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Swelling and drug release behaviour of xanthan gum matrix tablets

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Abstract

The swelling and drug release behaviour of xanthan gum matrix tablets were studied using three drugs having different properties, i.e., caffeine as a soluble neutral drug, indomethacin as an insoluble acidic drug, and the sodium salt of indomethacin as a soluble acidic drug. Swelling was ascertained by measuring the axial and the radial expansion of matrix tablets following exposure to media of physiological ionic strength. The mean drug dissolution time and swelling rate were calculated from dissolution and swelling experiments, respectively, and were used as responses for comparison under different experimental conditions. The dependence of drug release on the swelling of the polymer matrix and on the type of the drugs added was established. The former is mainly influenced by the ionic strength and buffer concentrations. The latter is affected by the solubility of the drug. The mechanism of matrix swelling follows Case I diffusion, whereas drug release from this polymer matrix conforms to Case II diffusion.

Keywords: Xanthan gum; Hydrophilic matrix; Axial swelling; Radial swelling; Zero-order drug release; Salt effect; Indomethacin; Sodium indomethacin

1. Introduction

Xanthan gum (XG) is a high molecular weight extracellular heteropolysaccharide, produced by fermentation with the gram-negative bacterium *Xanthamonas campestris*. The primary structure of this naturally produced cellulose derivative contains a cellulosic backbone (β-D-glucose residues) and a trisaccharide side chain of β-D-mannose-β-D-glucuronic acid-α-D-mannose attached with alternate glucose residues of the main chain. The terminal D-mannose residue may carry a pyruvate function, the distribution of which is dependent on the bacterial strain and fermentation conditions. The non-terminal D-mannose unit in the side chain contains an acetyl function. The anionic character of this polymer is due to the presence of both glucuronic acid and pyruvic acid groups in the side chain (Kang and Pettitt, 1993).

XG is widely used as a thickening agent in the food industry and in pharmacy practice it is used as a hydrocolloid to thicken, suspend, emulsify

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and stabilize water-based systems (Remington's Pharmaceutical Sciences, 1990). Recently, it has been reported by many authors (Gulley et al., 1982; Calanchi et al., 1985; Pankhania et al., 1987; Ingani and Moes, 1988; Baichwal and Staniforth, 1991; Fu Lu et al., 1991; Waaler et al., 1992; Dhopeshwarkar and Zatz, 1993; Saxena et al., 1993; Talukdar and Plaizier-Vercammen, 1993) that XG can be used as an effective excipient for sustained-release formulations. Moreover, it has been observed that a small amount of this microbial polysaccharide alone or in combination with galactomannan can significantly retard the drug release from tablets. This should allow the formulation of a high dose of drug with this excipient without an excessive increase in weight of the dosage form.

Xanthan gum not only retards in vitro drug release and provides time-independent release kinetics (Ingani and Moes, 1988; Baichwal and Staniforth, 1991; Fu Lu et al., 1991; Dhopeshwarkar and Zatz, 1993; Saxena et al., 1993; Talukdar and Plaizier-Vercammen, 1993) but can also work effectively in vivo and establish constant drug plasma levels (Fu Lu et al., 1991). Thus, economic as well as therapeutic advantages can be achieved with this polymer matrix.

No investigation has been performed on the swelling behaviour of this polymer for controlling drug release. Therefore, it was the objective of this work to study the swelling and drug release behaviour of xanthan gum matrix tablets. During the course of the present study it was presumed that (1) the increase in dimensions (axial/radial) is related to the degree of swelling, and (2) solvent penetration is the rate-limiting step of matrix swelling. In this study three drugs were used: (a) caffeine as a soluble neutral drug, (b) indomethacin as an insoluble acidic drug, and (c) the sodium salt of indomethacin as a soluble acidic drug. Since drug release from XG matrices is dependent on the ionic strength of the dissolution medium (Talukdar and Plaizier-Vercammen, 1993), it was a further objective to investigate the influence of ionic strength on the extent and nature of the swelling process of this polymer.

Numerous methods, e.g., weight gain, photographic technique, and image analysis are often used for probing swelling behaviour. This paper decribes a novel in vitro test for measuring the radial expansion of the sample during swelling in the fluid, which is non-invasive and uses experimental conditions similar to those of the USP paddle method for dissolution testing.

2. Materials and methods

2.1. Materials

The following were used: xanthan gum (Rheogel®) (Iranex, Rouen, France), 200 mesh, surface area 0.37 m^2/g (BET method using a Quantasorb® surface area analyzer), minimum viscosity 1500 mPa s (1% w/w in aqueous solution with 1% KCl at 60 rpm, Brookfield) according to the supplier; caffeine anhydride (Ph.Belg. VI), 80 mesh; indomethacin (BP 80), mean particle size 8.398 μm (measured with a Coulter multisizer II); sodium salt of indomethacin (MSD Research Lab., Rahway, NJ, USA; batch no. L-590,226-024T024); lactose (Ph.Belg. VI), 200 mesh and analytical grade of potassium dihydrogen phosphate; sodium hydroxide and sodium chloride.

In all preparations of solutions and buffers, Milli-Q water was used.

2.2. Viscosity measurement

The viscosity of 1% (w/w) xanthan gum solution was measured according to the USP XXII at 37° C using a Rheomat 115, MS-DIN 145, and module 4/3.

2.3. Preparation of tablets

A 10.00 g batch size of drug and excipient(s) was thoroughly mixed in a high-speed mill at about 10 000 rpm for 20 s. Predetermined amounts of powder mixture were fed manually into the die of a flat-surface single punch (11 mm diameter) instrumented Korsch MP1 tabletting machine and compressed to matrix tablets with a porosity of $15 \pm 2\%$ at a constant relative humidity (RH) of 42%. After compaction, the tablets were stored in an atmosphere of 42% RH until use.

Tablet porosity (P) was calculated using Eq. 1:

$$P = \left(1 - \frac{W_{tab}/V_{tab}}{\rho_{powder}}\right) \times 100 \quad (1)$$

where W_{tab} is the tablet weight, V_{tab} represents the volume of tablet and ρ_{powder} is the true density of powder.

Here, the true volume of powder and the tablet dimensions were measured with a Beckman helium pycnometer and a micrometer screw gauge, respectively.

2.4. Disintegration of tablets

Disintegration of matrix tablets was investigated according to the USP XXII using an Erweka disintegration tester without disks at 37° C in 900 ml of specified medium.

2.5. Swelling experiments

2.5.1. Measurement of radial dimension

The radial swelling of matrices was monitored by immersing the tablet into a beaker (11.5 cm × 6.0 cm) containing 500 ml of medium, which was placed on a heating plate (37° C) covered by a sheet of graph paper. A stirrer rotating at 50 rpm was assembled above the tablet according to the instructions of the USP paddle method for the dissolution experiment. At defined time intervals, the increase in tablet diameter was determined using the divisions printed on the graph paper.

2.5.2. Measurement of axial dimension

The tablet height was recorded with a dial indicator, placed on top of the tablet. For easy accessibility of the medium, the tablet was mounted between a sintered glass and a membrane filter (Sartorius type SM 13430). The height of the tablet was corrected by deducting the corresponding increment in height using the sintered glass and filter paper only.

2.5.3. Swelling index (SI)

SI was expressed as a percentage and calculated according to Eq. 2:

$$SI = \left(\frac{X_t - X_0}{X_0}\right) \times 100 \quad (2)$$

where X_0 is the initial diameter or height of the tablet and X_t denotes the diameter or height of the tablet at time t.

2.6. Dissolution experiment

Drug release was measured according to the USP paddle method under sink conditions at 50 rpm in 1000 ml dissolution medium at 37° C. At predetermined time intervals, samples (1 ml) were removed by an automated sampler (Gilson) and replaced with fresh solvent. Samples were assayed (caffeine at 273 nm and indomethacin at 320 nm) with a diode array spectrophotometer (Hewlett Packard 8452A).

2.7. Data treatment

Experimental results were fitted according to the exponential Eq. 3:

$$\frac{M_t}{M_\alpha} = Kt^n \quad (3)$$

where M_t/M_α is the fractional solvent absorbed or drug released at time t, K denotes a constant incorporating the properties of the macromolecular polymeric system and the drug, and n is a kinetic constant which depends on and is used to characterize the transport mechanism. For example, $n = 0.45$ for Case I or Fickian diffusion, $n = 0.89$ for Case II transport, $0.45 < n < 0.89$ for anomalous behaviour or non-Fickian transport, and $n > 1.0$ for Super Case II transport (Ritger and Peppas, 1987).

In order to characterize the drug release and matrix swelling, the mean dissolution time (MDT) and mean swelling time (MST) were calculated according to Eq. 4 from dissolution and swelling experiments, respectively (Mockel and Lippold, 1993):

$$MT = \frac{n}{n+1} K^{-(1/n)} \quad (4)$$

To compare the means at the different experimental conditions and to assess statistical significance, one-way analysis of variance (ANOVA) was carried out at the 5% level.

3. Results and discussion

3.1. Axial swelling of Rheogel single compact

These experiments were performed with 225 mg tablets of solely Rheogel. Fig. 1 illustrates typical axial swelling in water. Swelling of the gum was rapid and within 45 min the maximum, i.e., above 90% of the initial value, was reached. The persistence of maximum swelling until the end of the experiment, i.e., 60 min, indicates that quite a strong gel was formed, which was less susceptible to the pressure (approx. 25 g) exerted by the dial indicator. These results led us to conclude that during dissolution, tablets containing xanthan gum will instantly form a gel layer upon contact with the medium which will be strong enough to avoid premature disintegration as well as the so-called burst effect and will significantly retard drug release for a long period of time.

However, the major disadvantage of the method, applied for measuring axial swelling, is the pressure exerted by the dial indicator, which inhibits free swelling and for which correction is not possible. As a result, the swelling profiles in different media are indistinguishable (data not shown). Besides, it has already been shown that, regarding the access of water and swelling, the faces and edge of the tablet behaved in an identical manner (Papadimitriou et al., 1993). Therefore, for further study of swelling only radial expansion of the XG matrix tablet is considered. Above all, the experimental conditions applied to measure the radial swelling were very close to those of the in vitro dissolution test.

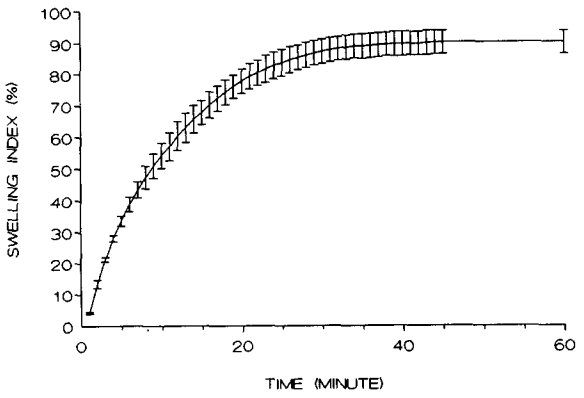

Fig. 1. Axial swelling of Rheogel single compact in Milli-Q water at 37° C (bars indicate the standard deviation of the mean of three experiments).

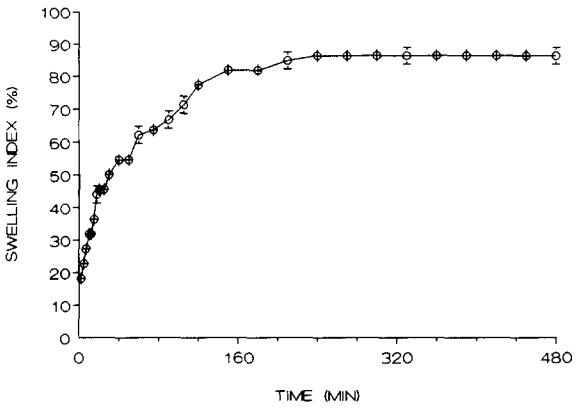

Fig. 2. Radial swelling of Rheogel single compact in Milli-Q water at 37° C (bars indicate the standard deviation of the mean of three experiments).

3.2. Radial swelling of Rheogel single compact

When the tablet is placed in the aqueous medium, liquid penetrates into the tablet and a gel is formed due to uncoiling of the structure of the XG molecules and the formation of hydrogen bonds with water molecules. As a result, the diameter of the tablet increases progressively and a distinct gel-sol boundary develops. Being hydrophilic in nature, XG, after hydration and swelling, goes into solution or erodes. Thus, the overall dimensions of the matrices are affected by the rate of swelling and that of dissolution/erosion.

Fig. 2 represents typical radial swelling of a Rheogel single compact in water. No lag time could be detected, which indicates that the gum hydrated quickly and a sufficient boundary gel formed immediately. This was visually observed during the experiment. In Fig. 2 it is also shown that the synchronization of swelling with dissolution/erosion processes of the matrix, which resulted in a constant tablet diameter, was reached at about 240 min and remained until 480 min.

Such synchronization maintained the surface area constant, which facilitates zero-order drug release kinetics being obtained from a matrix tablet.

In order to understand the mechanism of liquid penetration, i.e., swelling of the gum, the experimental data were fitted according to Eq. 3. The calculated value of n is 0.44, which indicates that the swelling kinetics conform predominantly to Case I diffusion (i.e., square root of time profile). This classical Higuchi-type swelling mechanism can be explained as a result of the rapid hydration of the polymer molecules on the surface of the tablets, which results in a gel or a highly viscous solution surrounding the matrix that restricts water penetration into the centre. The net result is a reduction of the rate of swelling as a function of time. The calculated mean swelling time (MST) was found to be 0.756 h. Since in most of the cases, maximum swelling was not reached within 8 h, the calculation of MST was not possible. Therefore, the swelling rate was calculated from the slope of the linear portion of a curve plotted according to the swelling index (%) vs square root of time and was used as a measure for statistical comparison.

As mentioned above, drug release from XG matrix tablets seems to be dependent on the ionic strength (μ) of the dissolution medium (Ingani and Moes, 1988; Talukdar and Plaizier-Vercammen, 1993). Therefore, it is necessary to investigate the influence of this parameter on swelling behaviour as well. In this study sodium chloride was used as an electrolyte in the medium, since this is the major representative electrolyte of the gastrointestinal (GI) fluid. Since the range of ionic strength in GI fluid is 0.010–0.166 (Johnson et al., 1993), the range of ionic strength of 0.00–0.20 was chosen for this study. Table 1 shows the effect of ionic strength on the swelling rate of the polymer in sodium chloride solutions and in USP phosphate buffer pH 7.4. From the data in Table 1 it was concluded that the medium has a significant ($p < 0.05$) influence on the swelling rate of XG up to a value of 0.1. The influence of electrolyte on this level can be explained as a consequence of salt dependence of the conformation of xanthan molecules.

The existence of conformational transition of xanthan gum in aqueous solution has been well established for many years. The disordered random coil conformation loses the ability to form a gel whereas the ordered elongated conformation is able to form a gel. The rate of formation of an ordered structure in xanthan has long been known to increase dramatically with increasing concentration of added salt. It has been proved that the presence of salt in the medium elevates the transition temperature (T_m) (Southwick et al., 1982; Yalpani, 1990). In addition, it has also been found that the hydrodynamic volume of this exopolysaccharide molecule changes with respect to ionic strength due to changes in intramolecular elec-

Table 1
Swelling and disintegration time of Rheogel single compact in media of different ionic strengths at 37° C (mean ± SD; $n = 3$)

Medium	Ionic strength	Matrix swelling (square root of time equation)		Disintegration time (min)
		Slope (%/√min)	R^2	
Milli-Q water	0.000	7.927 ± 0.049	0.979	
NaCl solution	0.050	5.275 ± 0.165	0.993	
NaCl solution	0.100	4.455 ± 0.256	0.996	
NaCl solution	0.200	4.451 ± 0.135	0.995	
HCl solution	0.100	2.317 ± 0.112	0.988	
USP buffer pH 7.4 (dilution = 100 ×)	0.001	7.308 ± 0.47	0.990	
USP buffer pH 7.4 (dilution = 10 ×)	0.011	5.827 ± 0.176	0.995	154 ± 4
USP buffer pH 7.4 (dilution = 5 ×)	0.022	5.501 ± 0.045	0.997	174 ± 8
USP buffer pH 7.4 (dilution = 2 ×)	0.055	5.064 ± 0.108	0.995	
USP buffer pH 7.4 (dilution = 1 ×)	0.114	4.525 ± 0.022	0.993	489 ± 5
USP buffer pH 7.4 (dilution = 1 × + NaCl)	0.200	4.450 ± 0.132	0.989	

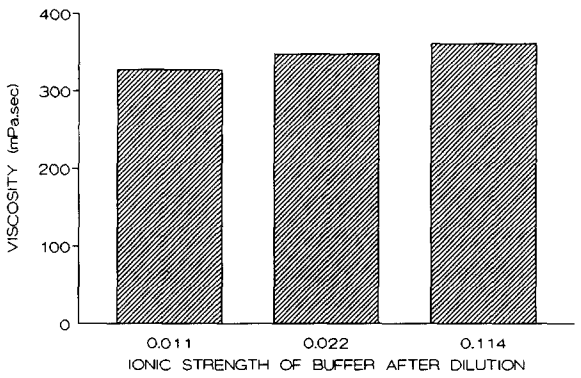

Fig. 3. Viscosity of Rheogel in USP phosphate buffer pH 7.4 of different ionic strengths.

trostatic repulsion by ions (Southwick et al., 1982; Yalpani, 1990). All these phenomena should reflect the viscosity and gelation properties of this polymer. The results (Fig. 3) of the viscosity measurements in different ionic strength clearly demonstrate that the viscosity of moderately dilute xanthan gum in aqueous medium is influenced by the ionic strength. This result is in accordance with published reports (Yalpani, 1990; Oviatt and Brant, 1993), where changes in ionic strength at constant temperature were found to affect the viscoelastic behaviour of XG. Whereas an increase in ionic strength reduces the viscosity of dilute xanthan solution, as expected for a polyelectrolyte, the addition of salt to XG solution in the concentration range from 0.2 to 3.0% causes the viscosity to increase. More recently, the observed increase in intrinsic viscosity, elastic (storage) modulus and viscous (loss) modulus from addition of NaCl to 2% xanthan solution was interpreted in terms of kinetic facilitation of ordered duplex structure formation (Oviatt and Brant, 1993).

However, above an ionic strength of 0.1, a further increase in this parameter does not lead to any significant ($p > 0.05$) difference in the swelling rate of the gum (Table 1). In the literature, it has been mentioned that under these conditions (0.1 M NaCl) XG is in a stable form due to helix formation (Callet et al., 1987). Therefore, further addition of salts has no influence on the rheological properties.

In this study it can be seen that the influence of salt on the swelling rate is exerted up to an ionic strength of 0.1 while most of the published data concerning this effect on the physico-chemical properties of XG have been reported to be below this level. This discrepancy may be due to a difference in acetate and pyruvate content in the XG molecule. The apolar acetate group seems to enhance the intramolecular binding force that contributes to the stability of the ordered helical conformation in solution, whereas pyruvate substituents tend to lower the stability of the ordered state (Callet et al., 1987; Shatwell et al., 1990). It has been shown that the pyruvate content of the sample is an important factor in determining the solution properties of XG, and a sufficient level of ionic strength is necessary to reduce the intramolecular electrostatic repulsion between the pyruvate groups (Yalpani, 1990).

Table 1 also demonstrates that there is no significant ($p > 0.05$) difference between the swelling rate of Rheogel in sodium chloride solutions and in USP potassium phosphate buffers of equal ionic strength, indicating that the nature of the ions has no influence. This again is consistent with published data showing that no selectivity of XG exists between monovalent counterions (Rinaudo and Milas, 1978). Therefore, for further study, USP phosphate buffer pH 7.4 was used as the medium for swelling and dissolution experiments.

The swelling profiles of Rheogel single compact in the same ionic strength (0.1) but at pH 1.2 (0.1 M HCl) and pH 7.4 (buffer) are listed in Table 1 and indicate that the swelling rate in extreme acidic medium is significantly ($p < 0.05$) lower than in neutral or alkaline solutions. It is obvious that, being an acidic polymer with a pK_a of 3.1, XG becomes less soluble at such a low pH value. From this result it can be predicted that swelling of this polysaccharide will be different in the stomach and in the intestine.

3.3. Radial swelling and drug release behaviour of Rheogel binary compact

A binary (1:1) mixture of polymer and caffeine was compressed in order to prepare tablets of 190

Table 2
Swelling and drug release behaviour of Rheogel binary (1:1) compact in USP phosphate buffer pH 7.4 of different dilution with Milli-Q water at 37° C (mean ± SD; $n = 3$)

Ionic strength of medium	Matrix swelling (square root of time equation)		Drug release behavior	
	Slope (%/√min)	R^2	MDT (h)	n
0.011	5.838 ± 0.059	0.997	7.653 ± 0.165	0.888 ± 0.006
0.022	5.364 ± 0.066	0.994	6.996 ± 0.113	0.820 ± 0.008
0.114	4.215 ± 0.149	0.996	6.403 ± 0.068	0.693 ± 0.012

mg. The swelling and drug release experiments were carried out in the same medium. The results (Table 2) indicate that the swelling and drug release in USP phosphate buffer are inversely proportional. This is clearly evident, since the release of a soluble drug like caffeine from hydrophilic matrices, e.g., xanthan gum, proceeds through the gel layer (boundary layer control) which is formed surrounding the tablet upon contact with the medium. As the gel thickness increases, the diffusion path length increases which in turn is the cause of the decrease in drug release from the matrix tablet.

Table 2 again shows that the ionic strength of the medium has a strong influence on both the swelling and drug release behaviour. The effect of salt (up to $\mu = 0.075$) on the release of theophylline from XG matrix tablets has also been previously reported by Ingani and Moes (1988). Here it is worth noting that neither the swelling rate nor the swelling kinetics (Table 2) was affected by the addition of 50% caffeine when compared with the single compact (Table 1) under the same experimental conditions.

The release of caffeine from this matrix approximately follows Case II diffusion, which is determined by the rate of polymer relaxation and diffusion rate and is referred to as a swelling-controlled drug delivery system with zero-order kinetics. This release mechanism is significantly influenced by the ionic strength and moves towards anomalous transport with increasing salt concentration in the dissolution medium. A similar result was obtained in our earlier work (Talukdar and Plaizier-Vercammen, 1993).

The shifting of the release mechanism of caffeine from Case II diffusion to anomalous behaviour as a function of ionic strength of the

Table 3
Swelling and drug release behaviour of Rheogel ternary (gum/drug/lactose = 5:2:3) compact with different drugs in USP phosphate buffer pH 7.4 of different ionic strengths at 37° C (mean ± SD; $n = 3$)

Drug	Ionic strength of medium	Matrix swelling (square root of time equation)		Drug release behaviour	
		Slope (%/√min)	R^2	MDT (h)	n
Caffeine	0.011	5.799 ± 0.049	0.989	5.955 ± 0.174	0.865 ± 0.027
Caffeine	0.022	5.220 ± 0.101	0.988	5.313 ± 0.091	0.813 ± 0.009
Caffeine	0.114	4.574 ± 0.322	0.991	4.737 ± 0.118	0.727 ± 0.003
Indomethacin	0.011	5.993 ± 0.032	0.993	16.376 ± 0.914	1.2677 ± 0.039
Indomethacin	0.022	5.262 ± 0.073	0.990	18.330 ± 0.557	1.060 ± 0.010
Indomethacin	0.055	5.024 ± 0.001	0.994	18.456 ± 0.603	1.032 ± 0.037
Indomethacin	0.114	4.590 ± 0.188	0.995	22.385 ± 1.624	0.829 ± 0.025
Na-indomethacin	0.011	8.371 ± 0.134	0.993	8.026 ± 0.288	0.784 ± 0.017
Na-indomethacin	0.022	7.273 ± 0.023	0.994	7.289 ± 0.288	0.783 ± 0.006
Na-indomethacin	0.114	5.921 ± 0.263	0.989	6.913 ± 0.074	0.732 ± 0.024

dissolution medium may be explained as follows. In the absence of salt, the polymer swells to the maximum extent, resulting in fewer or smaller regions of low microviscosity (water-filled pores or microvoids) present in the gel microstructure of the hydrated XG tablet. In this case, drug release is controlled by the degree of swelling of the polymer. Therefore, the release mechanism follows Case II diffusion. In contrast, in the presence of ions the polymer does not swell fully and there are larger regions of low microviscosity, which results in an increase in the free volume due to the presence of the micropores. This may manifest itself as a shift in the release mechanism.

3.4. Radial swelling and drug release behaviour of Rheogel ternary compact

A ternary mixture (5:2:3) of gum, drug (caffeine or indomethacin or sodium indomethacin) and lactose was compressed into a tablet of 180 mg. The results of swelling and dissolution experiments in buffer solutions of different ionic strength are presented in Table 3 which demonstrates that the swelling of matrix and the release of soluble drugs, e.g., caffeine and sodium indomethacin shows a reciprocal relationship, while the insoluble drug, indomethacin, exhibits a direct relationship. This difference in relationship can be explained by the difference in the release mechanism of the drugs. Indomethacin, being an insoluble drug, is released by the mechanism of erosion, while the soluble drugs, caffeine and sodium indomethacin, are released via a diffusion mechanism (Alderman, 1984; Dhopeshwarkar and Zatz, 1993).

The erosion-controlled mechanism of insoluble drug release can be explained as follows: the more the matrix swells, the more susceptible it is to erosion, which leads to an increase in the release of an insoluble drug like indomethacin. This susceptibility to erosion as a function of buffer dilutions was proved by a disintegration test (Table 1), where it can be seen that the disintegration time of XG matrices was reduced as a function of buffer dilutions.

However, dilution of the buffer also reduces the solubility of the drug, e.g., indomethacin (Table 4). This reduced solubility does not have a marked negative effect on the release profile of indomethacin. Rather, the release rate is increased with buffer dilutions, which indicates that swelling of the matrix plays a more important role in drug release than solubility of the drug.

It can be seen in Table 3 that replacing caffeine with lactose has no influence on the swelling rate and mechanism. However, the dissolution rate is increased when lactose is incorporated into the formulation. Since the solubility of lactose is 10-times higher than that of caffeine, this influence of lactose on drug release is attributed to the facilitation of penetrant sorption by increasing porosity of the matrix after hydration.

Although the solubility of sodium indomethacin (201.2 mg/ml) is greater than that of caffeine (21.7 mg/ml), it can be seen in Table 3 that the dissolution of caffeine was faster than that of sodium indomethacin. It is evident that the swelling rate of the matrix with sodium indomethacin is greater. The greater rate of matrix swelling with sodium indomethacin may be attributed to a plasticising or osmotic effect of the drug molecule, when it is compressed with the

Table 4
Solubility of indomethacin in Milli-Q water and in USP phosphate buffer pH 7.4 of different dilutions at 37° C (mean ± SD; $n = 3$)

Medium	Ionic strength of medium	Solubility of indomethacin (mg/l)
Milli-Q water	0.000	17.12 ± 2.3
Buffer (dilution = 10 ×)	0.011	780.54 ± 12.64
Buffer (dilution = 5 ×)	0.022	1140.44 ± 12.95
Buffer (dilution = 2 ×)	0.055	1649.91 ± 4.58
Buffer (dilution = 1 ×)	0.114	1933.40 ± 64.45

hydrogel (Siegel, 1993). Further research on this aspect is in progress. Again it comes to light that the swelling of the matrix is the principal rate-limiting factor for drug release from xanthan gum matrix tablets.

Moreover, as shown in Table 3, the prevailing release mechanism of all three drugs, used in this study, is almost Case II diffusion, i.e., zero-order kinetics and is influenced by the ionic strength of the dissolution medium. Here again it is important to note that zero-order drug release from this polymer matrix has also been reported using theophylline (Ingani and Moes, 1988; Fu Lu et al., 1991; Dhopeshwarkar and Zatz, 1993), neomycin (Saxena et al., 1993), furazolidone (Saxena et al., 1993), chlorpheniramine maleate (Baichwal and Staniforth, 1991), benzocaine (Dhopeshwarkar and Zatz, 1993) and propranolol HCl (Baichwal and Staniforth, 1991) as model drugs.

4. Conclusion

Within the range of physiological ionic strength, the swelling of xanthan gum matrix tablets shows a reciprocal relationship with salt concentration, which is independent of the nature of the electrolyte. Depending on the solubility of the product the drug release from this matrix is regulated by its swelling behaviour. The release of an insoluble drug follows a direct relationship with swelling of the polymer matrix, while a reciprocal relationship is observed with soluble drugs. Swelling of the XG polymer matrix shows a square root of time dependence whereas drug release is almost time independent.

References

Alderman, D.A., A review of cellulose ethers in hydrophilic matrices for oral controlled-release dosage forms. *Int. J. Pharm. Tech. Prod. Mfr*, 5 (1984) 1–9.

Baichwal, A.R. and Staniforth, J.N., Directly compressible sustained release excipient. *US Patent 4,994,276*, Feb. 1991.

Calanchi, M., Gentilini, L. Mapelli, L. and Marconi, M., *Italian Patent Application No. 8619675*, 1985.

Callet, F., Milas, M. and Rinaudo, M., Influence of acetyl and pyruvate contents on rheological properties of xanthan in dilute solution. *Int. J. Biol. Macromol.*, 9 (1987) 291–293.

Dhopeshwarkar, V. and Zatz, J.L., Evaluation of xanthan gum in the preparation of sustained release matrix tablets. *Drug Dev. Ind. Pharm.*, 19 (1993) 999–1017.

Fu Lu, M., Woodward, L. and Borodkin, S., Xanthan gum and alginate based controlled release theophylline formulations. *Drug Dev. Ind. Pharm.*, 17 (1991) 1987–2004.

Gulley, P., DeNeale, R. and Milosovich, G., *US Patent 4,309,405*, 1982.

Ingani, H.M. and Moes, A.J., Utilisation de la gomme xanthane dans la formation des matrices hydrophiles. *STP Pharm.*, 4 (1988) 188–195.

Johnson, J.L., Holinej, J. and Williams, M.D., Influence of ionic strength on matrix integrity and drug release from hydroxypropyl cellulose compacts. *Int. J. Pharm.*, 90 (1993) 151–159.

Kang, K.S. and Pettitt, D.J., Xanthan-Gellan-Welan and Rhamsan. In Whistler, R.L. and Bemiller. J.N. (Eds), *Industrial Gums: Polysaccharides and their Derivatives*, 3rd Edn, Academic Press, San Diego, CA, 1993, pp. 341–397.

Mockel, J.E. and Lippold, B.C., Zero-order drug release from hydrocolloid matrices. *Pharm. Res.*, 90 (1993) 1066–1070.

Oviatt, H.W. and Brant, D.A., Thermal treatment of semi-dilute acqueous xanthan solutions yields weak gels with properties resembling hyaluronic acid. *Int. J. Biol. Macromol.*, 15 (1993) 3–10.

Pankhania, M., Mella, C. and Lampard, J., *European Patent Application No. 0234670*, 1987.

Papadimitriou, E., Buckton, G. and Efentakis, M., Probing the mechanism of swelling of hydroxypropylmethyl cellulose matrices. *Int. J. Pharm.*, 98 (1993) 57–62.

Remington's Pharmaceutical Sciences, 18th Edn, Mack, Easton, PA, 1990, p. 1308.

Rinaudo, M. and Milas, M., Polyelectrolyte behaviour of a bacterial polysaccharide from Xanthomonas campestris: Comparison with carboxy methyl cellulose. *Biopolymers*, 17 (1978) 2663–2678.

Ritger, P.L. and Peppas, N.A., A simple equation for description of solute release: II. Fickian and Anomalous release from swellable devices. *J. Controlled Release*, 5 (1987) 37–42.

Saxena, J., Sharma, N., Makoid, M.C. and Banakar, U.V., Bioactive polymers 68-controlled release of neomycin-furazolidone biocomponent system from xanthan hydrogel. *J. Biomater. Appl.*, 7 (1993) 265–276.

Shatwell, K.P., Sutherland, I.W. and Ross-Murphy, S.B., Influence of acetyl and pyruvate substituents on the solution properties of xanthan polysaccharide. *Int. J. Biol. Macromol.*, 12 (1990) 71–78.

Siegel, R., Controlled drug release by water swelling hydrogels. *Int. Pharm. J.*, 7 (1993) SI23.

Southwick, J.G., Jamieson, A.M. and Blackwell, J., Conformation of xanthan dissolved in acqueous urea and sodium chloride solutions. *Carbohydr. Res.*, 99 (1982) 117–127.

Talukdar, M.M. and Plaizier-Vercammen, J., Evaluation of xanthan gum as a hydrophilic matrix for controlled-release dosage form preparations. *Drug Dev. Ind. Pharm.*, 19 (1993) 1037–1046.

Waaler, P.J., Graffner, C. and Muller, B.W., Optimization of a matrix tablet formulation using a mixture design. *Acta Pharm. Nord.*, 4 (1992) 9–16.

Yalpani, M., Structure/property relationship. In Yalpani, M., (Ed.), *Polysaccharides: Syntheses, Modifications and Structure / Property Relations*, Elsevier, Amsterdam, Ch. 10, 1990, pp. 405–480.