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Comparative study on xanthan gum and hydroxypropylmethyl cellulose as matrices for controlled-release drug delivery I. Compaction and in vitro drug release behaviour

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Abstract

A comparative investigation has been undertaken to assess the performance of xanthan gum (XG) and hydroxypropylmethyl cellulose (HPMC) as hydrophilic matrix-forming agents in respect of compaction characteristics and in vitro drug release behaviour. The overall compaction characteristics are found to be quite similar to each other and typical of polymer behaviour. But the flow characteristics are different, i.e., XG is more readily flowable than HPMC. The observed difference in drug release profiles between these two potential excipients are explored and explained by the difference in their hydrophilicity and subsequent hydration properties.

Keywords: Xanthan gum; Hydroxypropylmethyl cellulose; Hydrophilic matrices; Hydration; Controlled release

1. Introduction

Since its introduction, the hydrophilic matrix (HM) system is becoming an interesting industrial method to prepare controlled release dosage forms for oral administration. Its convenience and easiness to manufacture cut down the costs of the final product. Besides, this system offers several additional advantages, well exemplified in the literature (Melia, 1991), over other technologies for controlled release drug delivery. When such a device is exposed to an aqueous medium it does not disintegrate, but immediately after hydration it develops a highly viscous gelatinous surface barrier which controls the drug release from and the liquid penetration into the centre of the HM system. The overall release rate of a drug from this HM system is controlled by one or more of the following processes: transport of the solvent into the device, swelling of the associated matrix, diffusion of the solute through the swollen matrix,

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erosion of the swollen matrix, etc. (Rao and Devi, 1988).

The mechanism of, and the influence of various technological and formulation variables on, the drug release from HM systems have been well studied and reviewed by many authors (Lapidus and Lordi, 1968; Bamba et al., 1979; Salomon et al., 1979; Buri and Doelker, 1980; Harris and McGinity, 1982; Korsmeyer et al., 1983; Alderman, 1984; Doelker, 1987; Rao and Devi, 1988; Melia, 1991; Timmins et al., 1992; Vàzquez et al., 1992).

Until now a large number of natural and synthetic polymers, single or in a combination, were tested as HM excipients, e.g. cellulose ethers, polyvinyl alcohol, hydroxyethyl methacrylate, ethylene–vinyl alcohol, poly(ethylene oxide), thermally modified starch, chitosan, schleroglucan, γ-carrageenan, Na-alginate, gelatin, carbopol, veegum, etc. (Lapidus and Lordi, 1968; Bamba et al., 1979; Salomon et al., 1979; Buri and Doelker, 1980; Harris and McGinity, 1982; Korsmeyer et al., 1983; Alderman, 1984; Doelker, 1987; Rao and Devi, 1988; Melia, 1991; Timmins et al., 1992; Vàzquez et al., 1992). Nevertheless, among them only hydroxypropylmethyl cellulose (HPMC), a cellulose ether, is the excipient chosen by most formulators for HM system preparation. Most probably due to its claim as a fast gel formation to control initial release, and formation of strong, viscous gels to control drug release (The Dow Chemical Company, 1987). However, the major disadvantage with HPMC is that the drug release from this matrix-forming agent does not follow time-independent kinetics (Ford et al., 1985; Rao and Devi, 1988; Shah et al., 1993). Our previous studies (Talukdar and Plaizier-Vercammen, 1993; Talukdar and Kinget, 1995) with xanthan gum (XG), a natural derivative of cellulose, showed that the drug release from this microbial exocellular polysaccharide follows zero-order or almost time-independent release kinetics, which is in accordance with the finding of others (Ingani and Moès, 1988; Fu Lu et al., 1991; Dhopeshwarkar and Zatz, 1993; Dumitriu et al., 1993).

The objective of this work was to look into the matrix forming properties of XG and its use as a suitable HM system agent compared to an extensively investigated HM excipient, i.e., HPMC in respect of (1) compaction behaviour of these two potential excipients, (2) in vitro drug release rate, and (3) hydration rate of the polymers by image analysis. In this study three drugs with different properties, e.g. caffeine as a soluble neutral drug, indomethacin as an insoluble acidic drug, and sodium salt of indomethacin as a soluble acidic drug, were used.

2. Materials and methods

2.1. Materials

Xanthan gum (Rheogel®) (Iranex, Rouen, France), viscosity min. 1500 mPa·s (1% w/w in aqueous solution with 1% KCl at 60 rpm, Brookfield) according to the supplier, moisture content = 11%, 200 mesh, surface area = 0.716 m^2/g (B.E.T method), true density = 1.518 g/cc (with a Beckman helium pycnometer); hydroxypropylmethyl cellulose (Methocel K4M premium) (Dow Chemical Company, Midland, Michigan, U.S.), viscosity 4000 mPa·s (2% in H_2O at 20°C) according to the supplier, moisture content = 5%, 200 mesh, surface area = 0.731 m^2/g, true density = 1.318 g/cc; caffeine anhydride (Ph.Belg.VI), 80 mesh; indomethacin (BP.80), mean particle size 8.4 μm (measured with Coulter multisizer II); sodium salt of indomethacin (MSD Research Lab., Rahway, N.J., U.S.); lactose (Ph.Belg. VI.), 200 mesh and potassium dihydrogen phosphate; sodium hydroxide and sodium chloride of analytical grade were used.

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

2.2. Measurements of surface area and flow behaviour of polymers

The total surface area of powder polymers was measured by nitrogen gas adsorption using the Quantasorb surface area analyzer (Quantachrome, Greenvale, New York, U.S.) according to Michoel et al. (1986).

The flow characteristics of the materials were assessed by calculating the compressibility (Carr)

index (CI) from the data of bulk and tapped density of pure polymers (before sieving). The standard procedures and formulae were used to determine the bulk and the tapped density of powders as well as to calculate the CI (%) value (Fiese and Hagen, 1986).

2.3. Tabletting and Heckel plots

For drug release studies 180.0 mg weight of matrix tablets (porosity = 15 ± 2%) were prepared (at 42% RH) from a mixture of polymer-drug-lactose (5:2:3) using a flat-surface single punch (11 mm) instrumented Korsch MP1 tabletting machine according to the method described elsewhere (Talukdar and Kinget, 1995). After compaction tablets were stored in an atmosphere of 42% RH until used.

Approx. 200.0 mg weight of pure polymer or a powder mixture of polymer-caffeine (1:1) or polymer-caffeine-lactose (5:2:3) were used to obtain Heckel plots. The details of the procedure applied for Heckel plots have been previously reported by Michoel et al. (1986).

2.4. Matrix hydration and drug release study

For hydration study matrices containing 100% polymer were placed in a petridish containing water as penetrating medium, under a CCD-camera connected to a computer equipped with an image analysis system (DATA TRANSLATION®, Malboro, MA, US). At predetermined time intervals the images of the matrices were taken and, by counting the pixels from those images with a software package of PC-IMAGE for Windows (Foster Findlay Associate Ltd, Newcastle upon Tyne, UK), the area of the inner dry core and the area of the outer hydrated surface were calculated.

The drug release was measured according to the USP XXII paddle method under sink conditions at 50 rpm in 1000 ml dissolution medium at 37°C. At predetermined time intervals (10 min), samples (1 ml) were taken by 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).

2.5. Data treatment

The dissolution data were fitted according to the well-known exponential Eq. (1), which is often used to describe the drug release behaviour from polymeric systems:

$$\frac{M_t}{M_\alpha} = Kt^n \tag{1}$$

where, M_t/M_α is the fractional (0.1–0.7) drug release at time t; K is 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, in the case of a tablet, $n = 0.45$ 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).

Although the constant K in Eq. (1) is one of the measures of the drug release rate, it should not be used for comparison because there are different kinetics in different test conditions. Therefore, to characterize the drug release rate in different experimental conditions mean dissolution time (MDT) was calculated from dissolution data according to Möckel and Lippold (1993) using Eq. (2).

$$\mathrm{MDT} = \frac{n}{n+1} K^{-1/n} \tag{2}$$

Besides, to quantify the amount of drug released by Fickian diffusion and by polymer relaxation, the release data were also fitted with Eq. (3) using a software package of nonlinear regression analysis (XYmath ShareWare Version 2.4, C. Taylor, Sacramento, US).

$$\frac{M_t}{M_\alpha} = K_1\sqrt{t} + K_2 t \tag{3}$$

The first and the second terms on the right hand side of Eq. (3) represent the Fickian diffusion and the Case II relaxation contributions, respectively (Peppas and Sahlin, 1989).

To compare the means of three experiments at the different experimental conditions and to assess statistical significance between them, either one-

Table 1
Compaction behaviour of XG and HPMC with or without drug and lactose from Heckel plots

	Single compact (100% polymer)		Binary compact (polymer: drug = 1:1)		Ternary compact (polymer:drug:lactose = 5:2:3)	
	XG	HPMC	XG	HPMC	XG	HPMC
Hardness (KP)	7.6	18.1	3.7	8.7	1.6	6.7
Yield pressure (MPa)	72.7	48.9	88.9	86.4	93.0	76.6
Plastic deformation (%)	34	32	18	17	20	20
Fragmentation (%)	12	21	27	31	27	28
Elastic recovery (%)	13.9	16.2	8.4	9.0	8.8	9.4

way analysis of variance (ANOVA) or an unpaired two-tailed t-test was carried out at 5% level.

3. Results and discussion

3.1. Flowability and tabletting properties of XG and HPMC

Although the determination of flow rate (g/s) through a circular orifice is the direct assessment of flow properties of a powder material, the flow rate determination of HPMC was not possible due to development of electrostatic charge during flow.

Since the CI indirectly measures the flowability of powder mass (Fiese and Hagen, 1986), the CI value of XG and HPMC was measured and found to be 18 and 26% for XG and HPMC, respectively. This result is an indication that the transport through the hopper into the feed frame and for subsequent die filling could be better for the drug mixture with XG than with HPMC because it is known that the CI value above 23% indicates poor flowability (i.e. non-free-flowing) of a material (Fiese and Hagen, 1986).

The important tabletting characteristics of these polymers with and without drug and lactose are summarised in Table 1. Both pure polymers show plastic behaviour, indicated by their low yield pressure (Marshall, 1986; Sanghvi et al., 1993). The lower value for HPMC indicates a larger total deformation. The relative amount of useful deformation, namely the sum of percentage plastic deformation and percentage fragmentation, is also higher for HPMC. Therefore more bonding will occur in the case of HPMC, resulting in tablets with increased hardness. The tablets formed seem to be strong enough to counteract the negative effect of the rather high percentage of elastic recovery. Both plastic and elastic behaviour are typical for such polymers and are also shown by microcrystalline cellulose (Krycer et al., 1982).

Addition of 50% non-polymeric material as caffeine will decrease plastic behaviour, resulting in higher yield pressures. Tablets will be weakened, resulting in lower hardness values, as shown in Table 1. Replacing caffeine by lactose has only negligible effects on the overall behaviour of both excipients.

3.2. Release of caffeine from XG and HPMC matrices in water

When a dry HM tablet is placed in a medium, which is thermodynamically compatible with the polymer matrix, the solvent penetrates into the free spaces between macromolecular chains. After solvation of the polymer chains, the dimensions of the polymer molecule increase due to the polymer relaxation by the stress of the penetrated solvent. This phenomenon is defined as swelling and it is characterized by the formation of a gel-like network surrounding the tablet. With time the penetrant moves inward and simultaneously the thickness of the swollen region increases outward. Finally, the completely hydrated outer layer starts to disperse due to an attrition process which

furthermore allows the penetration of liquid to continue until the tablet completely disperses or disappears. Depending on the solubility of the drug the operative principle(s) of releasing the solute molecule from this HM system is/are diffusion through or/and erosion of the swollen polymer matrix (Alderman, 1984).

Fig. 1 represents a typical release profile of caffeine, in Milli-Q water, from XG and HPMC matrices expressed in percentage released vs. time. Fig. 1 shows that there are many differences in the release behaviour of caffeine between XG and HPMC matrices in respect of the following important considerations.

Firstly, an initial burst release of the drug is observed with HPMC matrices, which is absent with XG matrices. Such a burst effect with HPMC was also observed by other investigators and has already been reported in the literature (Rao and Devi, 1988). Here, it is important to note that this initial rapid release of the drug from the HM system is often therapeutically undesirable because the total amount of drug released is remarkably influenced by this initial control of release from the dosage form.

Secondly, the overall rate of release of caffeine from HPMC matrices is significantly ($P < 0.0001$) higher than that from XG matrices, which is confirmed from smaller MDT (3.15 ± 0.05 h) for HPMC and higher MDT (3.87 ± 0.02 h) for XG matrices. This result is a clear indication that XG has higher drug-retarding ability than HPMC. This is again in agreement with the literature (Dhopeshwarkar and Zatz, 1993), where it has been mentioned that three times more HPMC is needed than XG to get a similar sustained release profile of acetaminophen in the same medium. This makes XG economically more interesting because a comparatively large amount of drug can be loaded in XG matrices without excessive increase in weight.

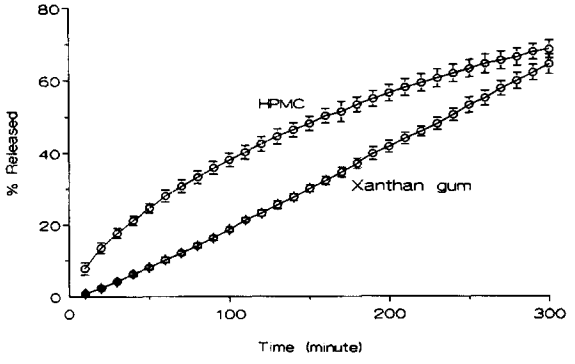

Fig. 1. Release profiles of caffeine in water from XG and HPMC matrices. Each data point represents the mean of three experiments and the error bar indicates the standard deviation from the mean.

Thirdly, the drug release from XG matrices is linear with time (i.e., zero-order kinetics) until the end of the experiment while the release of caffeine from HPMC matrices decreases with increasing time, which is typical for Case I diffusion behaviour and characterized by the Higuchi equation. This is also confirmed from the calculated value of the release exponent (n). It was found that the value of the exponent (n) approaches unity ($n = 1.1$) for XG while it approaches 0.5 ($n = 0.57$) for HPMC matrices. Here again it is noteworthy that to get constant drug level in the blood plasma zero-order release kinetics is a prerequisite and this can be achieved from XG matrices.

If the surface area of the polymer is not large enough to cover the drug particle at the surface of the matrix there is a great chance of burst effect in drug release. Again, if the polymer does not hydrate quickly, the surface barrier can not be formed immediately, which may cause a large portion of drug to be released during the fast initial phase of release profile. Thus the surface area as well as the hydration rate of the polymer can play an important role in drug release from matrix tablets, especially at the beginning of the release profile. Therefore, it is often mentioned in the literature (Alderman, 1984; The Dow Chemical Company, 1987) that quick hydration and subsequent gel formation is a foremost and important property of an excipient for it to be used for sustained release formulation.

Data from the determination of surface area of the same sieve fraction (200 mesh) suggest that the total surface areas of these two polymers are almost equal (XG, 0.716 m^2/g; HPMC, 0.731 m^2/g). This indicates that the observed discrepancy in initial drug release from XG and

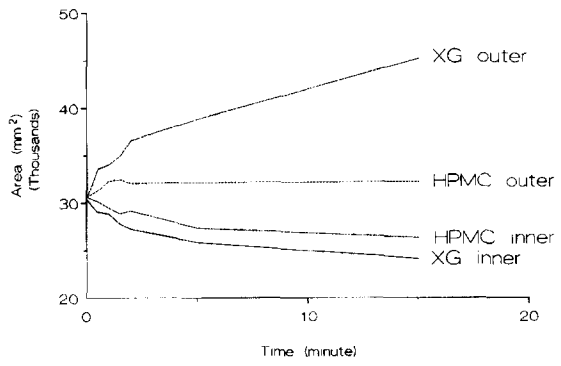

Fig. 2. Hydration of xanthan gum and HPMC compacts.

HPMC matrices can be attributed only to the slower hydration rate and extent of HPMC than XG. This is proved by the experimental results of matrix hydration and shown in Fig. 2. Here it is worthy to note that the grade of HPMC used during this study, Methocel K, is the fastest to hydrate among all HPMC family, because Methocel K products have a lower amount of the hydrophobic methoxyl substitution and a higher amount of the hydrophilic hydroxypropoxyl substitution (The Dow Chemical Company, 1987). Again the differences in hydration property between XG and HPMC can be explained by the difference in their hydrophilicity. Xanthan gum, being more hydrophilic than HPMC (Fig. 3), hydrates quickly and a protective barrier layer is formed immediately. The hydrophilicity of the polymers was determined by keeping the dry polymers in different saturated salt solutions and measuring the equilibrium moisture content in different relative humidity conditions.

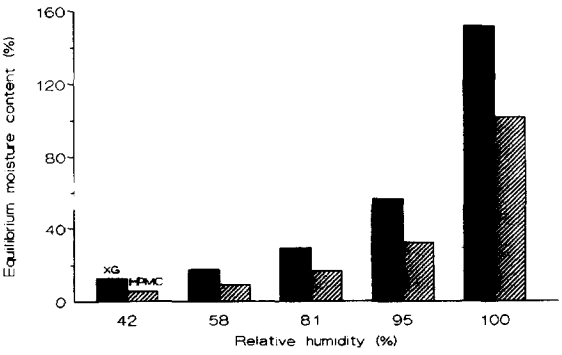

Fig. 3. Hydrophilicity of xanthan gum and HPMC.

The more the matrix swells, the longer the diffusion pathlength required for the drug to come out, which results in decreasing of release rate. As can be seen in Fig. 2, the outer surface area of the XG tablet is significantly higher, which is a distinct indication of the higher extent of swelling than for HPMC. This may explain the observed difference in release rate of caffeine between XG and HPMC matrices. Being a soluble drug, caffeine comes out from the HM system by the mechanism of diffusion. Besides, the mechanical properties of the surface-hydrated gelatinous barrier play an important role in overall drug release rate, especially when the drug is released by the erosion mechanism. A strong protective gel-barrier will be less susceptible to erosion, resulting in a decrease drug release. The viscoelastic measurement of 4% (w/w) and 7% (w/w) polymer solutions in Milli-Q water proved that XG shows gel-like properties and HPMC shows simple polymer solution behaviour. This indicates that the HPMC matrices are more susceptible to erosion than the XG matrices. The details of viscoelastic measurements will appear in our next communication.

3.3. *Influence of drug solubility and ionic strength of the medium on drug release*

Table 2 illustrates the release exponent (n), the ratio of diffusional (K_1) to relaxational (K_2) contribution, and the MDT of caffeine, indomethacin, and Na-indomethacin from XG and HPMC matrices in USP phosphate buffer pH 7.4 at different concentrations. From the careful observation of Table 2 the following can be noted:

(i) From both polymers the MDT of soluble drugs (e.g., caffeine and sodium indomethacin) are significantly lower than those of insoluble drugs (e.g., indomethacin). This indicates that the release of soluble drugs is faster than the release of insoluble drugs from both matrices. This discrepancy in release rate between soluble and insoluble drugs can be attributed to the difference in their release mechanisms. Being soluble drugs, caffeine and sodium indomethacin are released by the mechanism of diffusion, while indomethacin, being an insoluble drug, is released predominantly via erosion (Alderman, 1984).

Table 2
The mean dissolution time (MDT), the release exponent (n) and the ratio (K_1/K_2) of diffusional to relaxational contribution of different drugs from XG and HPMC matrices in USP phosphate buffer (pH 7.4) of different ionic strength (mean ± SD; $n = 3$)

Drug	Ionic strength (μ)	Xanthan gum			Hydroxypropylmethyl cellulose	
		MDT	n	K_1/K_2	MDT	n
Caffeine	0.01145	5.56 ± 0.17	0.78 ± 0.01	1.974	3.27 ± 0.51	0.61 ± 0.05
Caffeine	0.0229	4.91 ± 0.13	0.74 ± 0.01	2.818	3.41 ± 0.56	0.58 ± 0.02
Caffeine	0.1145	3.40 ± 0.10	0.68 ± 0.01	6.811	3.13 ± 0.85	0.56 ± 0.01
Indomethacin	0.01145	17.95 ± 0.74	1.18 ± 0.03		14.75 ± 1.69	0.97 ± 0.05
Indomethacin	0.0229	19.44 ± 0.52	1.01 ± 0.01	0.108	14.26 ± 3.85	0.99 ± 0.08
Indomethacin	0.1145	22.73 ± 1.46	0.82 ± 0.02	1.781	22.21 ± 1.60	0.81 ± 0.02
Na-Indomethacin	0.01145	7.74 ± 0.22	0.84 ± 0.01	1.360	5.52 ± 0.69	0.63 ± 0.01
Na-Indomethacin	0.0229	7.18 ± 0.22	0.79 ± 0.01	1.773	5.22 ± 0.76	0.63 ± 0.02
Na-Indomethacin	0.1145	6.79 ± 0.19	0.73 ± 0.02	3.034	7.66 ± 0.41	0.62 ± 0.03

(ii) The MDT of all three drugs from XG matrices are higher within the experimental range of ionic strength except the MDT of sodium indomethacin with ionic strength 0.1145, where it is lower (6.8 h) than HPMC matrices (7.7 h). Since the drug release from XG matrices is ionic strength-dependent (Ingani and Moès, 1988; Talukdar and Kinget, 1995), the exception at $\mu = 0.1145$ can be attributed to a high total ionic strength due to the contribution of the drug itself (i.e., sodium indomethacin) in the gel. Here it is worthy to note that the range of ionic strength chosen for this study was on the basis of the range of ionic strength of the gastro-intestinal tract (Johnson et al., 1993).

(iii) The standard deviation from the mean of three experiments is small from XG matrices with all drugs in all media. This is an indication of higher reproducibility in drug release from XG matrices. This result once again proves the superiority of XG over HPMC for controlling the drug release rate.

(iv) The rate as well as the mechanism of drug release from HPMC matrices are almost independent of the ionic strength of the medium while a log-linear relationship between ionic strength (μ) and *MDT* (Fig. 4) as well as between μ and release exponent (n) (Fig. 5) is found when XG is used as matrix forming agent. This dependency of the drug release on ionic strength has already been explained by the dependency of swelling of xanthan gum on ionic strength of the medium (Talukdar and Kinget, 1995).

(v) The diffusional contribution on the release of drugs from XG matrices increases with increasing salt concentration of the medium, i.e., the ratio of K_1 to K_2 increases with increasing μ. Comparing two soluble drugs, e.g. caffeine and sodium indomethacin, it is seen that the diffusional contribution is higher for the former than the latter in all the media used in this study, indicating a higher diffusional rate for caffeine than for the sodium salt of indomethacin. This difference may explain the lower MDT of caffeine than sodium indomethacin for the same ionic strength of the medium. A smaller molecular size for caffeine (molecular weight = 194) than for the

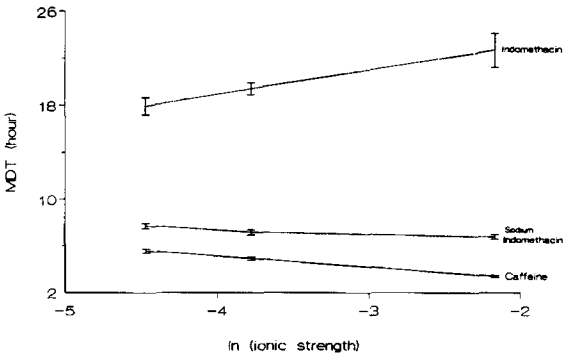

Fig. 4. The relationship between MDT of drugs from XG matrices and ionic strength (μ) of the dissolution medium. Each data point represents the mean of three experiments and the error bar indicates the standard deviation from the mean.

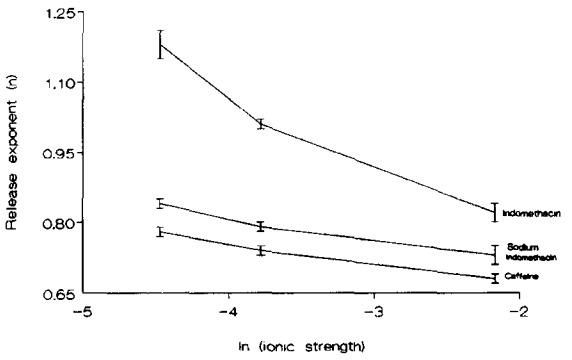

Fig. 5. The relationship between release exponent (n) of drugs from XG matrices and ionic strength (μ) of the dissolution medium. Each data point represents the mean of three experiments and the error bar indicates the standard deviation from the mean.

sodium salt of indomethacin (molecular weight = 380) may be the cause of higher diffusional contribution in case of caffeine than sodium indomethacin. Further research on diffusion of drugs from these matrices is in progress.

4. Conclusions

In respect of controlled drug release behaviour xanthan gum matrices have some important pharmaceutical as well as economical advantages (e.g., absence of initial burst release, higher drug-retarding ability, more reproducibility in drug release, and the possibility of zero-order release kinetics) over HPMC matrices. Considering the influence of ionic strength of the medium on drug release behaviour xanthan gum has a disadvantage that the drug release is influenced by the total salt concentration within the range of gastro-intestinal tract, while the drug release from HPMC matrices is independent of ionic strength. But this ionic strength dependency should not be considered as a total failure of XG for controlling the drug release. Compaction characteristics between the two polymers are quite similar, but the flowability of xanthan gum is better than that of HPMC.

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