than the XG(SD), probably due to the greater particle size of the galactomannan, different hydration rate and worse distribution of this polymer in the former. The swelling process of XG(VO) tablets was not uniform and the zones of high galactomannan concentration appeared more swelled. In case of XG(VO) 8% matrix, a rapid erosion of the hydrated layer was readily noticeable, releasing almost the drug content after 4 h of experiment. The results

obtained pointed out the role of the drying method of galactomannan in the drug release behaviour from the matrices. However, the G(SD) alone matrices, except at 25% gum concentration, neither showed a uniform swelling and these matrices presented capping during the friability test.

For all formulations, the polymer concentration higher than 8% of each gum showed an excessive sustained drug release effect (Fig. 1a and b), while the XG(SD) 8% tablets showed a near zero-order drug release, with about 90% of theophylline released after 8 h. Similar result was observed by Billa and Yuen (2000) in tablets with 15% of xanthan and 35% of microcrystalline cellulose. These authors studied the drug release at laboratory and scale up of xanthan gum matrices containing diclofenac sodium and made by wet granulation.

In order to evaluate the role of XG mixture, the drug release of theophylline tablets with xanthan or galactomannan (SD) alone, in the same concentration of the total polysaccharide, was carried out and the results are shown in Fig. 2.

The drug release was slower from the matrices with X alone (8–25%) compared to the XG matrices in the same total polymer concentration (Figs. 1a and 2a). On the other hand, the tablets with G(SD) alone at 8 and 12.5% concentration released most of theophylline after 4 h (Fig. 2b). These results pointed out the major role of xanthan in the drug release of matrices containing XG(SD) mixtures. However, at 4%, X alone does not shows sustained release of drug (Fig. 2a). At 25% polymer concentration, for any type of polymer used, alone or in mixture, the tablets showed an excessive sustained drug release effect.

Generally, X matrices leaded to more precise results than G matrices, as showed by the standard deviation values (Fig. 2). Probably, the better uniformity of the former is due to the lower average size of X ($61 \pm 38\ \mu m$), allowing a good distribution of powder in the bulk formulation and the consequent gel layer uniformity with the tablet hydration in the dissolution media.

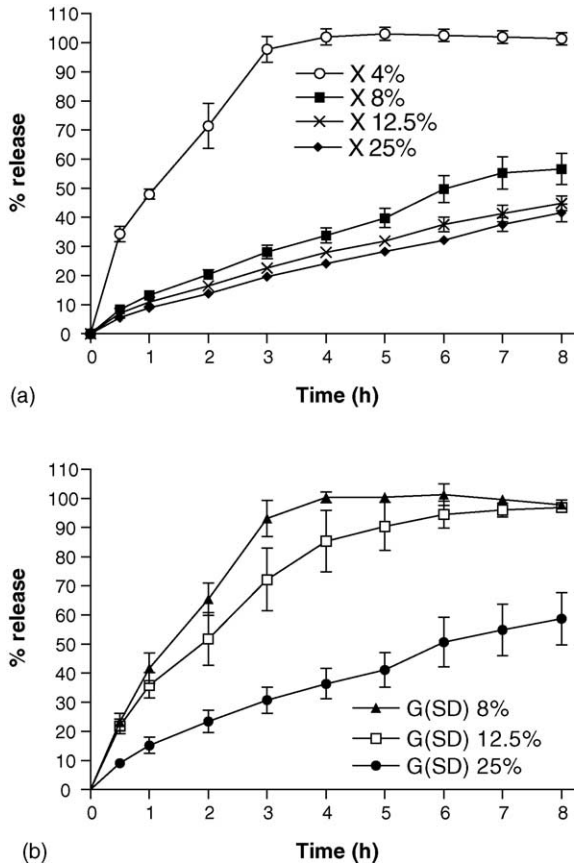

Fig. 2. In vitro release profiles of theophylline from tablets containing X (a) or G(SD) (b) in different concentration (4–25%). Each data point represents the mean of three experiments and the bar represents the standard deviation from the mean.

3.4. Swelling and erosion studies

The swelling and erosion studies were carried out with XG(SD) 8% formulation, which resulted in the better dissolution profile. The results of these tests are provided in Fig. 3. The swelling behaviour indicates the rate at which this formulation absorbs water from dissolution media and swells. The changes in weight, characteristic of water uptake and swelling, started from the beginning and continued until 7 h of experiment (Fig. 3a). These matrix showed a high ability to swell. Visual observation denoted that the matrices appeared swollen almost from the beginning, a viscous gel mass was created when they came into contact with the liquid. The matrix erosion measured the weight loss from matrix tablets immersed in dissolution media as a function of time. Weight loss from the tablets was in constant progression until the end of 7 h (Fig. 3b) and was around 70%. Billa and Yuen (2000) observed a similar profile with xanthan ma-

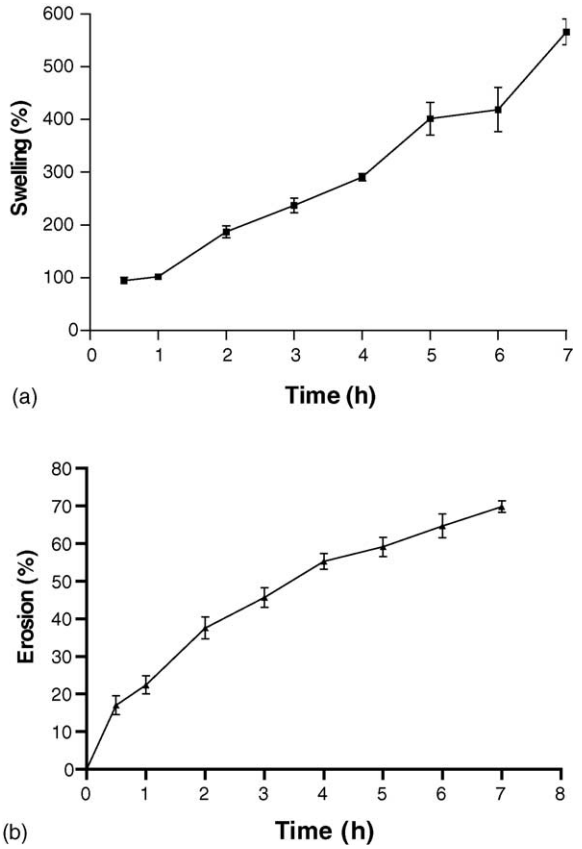

Fig. 3. Analysis of XG(SD) 8% at pH 6.8: (a) swelling behaviour; (b) erosion behaviour. Each point represents the mean value of three samples and error bars show ± standard deviation.

trices containing diclofenac sodium obtained by wet granulation.

A high erosion rate for these tablet was observed in pH of 6.8. Than, following exposure to an acidic media the matrix hydration process may differ in the dissolution study (pH of 1.4–6.8) when compared with erosion study (constant pH of 6.8) and may be expected higher in the last. At pH 6.8 the xanthan underwent hydration as soon as the matrix came in contact with the test medium, and the polymer hydration continued. But these results (Fig. 3) shows the importance of swelling and erosion for the drug release of XG(SD) 8% matrix.

3.5. Determination of the release kinetics

To evaluate the drug release kinetics, formulations showing a significant slow release were chosen. In general, the mechanism of drug release from polymeric matrices can be described by the swelling phenomenon. The solvent molecules move inside the polymeric matrix like a "front" defined at an exact speed; simultaneously, the thickness of the area increased with time in the opposite direction (Ranga et al., 1990). The mechanism of drug release can be described by a second phenomenon that involves the disentanglement and erosion of the polymer (Hogan, 1989). Khullar et al. (1998) described that, for guar-galactomannan tablets, the release process involves the penetration of water in the dry matrix, hydration and swelling of the polymer, and diffusion of the drug dissolved in the matrix.

Using Korsmeyer and Peppas model (Korsmeyer and Peppas, 1981) Eq. (3), n values between 0.63 and 0.83 (Table 3) were obtained for all formulations. These values are characteristic of anomalous kinetics (non Fickian), suggesting that more than one mechanism may be involved, but approaching Case-II transport.

These results are in agreement with the ones published by Sujja-areevath et al. (1998), that established a correlation among the swelling, erosion and drug release in hydrophilic matrices elaborated from natural gums as xanthan, karaia and locust bean gum. The anomalous kinetic was also observed by Cox et al. (1999) for xanthan mini-matrix tablets containing S(+)-ibuprofen prepared by the wet granulation method.

The Peppas and Sahlin equation (Peppas and Sahlin, 1989) 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 for these matrices was 0.45, according to their aspect ratio. Table 4 shows the k_1 and k_2

Table 3
Values of n (exponent for release kinetics)

Formulations	n Values	R^2
XG(SD) 8%	0.83	0.9994
XG(SD) 12.5%	0.69	0.9990
XG(VO) 12.5%	0.63	0.9962
XG(SD) 25%	0.72	0.9929
XG(VO) 25%	0.66	0.9862
X 8%	0.70	0.9955
X 12.5%	0.67	0.9982
X 25%	0.73	0.9983
G(SD) 25%	0.67	0.9981

R^2 determination coefficient.

Table 4
Values of k_1 and k_2

Formulations	k_1	k_2	R^2
XG(SD) 8%	0.037	0.126	0.9987
XG(SD) 12.5%	0.072	0.067	0.9970
XG(VO) 12.5%	0.118	0.070	0.9961
XG(SD) 25%	0.040	0.062	0.9921
XG(VO) 25%	0.032	0.057	0.9882
X 8%	0.055	0.068	0.9924
X 12.5%	0.071	0.043	0.9988
X 25%	0.026	0.052	0.9992
G(SD) 25%	0.115	0.049	0.9963

R^2 determination coefficient.

values. The XG(VO)12.5% formulations show k_1 significantly higher than k_2, suggesting the diffusional contribution as the major factor controlling drug release. Considering the formulations with the mixture XG(SD), specially at 12.5 and 25% of polymer, and X matrices, the k_1 and k_2 values were more similar and probably, the diffusion and relaxational (swelling and erosion) mechanisms might coexist and contribute in some manner to drug release. For XG(SD)8%, the relaxational contribution was predominant in agreement with swelling/erosion study (Fig. 3).

The percentage contributions of Fickian diffusion (F) and relaxation (R/F) over the first 60% of drug release from XG(SD) and X matrices are shown graphically in Fig. 4a and b, respectively.

For both theophylline matrix formulations, the contribution of polymer relaxation occurs throughout the entire dissolution time period. This was also apparent from the n values obtained (Table 3), which approaches Case II transport. In general, the relaxational contribution was higher for the formulations with higher n values (Table 3 and Fig. 4). The XG(SD) 8% formulation showed the highest contribution of polymer relaxation, in agreement with Peppas and Sahlin analysis (Table 4) and swelling/erosion studies (Fig. 3). The 12.5% gum concentration, for both XG(SD) and X matrices, showed the lowest n and R/F values, approaching Fickian diffusion.

The tablets with G(SD) resulted in more uniform drug release matrices than G(VO), probably due to the smallest average size of the galactomannan particles. Xanthan gum produced a greater sustaining effect on the release of theophylline than galactomannan (*M. scabrella*) alone or XG matrices. Some XG

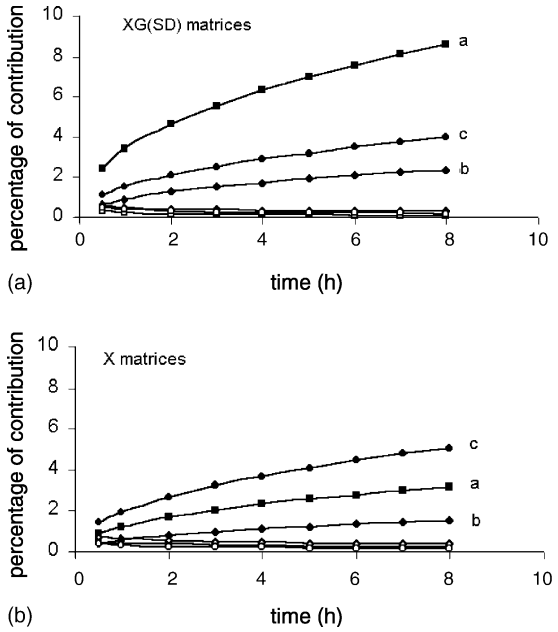

Fig. 4. The percentage contributions of Fickian diffusion, F (empty symbol) and polymer relaxation R/F (full symbol) mechanisms over the first 60% of drug release from theophylline-XG(SD) matrices (a) and theophylline-X matrices (b). For both figures (a) 8%; (b) 12.5% and (c) 25% gum concentration.

matrices, made simply mixing with the previous drug-lactose granulate, were able to produce near zero-order drug release. The XG(SD) 8% formulation was found to provide the required release rate, with release kinetics of zero-order (drug release about 90% at the end of 8 h). At the same total concentration, the galactomannan alone did not show release control properties, at these concentrations. The predominant release mechanism varied with matrices composition and drug release was controlled by both diffusion and relaxation, with predominance of the latter mechanism mainly in XG(SD) 8% tablets.

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