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Comparative study on xanthan gum and hydroxypropylmethyl cellulose as matrices for controlled-release drug delivery. II. Drug diffusion in hydrated matrices

Mohammad Mahiuddin Talukdar *, Renaat Kinget

Laboratory of Galenical and Clinical Pharmacy, Campus Gasthuisberg, Katholieke Universiteit Leuven, 3000 Leuven, Belgium

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Abstract

In order to look up the reason for previously observed difference in the retarding ability of drug-release from xanthan gum (XG) and hydroxypropylmethyl cellulose (HPMC) matrix tablets, diffusion of three model drugs, e.g. indomethacin, indomethacin sodium and caffeine in hydrated gels of the two polymers, were measured. For measuring the diffusivity, the drug desorption from the polymeric gels into the stirred bulk medium was continuously monitored by their UV absorbance. Under identical experimental conditions, the drug diffusivity in HPMC gel is higher than in XG gel. This difference in hindered transport of the drug molecules within the two polymeric systems brings out the real cause for the reported higher retarding ability of drug-release from a XG matrix tablet than from a HPMC matrix tablet. In view of salt effects, the diffusion through the hydrated XG matrices back up the release characteristics of water soluble drugs from XG matrix tablets, suggesting that the diffusion of drug molecules in the hydrated gel of a XG matrix tablet is the main mechanism of overall release for soluble drugs like caffeine and the sodium salt of indomethacin. On the contrary, no reflection of indomethacin diffusivity through XG gels was found in its release profiles from XG matrix tablets, suggesting that diffusion through the hydrated polymer mass is not the dominant factor for the release of an insoluble drug like indomethacin from a XG matrix tablet. © 1997 Elsevier Science B.V.

Keywords: Xanthan gum; Hydroxypropylmethyl cellulose; Hydrated matrices; Drug diffusion; Controlled release; Indomethacin; Indomethacin sodium; Caffeine

1. Introduction

Since, XG and HPMC are hydrophilic polymers and upon contact with aqueous fluid both

* Corresponding author.

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are able to form quite viscous gel, they are used to retard the drug release rate for developing controlled-release (CR) oral drug delivery formulations. In our previous work (Talukdar et al., 1996a), during a comparative study on the performance of XG and HPMC as hydrophilic matrix (HM) tablets for CR drug delivery, it was observed that the in vitro drug release rates and release mechanisms are quite different. The XG showed higher ability to retard the release rate of a drug than the HPMC in identical formulations and experimental conditions. The release of a drug from XG matrices followed almost time-independent kinetics while the release from HPMC matrices followed time-dependent kinetics.

It is generally accepted that a drug release from a HM system is governed sequentially by the following processes: (1) hydration or swelling of the matrix which results in the formation of a gel; (2) dissolution of the drug into that hydrated matrix/gel; (3) diffuse out of the drug molecules through that hydrated matrix; and finally (4) surface erosion and/or dissolution of that formed gel-matrix.

The objective of the present work was to study the diffusion behaviour of drugs in the hydrated matrices/gels of these two polymers in order to predict the diffusant transport and thereby explain the difference in their ability to retard the drug release rate. Indeed, diffusion of the drug through the swollen gelatinous polymer–drug–excipient mass is one of the most important determinant factors when a hydrophilic polymer is used as a drug carrier for CR drug delivery formulation (Alderman, 1984). Moreover, recently the importance of drug diffusion in the hydrated matrices is well described in the literature (Colombo et al., 1995).

Since the drug release from XG matrices is influenced by the salt concentrations of the dissolution medium (Talukdar et al., 1996a), it was a further objective to investigate the influence of the salt concentration of the medium, used for preparing the gels, on the transport behaviour of solute through the hydrated XG matrices.

In this study the same drugs as used in the first part of this series of studies (Talukdar et al., 1996a) were investigated. They differ in solubility as indomethacin can be considered as an water insoluble drug (solubility = 0.002% w/v in water), while sodium indomethacin is very water soluble drug (solubility = 20% w/v in water), and caffeine is a moderately water soluble drug (solubility = 2% w/v in water).

Several methods, e.g. the membrane permeation method, the sorption/desorption method etc. were described in the literature (Kuu et al., 1992) to determine the diffusion coefficient of solute in gels and swollen polymers. Recently, methods for measuring diffusion coefficients in gels were reviewed, and their capabilities, limitations and requirements were discussed by Westrin et al. (1994). A comparison was made with regard to accuracy and precision of four methods, i.e. the diaphragm cell, uptake/release from beads, holographic laser interferometry and nuclear magnetic resonance (FT-PGSE).

In the reported study, drug diffusion coefficients in the hydrated matrices were calculated from the measurement of the rate of desorption of a drug dissolved/dispersed in the swollen polymer gel into a stirred infinite reservoir. The principle of this method is the same as that of the release from beads except that the hydrated matrix is taken in a cup of fixed size and shape instead of using the gel beads. This method is relatively simple but efficient and close to the USP drug dissolution test method. Indeed, considering the above mentioned four processing factors for overall drug release from HM devices, this method can serve our purpose quite adequately. However, the principle and advantage of the method applied in this paper for such study were already described in details by others (Mitchell et al., 1993; Fares and Zatz, 1995).

2. Experimental section

2.1. Materials

The details about materials used in this study can be found elsewhere (Talukdar et al., 1996a). Briefly, xanthan gum (XG), Rheogel®, (Iranex, Rouen, France); hydroxypropylmethyl cellulose (HPMC) (Methocel K4M premium) (Dow Chem-

ical Company, Midland, Michigan, US.); caffeine anhydride (Ph. Belg. VI); indomethacin (BP.80); sodium indomethacin (MSD Research Lab., Rahway, NJ, US); lactose 200 mesh (Ph. Belg. VI.); and analytical grade potassium dihydrogen phosphate, sodium hydroxide, and sodium chloride were used. All buffers were made, and dilutions of the buffer were done, with Milli-Q water.

2.2. Gel preparation

Polymer solutions (4, 7 and 10% w/w) were prepared by adding the required amount of polymer–drug or polymer–drug–lactose powder mixture to the medium (water/USP phosphate buffer pH 7.4 with or without dilution), which was maintained at 37°C with continuous stirring. In order to complete the hydration of the polymer, the gel was kept at rest overnight. Here, it is important to mention that since HPMC possesses surface active properties, the gels made with HPMC contained foam which was absolutely necessary to remove before performing the diffusion experiments. Within 24 h from preparation, the gel was centrifuged (at 14 000 × g, for 15 min, and 22°C) in order to remove the entrapped air or foam, when it was needed.

2.3. Diffusion study

The drug diffusion study has been carried out according to the following instructions: the gel was poured into a tarred cup, depicted in Fig. 1. Excess amount of gel was removed with a stainless steel spatula with care that the surface of the gel remains plain. The cup containing the gel was weighed again to obtain the gel weight ($\approx 2.25 \pm 0.05$ g) and covered with a Sartorius membrane filter type SM11302 (pore size = 3.0 μm) to maintain surface area constant (10 cm^2). Finally the washer was placed over the membrane, and it was tied up with the screw. Then the cup was placed in USP XXII dissolution vessel containing 1000 ml medium as an acceptor compartment maintained at 37°C. The paddle apparatus (at 2.5 cm above the sample cup) was operated at 50 rpm, which was sufficient enough to overcome the boundary effect. The amount of drug diffused into the bulk medium was continuously assayed (caffeine at 273 nm and indomethacin at 320 nm) with a diode array spectrophotometer (Hewlett Packard 8452A).

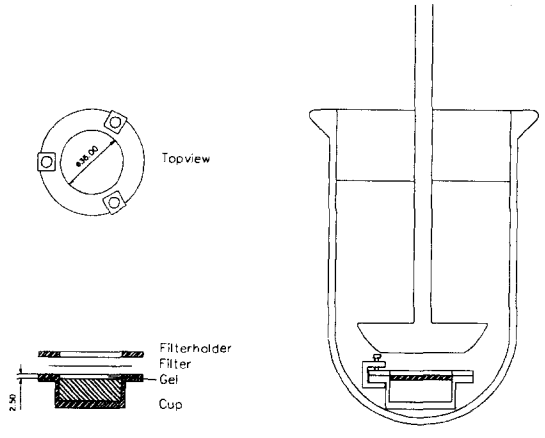

Fig. 1. Apparatus used to measure drug diffusion in the gels.

2.4. Data treatment

The drug diffusion coefficient was calculated from the slope of amount of drug (10%–70%) diffused out, from the sample cup into the external medium, versus square root of time using one of the following equations (Doelker, 1987).

1. When drug concentration was just exceeding drug solubility in the hydrated matrix, i.e. $C_0 > C_s$

$$M_t = [DC_s(2C_0 - C_s)]^{1/2} \cdot t^{1/2} \quad (1)$$

where M_t is the amount of drug diffused out of the gel after time, t, per unit exposed area, mg/cm^2; D is the diffusion coefficient of the drug in the matrix phase, cm^2/s; C_s is the solubility of the drug in the matrix substance, mg/ml; C_0 is the total amount of drug present in the matrix per unit volume, mg/ml.

2. When drug concentration was very much higher than drug solubility in the hydrated matrix, i.e. $C_0 \gg C_s$

$$M_t = [DC_sC_0]^{1/2} \cdot t^{1/2} \quad (2)$$

3. When drug concentration was lower than drug solubility in the hydrated matrix, i.e. $C_0 < C_s$

$$M_t = 2C_0\left(\frac{D}{\Pi}\right)^{1/2} \cdot t^{1/2} \quad (3)$$

The above mentioned equations were used for the calculation of diffusion coefficients of drugs with the assumptions that: (a) drug penetration through the polymeric matrix is governed solely by Fickian diffusion; (b) diffusion coefficient in the polymer, as well as in the solvent, is constant; (c) concentration of drug in the bulk is low, i.e. perfect sink conditions exist in the external media; and (d) there is no interaction, e.g. chemical interaction or ion exchange, between the drug molecules and the matrix.

2.5. Statistics

To compare the means of three experiments at the different experimental conditions and to assess statistical significance between them, either one-way analysis of variance (ANOVA) or an unpaired two-tailed t-test was carried at 5% level.

3. Results and discussion

3.1. Diffusion of caffeine in hydrated XG and HPMC matrices

The drug diffusion in a hydrated matrix, discussed in this paper, means the transport of a drug molecules through a swollen polymer mass/gel across a porous membrane into a bulk medium where perfect sink conditions prevail. Subsequently, the drug diffusion rate means the rate of transferring of a drug from a swollen gel. into an external medium. The diffusion of all drugs, used in this study, in the hydrated matrices followed square root of time dependency ($r > 0.996$). This is an indication that Fickian diffusion of the drug molecules in the swollen polymer matrices prevails. Fig. 2 clearly indicates that under similar experimental conditions the diffusion rate of caffeine in HPMC gel is significantly ($p < 0.0001$) higher than in XG gel. It was confirmed from the slope values (i.e. for HPMC = 9.84 ± 0.10 and for XG = 6.67 ± 0.26) of the two plots. The calculated (using Eq. (3)), since $C_0 = 1.6\%$ and $C_s = 2\%$) diffusion coefficient of caffeine

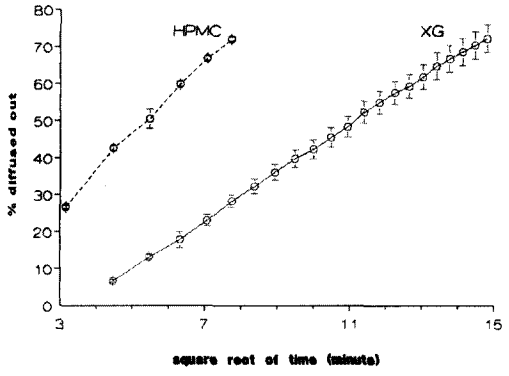

Fig. 2. Typical plots of diffuse out of caffeine from 4% XG and HPMC gels into water. Each data point represents the mean of three experiments and the error bar indicates the standard deviation from the mean.

in HPMC and XG gels were found to be 5.49×10^{-6} cm^2/s and 2.48×10^{-6} cm^2/s, respectively.

Since binding of drug molecules to polymer molecules can have influence on overall solute transport between the gel and bulk medium, the partition coefficients of caffeine have been calculated from its solubility determination in the respective polymer solution and the bulk medium. In the presence or absence of either of the two polymers (i.e. XG or HPMC) the solubility of caffeine in the medium are indifferent. This result indicates that there is no interaction occurs between the polymer and the drug. The discrepancy observed in solute diffusion through XG and HPMC gels is not originated from differences in binding behaviour of the two polymers.

However, these findings together with the results of diffusion study strongly suggest that the XG polymer has a higher ability to hinder drug transport through its gel than the HPMC polymer. This difference in obstructive effect of HPMC and XG polymers on the solute diffusivity in their respective swollen matrices well explain the reported (Talukdar et al., 1996a) difference in observed drug release behaviour of the two potential excipients used as matrix forming agent for CR drug delivery formulations.

Furthermore, the observed difference in diffusivity of caffeine in 4% XG and HPMC hydrated matrices is in agreement with rheological charac-

Table 1
Diffusion rate and diffusion coefficient (Eq. (3)) of caffeine in different types of xanthan gum gels (mean ± S.D.; $n = 3$)

Gel type	Medium used[b]	Diffusion rate		Diffusion coefficient ($D \times 10^6$, cm^2/s)
		$\%/min^{1/2}$	$mg/cm^2/min^{1/2}$	
4% XG 1.6% caffeine	Water	6.12 ± 0.42	0.228 ± 0.015	2.32 ± 0.41
4% XG 1.6% caffeine[a]	Water	6.67 ± 0.26	0.239 ± 0.009	2.48 ± 0.63
4% XG 1.6% caffeine	Buffer = 1 ×[c]	8.03 ± 0.26	0.299 ± 0.004	3.70 ± 0.41
7% XG 1.6% caffeine	Buffer = 1 ×[c]	7.30 ± 0.12	0.289 ± 0.007	3.00 ± 0.58
4% XG 1.6% caffeine 2.4% lactose[a]	Buffer = 1 ×[c]	8.99 ± 0.73	0.324 ± 0.003	4.81 ± 0.29
4% XG 1.6% caffeine 2.4% lactose	Buffer = 1 ×[c]	8.92 ± 0.77	0.320 ± 0.009	4.84 ± 0.36
4% XG 1.6% caffeine 2.4% lactose	Buffer = 5 ×[c]	6.88 ± 0.33	0.278 ± 0.001	2.64 ± 0.35
4% XG 1.6% caffeine 2.4% lactose	Buffer = 10 ×[c]	6.18 ± 0.05	0.243 ± 0.013	2.08 ± 0.37

[a] After centrifugation of the gel.
[b] For preparing the gel and in the acceptor compartment during corresponding diffusion measurement.
[c] Buffer dilution.

teristics of the two polymers. By performing dynamic oscillatory test on XG and HPMC solutions it was shown in our recent study (Talukdar et al., 1996b) that 4% XG in aqueous media exhibits gel-like properties while 4% HPMC behaves as a polymer solution. This was an indication that there is the presence and absence of structure in XG and HPMC solutions, respectively. This solution structural differences between the XG and HPMC polymers might be the possible reason for slowing down the drug diffusion in XG gel compare to that in HPMC gel.

The values of diffusion rates and the calculated (Eq. (3)) diffusion coefficients of caffeine in different types of XG gels under different experimental conditions are tabulated in Table 1. In order to mimic the infiltration effect of the medium into the gel, the gels were prepared with the acceptor solution used. It is shown in Table 1 that a remarkable reproducibility was obtained and the average diffusion coefficient of three experiments is typical of these observed in highly swollen polymer gels. Indeed, Reinhart and Peppas (1984) have indicated solute diffusion coefficient in the range of 10^{-6} to 10^{-7} cm^2/s for diffusion in such gels. However, from careful observation of Table 1 following conclusions can be drawn:

1. Before and after centrifugation treatment the diffusivity of caffeine is the same in XG gel, containing 4% XG and 1.6% caffeine, made with water. This is an indication that the possible influence of the air component on the transport of caffeine in XG gels is negligible.
2. The diffusivity of caffeine in XG gel made with USP phosphate buffer pH 7.4 (without dilution) decreases (Fig. 3) with increasing polymer concentration from 4% to 7%. This is obvious, since in solution the chain overlapping concentration (c^*) for XG polymer (Lim et al., 1984) is $\approx 0.02\%$ and the polymer concentrations used in this study were far above c^*. Therefore, the increased polymer chain entanglement in the gel containing higher contents of XG will result in more convolution of the diffusion path.
3. The diffusion of caffeine in 4% XG gel significantly ($p < 0.02$) increases with the addition of 2.4% lactose. This is most likely attributed to the simultaneously diffusion out of lactose with caffeine from the gel matrix into the external medium that results in increase of any physical forces, like osmotic or convective forces, on the diffusion of caffeine. This result is in agreement with the observation that the in vitro release rate of caffeine from XG matrix tablet increases with the addition of lactose in the formulation (Talukdar and Kinget, 1995).

This seems to be in contradiction with an observation by Gao and Fagerness (1995). Recently they have reported that adenazolam mesylate diffusivity in HPMC gel decreases by the presence of lactose in the system. In their study

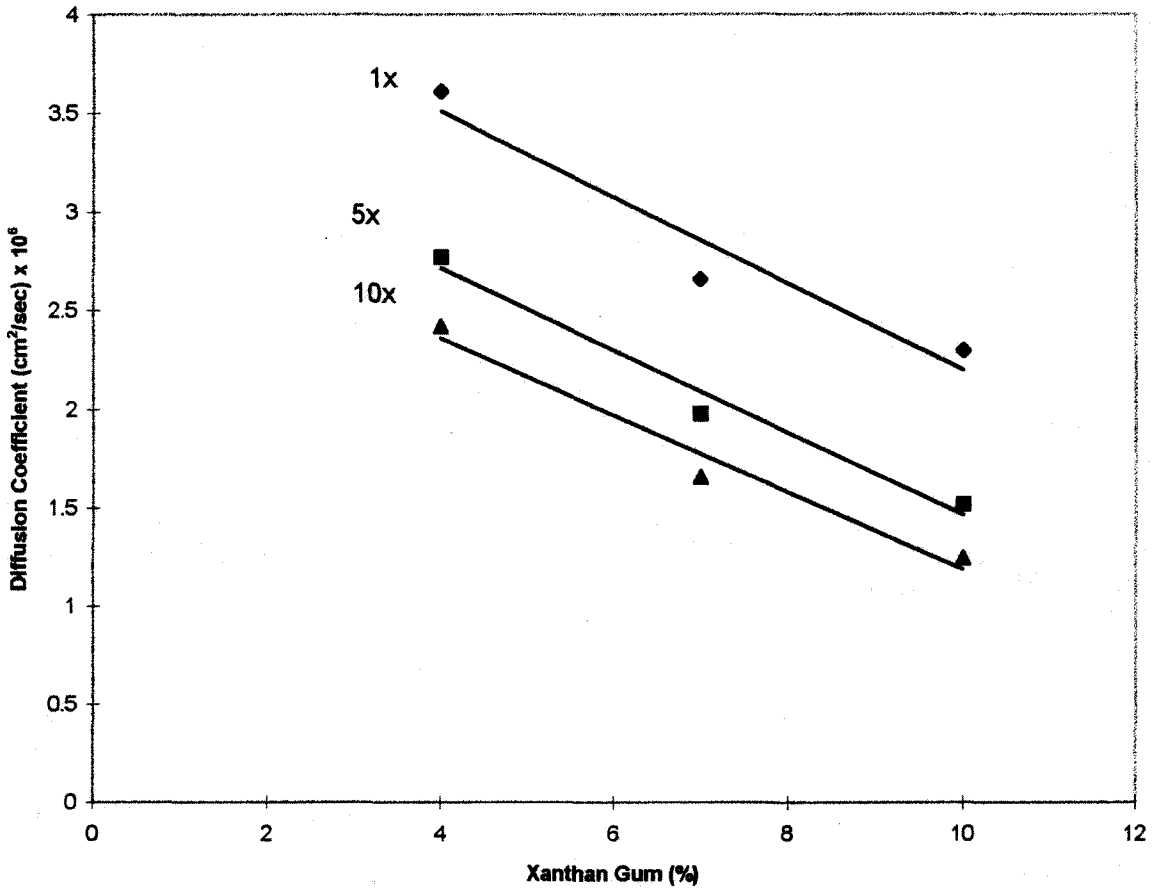

Fig. 3. Influence of buffer dilution on the diffusion of caffeine in XG gels of different polymer concentrations. Each data point represents the mean of three experiments and the solid line indicates the regression line.

they have used pulsed-field-gradient spin-echo (PFGSE) NMR techniques to measure the self-diffusion coefficient of the drug. Since, self-diffusion coefficient is a measure of transport due to the Brownian motion of molecules in the absence of any other physical or chemical driving forces, the applied principles used for measuring the solute diffusivity were quite different than that for the present study.

4. The diffusivity of caffeine in 4% binary or ternary mixture of XG gels is Strongly ($p < 0.01$) dependent on the salt concentrations of the medium used. The higher the ionic strength of the medium, the higher is the diffusivity of the drug.

In order to obtain more evidences, for supporting this conclusion, the present study has been extended by performing the experiments in three different polymer concentrations, i.e. 4, 7 and 10% XG solutions and the results are shown in Fig. 3. These concentrations of XG have been chosen for this study, in order to simulate the outer surface of a hydrated HM tablet. Because recently it was shown that after hydration, the most outer surface of a HM tablet contains about 5% polymer and the polymer concentration increases gradually towards the core of the tablet (Gao and Meury, 1996). The drug diffusion occurs only through the outer hydrated layer (i.e.

Table 2
Diffusion rate and diffusion coefficient (Eq. (3)) of the sodium salt of indomethacin in different types of xanthan gum gels (mean ± S.D.; $n = 3$)

Gel type	Medium used[b]	Diffusion rate		Diffusion coefficient ($D \times 10^6$, cm^2/s)
		%/$min^{1/2}$	mg/$cm^2/min^{1/2}$	
4% XG 2.4% lactose 1.6% Na-indomethacin	Buffer = 1 ×[a]	5.72 ± 0.19	0.207 ± 0.002	1.86 ± 0.30
4% XG 2.4% lactose 1.6% Na-indomethacin	Buffer = 5 ×[a]	5.26 ± 0.18	0.189 ± 0.002	1.55 ± 0.24
4% XG 2.4% lactose 1.6% Na-indomethacin	Buffer = 10 ×[a]	4.45 ± 0.18	0.161 ± 0.001	1.10 ± 0.17

[a] Buffer dilution.
[b] For preparing the gel and, in the acceptor compartment during corresponding diffusion measurement.

the diffusion layer) of the matrix. However, Fig. 3 also demonstrates that the diffusion coefficient of caffeine in XG gels significantly increases with increasing salt concentrations in all three polymer solutions.

3.2. Diffusion of indomethacin sodium in hydrated XG matrices

The various values obtained from the diffusion studies of the sodium salt of indomethacin in different types of XG gels are shown in Table 2. The values of diffusion coefficient were also calculated using Eq. (3), since during the experiment $C_0 \gg C_s$ condition prevails. The similar trend in diffusivity of this drug, as noted for caffeine (see Table 1), can be seen in Table 2. The rank order of diffusivity of caffeine and sodium salt of indomethacin in XG gels made with the buffer after different dilutions is: buffer 1 × > buffer 5 × > buffer 10 × .

Since, both the drugs release (Talukdar et al., 1996a) from XG matrix tablet and the drugs diffusivity in the swollen XG matrices increase with increasing the salt concentrations of the buffer, the release of caffeine and indomethacin sodium from XG matrix tablet is controlled by the diffusion mechanism. If the diffusion through hydrated XG matrices would not be the main mechanism for the release of these drugs, then one would expect different/opposite dependence on salt concentration of drug diffusivity in XG gels and drug release rate from XG matrix tablets. This conclusion is in agreement with a general statement that a soluble drug released from a HM device is controlled by the mechanism of diffusion through the surface hydrated drug–polymer–excipient mass which is immediately formed upon contact with aqueous fluid.

Comparing the diffusivity of the two drugs, i.e. caffeine and indomethacin sodium in XG gels (Fig. 4) it is seen that the diffusion rates of both drugs linearly decrease with increasing buffer dilutions and the diffusivity of caffeine is higher than the sodium salt of indomethacin. Two identical slopes suggest that there is no difference in activity of these two drugs on the media, used for

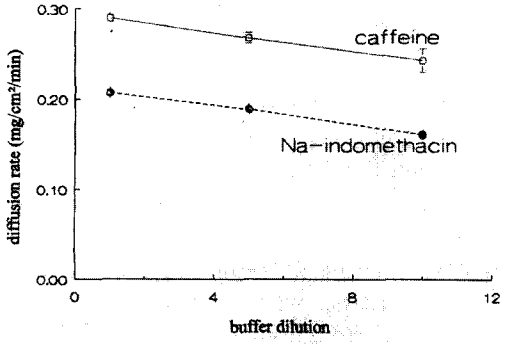

Fig. 4. Diffusivity of caffeine and indomethacin sodium in 4% XG gels. Each data point represents the mean of three experiments and the error bar indicates the standard deviation from the mean.

Table 3
Diffusion rate and diffusion coefficient (Eq. (2)) of indomethacin in different types of xanthan gum gels (mean ± S.D.; $n = 3$)

Gel type	Medium used[b]	Diffusion rate		Diffusion coefficient ($D \times 10^6$, cm^2/s)
		$\%/min^{1/2}$	$mg/cm^2/min^{1/2}$	
4% XG 2.4% lactose 1.6% indomethacin	buffer = 1 ×[a] ($C_s = 2.0$)	2.22 ± 0.11	0.081 ± 0.002	1.55 ± 0.12
4% XG 2.4% lactose 1.6% indomethacin	Buffer = 5 ×[a] ($C_s = 1.6$)	1.69 ± 0.02	0.060 ± 0.001	1.08 ± 0.09
4% XG 2.4% lactose 1.6% indomethacin	Buffer = 10 ×[a] ($C_s = 1.2$)	1.37 ± 0.03	0.048 ± 0.001	0.94 ± 0.06

C_s, solubility of the drug in the matrix substance, mg/ml.
[a] Buffer dilution.
[b] For preparing the gel and, in the acceptor compartment during corresponding diffusion measurement.

preparing the gels. The discrepancy observed between the mobility of caffeine and indomethacin sodium in the swollen polymer mass is due to a difference in either their molecular structural form and size or in activity on the polymer molecules. Indeed this difference in diffusivity could be attributed to a difference in their plasticising effect. Indomethacin sodium enhances the swelling of XG molecule (Talukdar and Kinget, 1995) and caffeine does not. The diffusivity of the former could be slowed down more than the latter in the same gel.

Furthermore, although there is no molecular size screening effect on the transport of small solute in polymer solution/gel (Phillips et al., 1990), it is likely that the mobility of a smaller molecule will be much easier than a larger one. Since the molecular weight of the sodium salt of indomethacin is 379.78 which is nearly double of the molecular weight of caffeine, i.e. 194.2, the diffusion of indomethacin sodium might be more difficult than the diffusion of caffeine in the same gel. Indeed, further study is required to clarify this.

However, the results from diffusion studies are again in accordance with the in vitro release profiles of caffeine and indomethacin sodium from XG matrix tablets, where it was seen that the release rate of the former is higher than the later under the same experimental conditions (Talukdar et al., 1996a).

3.3. Diffusion of indomethacin in hydrated XG matrices

The diffusion coefficients of indomethacin in different types of XG gels were calculated using Eq. (2), since $C_0 \gg C_s$ condition prevails, and are shown in Table 3 together with the values of diffusion rate. Table 3 clearly shows that the diffusion of indomethacin increases with increasing salt concentration as in the case of its sodium salt and caffeine. Again the rank order of indomethacin diffusivity observed in the gel made with buffer is 1 × > buffer 5 × > buffer 10 × .

But this transport behaviour of indomethacin in XG gels is not in accordance with the observed in vitro release rate of indomethacin from XG matrix tablet, since the rank order of indomethacin release rate from XG matrix tablet (Talukdar et al., 1996a) is in buffer 10 × > in buffer 5 × > in buffer 1 × .

This result suggests that indomethacin release from XG matrix tablet is not controlled by the diffusion mechanism. If the release of indomethacin would be controlled by the diffusion of the drug through the swollen polymer mass, one would expect qualitatively the similar rank order for the release rate from the matrix tablet and for the diffusivity in the hydrated XG gels as it was found in case of soluble drugs, i.e. caffeine and indomethacin sodium. Indeed, our recent study (Talukdar et al., 1996c) proved that the release of indomethacin from XG matrix tablet is controlled by the erosion mechanism.

However, comparing the diffusion of indomethacin (Table 3) and its sodium salt (Table 2) it seems that the diffusivity of indomethacin tends to be lower than that of its sodium salt in an identical XG gel. This might be due to one or more of the following reasons:

1. The drug, indomethacin sodium, itself contributes additional salt concentrations in the gel system, which can have the similar influence on its own mobility as it is seen earlier that the increase of salt concentrations causes the increase of the solute transport in the XG gels.
2. The rheological characterization of this polymer solution showed that the presence of indomethacin sodium leads to increase the solution structure of 4% XG in aqueous medium thereby increase the gel strength.
3. During diffusion experiment visually it was observed that the gel containing indomethacin sodium exerts relatively more osmotic pressure on the filter paper used.

4. Conclusions

Drug diffusion in hydrated HPMC matrices is higher than in hydrated XG matrices. This differences in drug diffusion between the two polymer solution well explain the reason for previously observed higher ability of XG than HPMC to retard the release of a drug when they used as matrix forming agent, for controlled-release drug delivery. Both the release rate from the matrix tablets and the diffusivity in the hydrated matrices of soluble drugs, like indomethacin sodium and caffeine, increase with increasing the salt concentration of the medium. This findings suggest that the diffusion mechanism is operative for the release of these drugs from XG matrix tablets. While in the case of insoluble drug, like indomethacin, the release rate decreases and the diffusivity increases with increasing the salt concentration. This indicates that other than diffusion mechanism, like matrix erosion is operative for the release of insoluble drug from XG matrix tablets.

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