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Microviscosity of hydroxypropylcellulose gels as a basis for prediction of drug diffusion rates

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Abstract

This study investigated the influence of the rheological properties of hydroxypropylcellulose (HPC) gels on the in vitro release of theophylline included in the gel at 0.2 g/l. Experiments were performed with six HPC varieties (mean molecular weight between 5×10^5 and 1.2×10^6, nominal viscosity between 100 and 4000 mPa·s) at concentrations of 0–2% (w/w). Theophylline diffusion coefficients at 37°C ranged from 3.5×10^{-7} to 1.1×10^{-3} cm^2/min, and were in all cases markedly higher than those predicted on the basis of gel macroviscosity as determined by capillary viscometry. In general, the theophylline diffusion coefficient declined exponentially with HPC concentration; in the case of the lowest-molecular-weight HPC, however, the diffusion coefficient remained constant to HPC concentrations of up to 0.8%, probably because of the high entanglement concentration of the HPC. Gel microviscosities as determined by dynamic light scattering (DLS) with latex microspheres (162 nm diameter) were considerably lower than the macroviscosities determined by capillary viscometry, and similar to microviscosities estimated on the basis of theophylline diffusion. Nevertheless, macroviscosity was correlated with microviscosity, suggesting that it is of value for approximate estimates of rates of diffusion of theophylline from HPC gels.

Keywords: Diffusion; Dynamic light scattering; Gels; Hydroxypropylcellulose; Theophylline; Viscosity

1. Introduction

Cellulose ethers are common components of pharmaceutical preparations, whether for topical use (Babar et al., 1992; Demou et al., 1994; Wu et al., 1998) or oral administration (Vázquez et al.,

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1992; Sung et al., 1996). In solid and semisolid dosage forms of this type, the rate of diffusion of the drug through the gel formed on hydration of the polymer is typically the key factor determining release rate (Vázquez et al., 1992; Demou et al., 1994; Gao et al., 1995). As a result, the effects of formulation variables on drug diffusion rate are of considerable practical relevance (Sarisuta and Parrott, 1983; Phillies and Clomenil, 1993; Sung et al., 1996; Lu and Jun, 1998).

Drug diffusion rates in aqueous dispersions of polymers are basically governed by the restrictive effects of the polymer on drug mobility, whether due to a reduction in free volume or an increase in medium viscosity (Sarisuta and Parrott, 1983; Demou et al., 1994; Kumar and Himmelstein, 1995; Suh and Jun, 1996). Systems of this type generally show an inverse relationship between release rate and gel viscosity, of the type predicted by the Stokes–Einstein equation (Nelson and Shah, 1987; Shah and Nelson, 1987; Wan et al., 1992), so that apparent viscosity has been widely used as a routine predictor of a gel's resistance to diffusion. However, studies performed with dispersions of certain hydrophilic cellulosic (Smidt et al., 1991) and non-cellulosic polymers (Smidt et al., 1991; Suh and Jun, 1996) have indicated that drug diffusion rate scarcely changes over wide polymer concentration ranges that show considerable variation in apparent viscosity. It has been suggested that this non-compliance with the Stokes–Einstein equation is because drug diffusion rate when polymer concentration in the medium is low is affected largely by solvent viscosity, the effects of the polymer molecules being less important (Nelson and Shah, 1987). In other words, the effects of the polymer molecules on the macroscopic flow properties of the system (i.e. on macroscopic movement, evaluated as viscosity) do not necessarily correlate with effects on diffusion (i.e. movement at the microscopic scale). This has led some workers to suggest that the property known as microviscosity (i.e. a measure of viscosity at the microscopic scale) should be used instead of macroviscosity as a predictor of drug diffusion rate in systems of this type (Al-Khamis et al., 1986; Smidt and Crommelin, 1991). It is often unclear which approach is preferable for a given system (Amstrong et al., 1987; Gebre-Mariam et al., 1991).

In the present study, we evaluated drug diffusion rate in hydroxypropylcellulose (HPC) gels containing between 0.2 and 2.0% HPC. We also determined both the micro- and macroviscosities of HPC gels containing different proportions of HPC, in order to assess which parameter was the most effective for predicting drug diffusion rate. The drug used was theophylline, which is frequently administered in controlled-release solid dosage forms or gels (Martindale, 1998).

2. Materials and methods

2.1. Materials

Hydroxypropylcelluloses Klucel® GF (nominal viscosity 100–400 mPa·s) (lot FP10-10293) and Klucel® MF (n.v. 1000–4000 mPa·s) (lot 7857) were from Aqualon, Hercules Inc. (USA). Hydroxypropylcelluloses Nisso® M (n.v. 100–400 mPa·s) (lots BJ-031, DC-631 and JD-471) and Nisso® H (n.v. 1000–4000 mPa·s) (lots BJ-141 and JE-161) were from Nippon Soda Co. (Japan). Triton® X-100 (polyethyleneglycol *tert*-octylphenyl ether) was supplied by Analema (Spain). Polystyrene latex microspheres, diameter 162 nm, were from Duke Scientific Co. (Palo Alto, CA, USA).

2.2. Characterization of polymers

2.2.1. Intrinsic viscosity and molecular weight

The viscosity of aqueous dispersions (0.015, 0.030, 0.045, 0.060 or 0.075% (w/w) of HPC) at 25°C was measured in a Cannon–Fenske capillary viscometer (six determinations per product). Intrinsic viscosity was estimated by fitting Martin's equation (Bardet and Alain, 1975) to the results thus obtained. Mean molecular weight (M) was estimated by the Mark–Houwink equation:

$$[\eta] = KM^a \quad (1)$$

where $[\eta]$ is intrinsic viscosity, and K and a are constants assigned values of 6.25×10^{-5} and 0.84, respectively (Wirick and Waldman, 1970).

2.2.2. Heat of hydration-solution

The heat of hydration-solution of each HPC at 25°C was determined in duplicate in a Tronac 458 (Tronac Inc., Utah, USA) isoperibol titration calorimeter (Tronac Inc, 1992). All assays used 0.050–0.100 g of sample that had been dried for 1 h at 70°C and 50 ml of distilled water.

2.2.3. Cloud point

Cloud point (i.e. temperature at which transmittance is half that at room temperature) was determined in 2.0% dispersions by measuring transmittance (800 nm, Shimadzu UV-240, Kyoto, Japan) at increasing temperatures (5°C steps until close to cloud point, then 0.2°C steps) (Mitchell et al., 1990). Cloud point was also determined in suspensions made up in the same way but containing 0.2 g/l theophylline.

2.2.4. Characteristic entanglement concentration

Characteristic entanglement concentration (Cec) was estimated on the basis of rotational viscometry (Brookfield DVII apparatus, Stoughton, USA) of 0.4, 0.8, 1.2, 1.6, 2.0 and 2.8% HPC dispersions at 37°C (three replicate determinations per dispersion). First, low- and high-shear viscosities were calculated for each flow curve by fitting the Caramella et al. (1989) modification of the Cheng–Evans equation. Cecs were then determined by fitting third-order polynomial functions to the plots of low-shear viscosity against concentration and high-shear viscosity against concentration (Caramella et al., 1989).

2.3. Rheologic characterization of HPC dispersions

2.3.1. HPC–surfactant interactions

Interactions of this type were investigated by rheometric characterization at 37°C of 2% HPC gels with and without Triton X-100. Creep–recovery profiles were obtained, and elastic modulus (G') and viscous modulus (G'') were determined by oscillatory shear. All determinations were done in triplicate in a Rheolyst AR-1000N rheometer (TA Instruments, Newcastle, UK) equipped with an AR2500 data analyser and a thermostatted concentric-cylinder adapter. First, the linear viscoelasticity interval was determined with a strain sweep at 1 rad/s. Creep–recovery profiles were then obtained by application of 0.1 Pa for 5 min. Finally, for determination of G' and G'', we performed frequency sweeps over the range 0.05–50 rad/s. The viscoelasticities of HPC dispersions made up in 1 g/l Triton X-100 were determined by a similar procedure.

2.3.2. Macro- and microviscosity

The macroviscosity of aqueous dispersions of polymer at concentrations ranging from 0.0 to 1.2% in water and in 1 g/l Triton X-100 was determined in triplicate at 37°C with Cannon–Fenske capillary viscometers, following USP procedures (United States Pharmacopeia, 1990). The microviscosity of these dispersions was estimated from diffusion coefficients for polystyrene latex microspheres (162 nm diameter) (Duke Scientific Co., Palo Alto, CA, USA) using Eq. (2):

$$\frac{\eta}{\eta_0} = \frac{D_0}{D} \tag{2}$$

where η and η_0 are the viscosities (mPa·s) of the polymer dispersion and of medium without polymer, respectively, and D and D_0 are diffusion coefficients (cm^2/min) for the microspheres in the presence and absence of polymer, respectively.

Diffusion coefficients were in each case estimated on the basis of six replicate assays, by dynamic light scattering (DLS) in a Zetasizer 3 apparatus (Malvern Instruments Ltd., UK) equipped with an AZ10 measurement cell, an He–Ne laser and a Multi 8 integrator–correlator (7032 CN). Measurement angle was 90°, temperature 37°C and data acquisition time 30 s.

To investigate the relationship between diffusion coefficients and polymer concentration, we used the simplified exponential equation proposed by Phillies et al. (1985):

$$\frac{D}{D_0} = \exp(-\alpha c^{\nu}) \tag{3}$$

The dependence of the parameter α on the molecular weight of the polymer, and relationships between micro- and macroviscosity, were evaluated by non-linear regression with the aid of the statistics package Statgraphics®.

Table 1
Basic properties of the HPCs studied[a]

Polymer	Molecular weight	Heat of hydration-solution (J/g)	Cloud point (°C)	Entanglement concentration (%)
Klucel® GF	479000	83.84 (1.87)	41.5 (0.1)	1.20
Nisso® M-BJ	599000	96.16 (0.38)	46.0 (0.1)	0.80
Nisso® M-DC	570000	97.11 (1.34)	46.4 (0.1)	0.80
Nisso® M-JD	537000	98.08 (0.23)	46.5 (0.1)	0.80
Nisso® H-BJ	1070000	97.69 (1.23)	45.5 (0.1)	0.42
Nisso® H-JE	1130000	99.80 (0.85)	45.4 (0.1)	0.42
Klucel® MF	1228000	82.95 (0.54)	41.5 (0.1)	0.41

[a] All values are means of six replicate determinations; values in parentheses are S.D.

2.4. Theophylline diffusion

2.4.1. Preparation of gels

Each of the HPCs was used to make up gels containing 0.2, 0.4, 0.8, 1.2, 1.6, 2.0 or 2.8% (w/w) polymer. The required amount of polymer was dispersed in 100 ml of a solution of theophylline at 0.2 g/l in distilled water. After shaking until a homogeneous appearance had been obtained, the system was left to stand for 24 h at 4°C. Gels were characterized after at least 10 min at 37°C, once probed that this time is long enough for thermal equilibration.

2.4.2. Macroviscosity

The macroviscosity of each dispersion was determined as described in Section 2.3.2.

2.4.3. Diffusion assays

Assays for the characterization of theophylline release from the different gels were performed in triplicate in Franz–Chien vertical diffusion cells (Vidra Foc, Valencia, Spain) fitted with cellulose acetate membrane filters (0.45 μm pore size) (CA502500, Teknokroma, Barcelona, Spain) between the donor and recipient compartments. A sample of 2.00 ml of the test formulation, at 37°C, was placed in the donor compartment; the recipient compartment contained 5.20 ml of distilled water, thermostatted at 37°C and stirred with a magnetic rod. The area available for diffusion was 0.785 cm^2. Samples (0.50 ml) were taken from the recipient compartment at intervals over an 8-h period, for determination of theophylline on the basis of absorption at 271 nm (Shimadzu UV-240, Kyoto, Japan); in each case, recipient medium volume was immediately made up with distilled water. Diffusion coefficients were estimated by fitting the Higuchi (1962) equation:

$$\frac{Q}{A} = 2C_0\left(\frac{Dt}{\pi}\right)^{1/2} \quad (4)$$

where Q is the amount of theophylline (mg) released by time t (s), A is diffusion area (cm^2), C_0 is the initial concentration of theophylline in the formulation (mg/ml), and D is the diffusion coefficient (cm^2/s).

To investigate the dependence of the diffusion coefficient on polymer concentration in the gel, and thus to estimate microviscosity of the medium, we used the procedure described in Section 2.3.2.

3. Results and discussion

Table 1 summarizes the basic properties of the HPCs studied. As can be seen, the different products showed a wide range of molecular weights and effects on medium viscosity. Furthermore, the different products vary widely in hydrophilicity, as indicated by the values obtained for heat of hydration-solution and cloud point (see Robitaille et al., 1991; Joshi and Wilson, 1992).

To evaluate the microviscosity of HPC dispersions, we used the DLS method (Gebre-Mariam et al., 1991; Smidt and Crommelin, 1991). When using this technique, it must be borne in mind

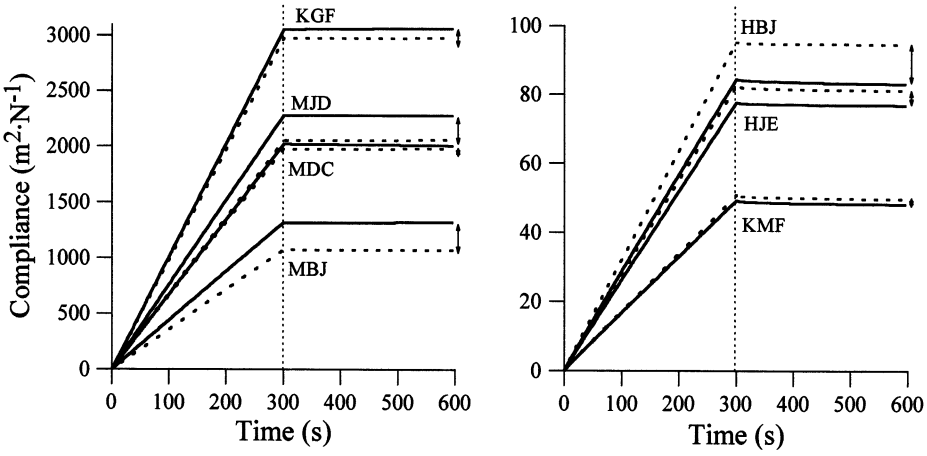

Fig. 1. Creep–recovery profiles of 2% dispersions of HPCs at 37°C, in the presence (dotted line) or absence of 1 g/l Triton X-100. Force (0.1 Pa) was applied for the first 300 s.

that cellulose ethers tend to adsorb to the surface of polystyrene latex particles, leading to aggregate formation (Yang and Jamieson, 1988; Hörner et al., 1997). In the present study, as a result of this phenomenon, we observed particle sizes two or even three times those observed in the absence of cellulose ethers. One way of preventing aggregation is to use non-ionic surfactants (Yang and Jamieson, 1988; Phillies and Clomenil, 1993; Phillies and Lacroix, 1997). In our assays for the evaluation of microviscosity, we therefore included 1 g/l Triton X-100 (i.e. 1.6×10^{-3} M) in the assay mixtures. This surfactant has a critical micellization concentration (cmc) of 2.90×10^{-4} M at 25°C, and each surfactant molecule associates with 40 water molecules (Qiao and Easteal, 1996). The high proportion of water (more than 98%) in all the dispersions studied led to the obtention of homogeneous water–HPC–Triton systems (see Gerharz and Horst, 1996).

Because of the strongly hydrophilic character of Triton X-100, we considered it important to evaluate its effects on the rheology of the polymer dispersions, in view of the likely influence of such effects on drug diffusion. Fig. 1 shows creep and recovery profiles of 2.0% HPC dispersions with and without surfactant. The presence of Triton X-100 in the dispersions of HPCs of lower molecular weight (Klucel GF and Nisso M-BJ, M-DC and M-JD) led to a slight drop in compliance, indicating a slight increase in viscosity. In dispersions of the HPCs of higher molecular weight (Nisso H-BJ and H-JE, and Klucel MF), the opposite effect was observed, namely an increase in compliance, in no case exceeding 10%.

The effect of inclusion of surfactant on G' and G'' was negligible over the oscillation frequency range considered. As an example, Table 2 shows the values of the two moduli obtained at 0.92 and 5.64 rad/s. In general, the interaction between a polymer and a surfactant is a cooperative process that commences at a concentration below the cmc (Persson et al., 1996). For a given type of polymer, the molecular weight and hydrophilicity of the macromolecules are determinants of the intensity of the interaction (Duro et al., 1998). The slight surfactant-induced increase in viscosity observed in dispersions of lower-molecular-weight HPCs may be a consequence of the formation of polymer–surfactant aggregates due to hydrophobic interactions between polymer and surfactant molecules (Cavallaro et al., 1993). The opposite effect observed in assays with dispersions of the high-molecular-weight polymer Klucel MF may reflect competition for water molecules between the polymer and the surfactant, which may lead to poor hydration and thus to reduced swelling of the polymer molecules, so that they adopt a tighter, more close-coiled configuration. The fact that dynamic viscosity scarcely changed when sur-

Table 2
Elastic moduli (G') and viscous moduli (G'') of 2% dispersions of the different HPCs, with or without 0.1% Triton X-100, determined at 37°C at oscillation frequencies of 0.92 or 5.64 rad/s[a]

Polymer	0.92 rad/s				5.64 rad/s			
	Without Triton® X-100		With Triton® X-100		Without Triton® X-100		With Triton® X-100	
	G' (Pa)	G'' (Pa)	G' (Pa)	G'' (Pa)	G' (Pa)	G'' (Pa)	G' (Pa)	G'' (Pa)
Klucel® GF	n.d.	0.068	n.d.[b]	0.084	n.d.	0.43	n.d.	0.51
Nisso® M-BJ	n.d.	0.26	n.d.	0.20	n.d.	1.55	n.d.	1.21
Nisso® M-DC	n.d.	0.17	n.d.	0.13	n.d.	1.04	n.d.	0.81
Nisso® M-JD	0.51	0.13	n.d.	0.13	n.d.	0.75	n.d.	0.80
Nisso® H-BJ	0.58	2.39	0.47	2.26	4.22	9.78	3.97	9.34
Nisso® H-JE	1.16	2.29	0.42	2.05	4.17	8.99	3.51	8.51
Klucel® MF	n.d.	3.85	1.12	4.23	7.64	13.9	8.24	15.0

[a] All values are the mean of three determinations.
[b] n.d., not detectable.

factant was added to dispersions of Nisso H-BJ and Nisso H-JE may reflect the more hydrophilic nature of these polymers by comparison with the Klucel varieties (see Persson et al., 1996; Thuresson and Lindman, 1997). Taken together, these results suggest that the interactions occurring in aqueous medium between Triton X-100 and the different HPCs studied are very weak, so that the diffusion data for latex microspheres obtained in this medium can be analysed using hydrodynamic theories valid for inert spheres in polymeric matrices (Johnson, 1993; Phillies and Lacroix, 1997).

The values of the diffusion coefficients for latex microspheres, as estimated on the basis of DLS, are shown in Table 3. As can be seen, there is a clear inverse relationship between the value of the diffusion coefficient and the proportion of polymer present in the gel. Table 4 shows the values obtained when the hydrodynamic model of Phillies et al. (1985) (Eq. (3)) is fitted to the diffusion coefficient data. As can be seen, the values of the α coefficient are strongly dependent on polymer molecular weight (Fig. 2). Phillies et al. (1985) and Yang and Jamieson (1988) reported similar relationships in studies of aqueous dispersions of other HPC varieties. However, the values of ν obtained in the present study are relatively high. In this regard, it is interesting to note that values of ν between 0.5 and 0.75 are indicative of systems in which polymer molecular weight is sufficiently high to ensure that chain entanglement occurs and that water will act as a good solvent (Phillies and Clomenil, 1993); under θ conditions, by contrast, ν approaches 1. These observations, together with the temperature dependence of the solubility of HPCs and the weakness of the observed interaction between HPCs and surfactant, suggest that at 37°C water begins to be a poor solvent for HPCs.

Table 5 shows the microviscosities of the dispersions tested, as estimated on the basis of DLS, together with the corresponding macroviscosities. In all cases, microviscosity was lower than macroviscosity, and the difference between the two variables increased with increasing polymer concentration and molecular weight. This is reflected in the power relationship between the two variables obtained by non-linear regression (Fig. 3). Similar behaviour has been observed in studies of dispersions of carbopol 940 (Al-Khamis et al., 1986), glycerogelatin (Amstrong et al., 1987), starch (El-Khordagui, 1991) and sodium carboxymethylcellulose (Smidt and Crommelin, 1991).

Prior to the diffusion studies, we quantified the macroviscosity of the gels at 37°C by capillary viscometry. We also evaluated the compatibility of the HPCs with theophylline, by determining cloud point temperatures of 2% dispersions of each HPC in the presence of theophylline at a

Table 3
Mean diffusion coefficients (cm^2/min) ($\pm$ S.D.) for latex microspheres in dispersions of the various HPCs at the concentrations indicated[a]

% Polymer	KGF	MBJ	MDC	MJD	HBJ	HJE	KMF
0.2	1.195×10^{-6} (1.441×10^{-8})	1.074×10^{-6} (2.865×10^{-8})	1.105×10^{-6} (3.022×10^{-8})	1.110×10^{-6} (2.695×10^{-8})	8.688×10^{-7} (1.875×10^{-8})	8.982×10^{-7} (2.753×10^{-8})	9.210×10^{-7} (2.237×10^{-8})
0.4	7.260×10^{-6} (1.935×10^{-8})	5.688×10^{-7} (1.956×10^{-8})	5.875×10^{-7} (2.097×10^{-8})	6.360×10^{-7} (1.138×10^{-8})	4.514×10^{-7} (1.969×10^{-8})	4.591×10^{-7} (1.162×10^{-8})	3.809×10^{-7} (5.871×10^{-9})
0.8	3.211×10^{-7} (1.035×10^{-8})	2.015×10^{-7} (1.035×10^{-8})	1.918×10^{-7} (1.008×10^{-8})	2.715×10^{-7} (1.173×10^{-8})	7.698×10^{-8} (1.015×10^{-8})	9.162×10^{-8} (5.280×10^{-9})	6.570×10^{-8} (2.957×10^{-9})
1.2	1.939×10^{-7} (9.820×10^{-9})	9.078×10^{-8} (9.468×10^{-9})	1.068×10^{-7} (7.512×10^{-9})	1.175×10^{-7} (8.016×10^{-9})	3.564×10^{-8} (1.429×10^{-9})	3.189×10^{-8} (3.008×10^{-9})	2.708×10^{-8} (2.284×10^{-9})

[a] $D_0 = 1.716\times10^{-6}$ cm^2/min.

Table 4
Mean values (S.D.) of the parameters obtained by fitting Eq. (3) (Phillies et al., 1985) to the latex microsphere diffusion data (2 and 28 d.f.; $\alpha < 0.05$ in all cases)

Parameter	KGF	MBJ	MDC	MJD	HBJ	HJE	KMF
α	1.91 (0.02)	2.53 (0.02)	2.45 (0.03)	2.26 (0.01)	3.39 (0.05)	3.42 (0.03)	3.64 (0.05)
v	0.88 (0.03)	0.93 (0.02)	0.89 (0.03)	0.94 (0.01)	0.92 (0.03)	0.97 (0.02)	0.93 (0.03)
r^2	0.9911	0.9943	0.9866	0.9979	0.9868	0.9941	0.9866
F	4035	6221	2644	17258	2641	5837	2568

concentration close to its solubility coefficient. In all cases the cloud point temperature was very close to that obtained in the absence of theophylline. Similar results were obtained by Mitchell et al. (1990) with different hydroxypropyl methylcelluloses, and are attributable to the scant capacity of theophylline to compete for water molecules.

Diffusion coefficients of theophylline were estimated by fitting to the Higuchi (1962) equation. In all cases a linear relationship between the amount of drug released and the square root of the time over the 8 h of the assay was observed. The pore size of the hydrophilic and no adsorbent cellulose acetate membrane filter used to separate the donor and the receptor compartments, ensured that the membrane was not limiting the diffusion (Barry and Brace, 1977). As the donor and the receptor media were isosmotic, no back transfer of water was observed.

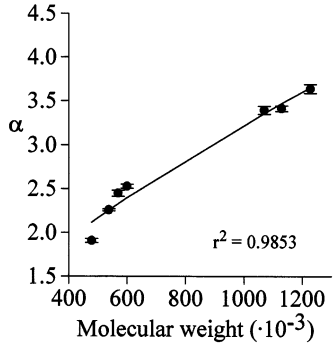

Fig. 2. Relationship between the parameter α, estimated by fitting Eq. (3) (Phillies et al., 1985) to the latex microsphere diffusion data, and molecular weight. Each point represents the mean value of α (six determinations of diffusion; vertical bars show S.D.) for a given HPC variety ($\alpha = 0.532 + 1.289 \times 10^{-4}\ M^{0.72}$; $F_{1,5} = 166.7$; $\alpha < 0.01$).

Fig. 4 illustrates the dependence of the relative diffusion coefficient for theophylline (i.e. D/D_0; see Table 6) on HPC concentration. Fitting of the equation of Phillies et al. (1985) to the experimental data confirms the expected exponential relationship between the two parameters, except when the HPC is Klucel GF (Table 7). Again, the characteristic power relationship between α and polymer molecular weight (see Yang and Jamieson, 1988) is observed (Fig. 5). Furthermore, the values of v obtained for lower-molecular-weight polymers were close to unity (indicating that the system is close to θ conditions), while the values obtained for higher-molecular-weight polymers were around 0.75. Comparison of these results with those obtained on the basis of latex microsphere diffusion suggests that, in the absence of surfactant, water is a more effective solvent, as reflected in the higher α values obtained with Nisso H-BJ, Nisso H-JE and Klucel MF (Phillies and Clomenil, 1993).

The apparently anomalous relationship between diffusion coefficient and polymer concentration observed with the lowest-molecular-weight HPC tested (Klucel GF) is probably related to the higher entanglement concentration of this polymer (see Table 1), so that, in dispersions with low Klucel GF concentration, the diffusion of drug molecules is influenced almost exclusively by the viscous resistance of the solvent (Nelson and Shah, 1987; Lu and Jun, 1998). In accordance with this view, the theophylline diffusion coefficient was scarcely affected by Klucel GF concentration over the concentration range 0–0.8% (Fig.

Table 5
Microviscosities (determined by DLS with latex microspheres or by theophylline diffusion) and macroviscosities (capillary viscometry) of dispersions of the different HPCs at the concentrations indicated[a]

HPC (%)	Viscosity	KGF	MBJ	MDC	MJD	HBJ	HJE	KMF
0.2	Microviscosity							
	Microspheres	1.02 (0.01)	1.13 (0.03)	1.10 (0.03)	1.09 (0.02)	1.39 (0.03)	1.35 (0.04)	1.32 (0.03)
	Theophylline	0.71 (0.07)	1.12 (0.11)	1.15 (0.11)	1.09 (0.10)	1.86 (0.19)	1.76 (0.17)	3.00 (0.01)
	Macroviscosity	1.35 (0.01)	1.53 (0.01)	1.45 (0.00)	1.44 (0.00)	2.52 (0.00)	2.55 (0.00)	2.91 (0.01)
0.4	Microviscosity							
	Microspheres	1.67 (0.04)	2.13 (0.07)	2.07 (0.07)	1.90 (0.03)	2.69 (0.11)	2.64 (0.06)	3.19 (0.05)
	Theophylline	0.68 (0.06)	1.74 (0.10)	1.78 (0.10)	1.70 (0.10)	6.67 (0.37)	5.95 (0.35)	7.09 (0.39)
	Macroviscosity	2.43 (0.00)	3.09 (0.00)	3.02 (0.01)	2.72 (0.00)	7.88 (0.01)	8.03 (0.01)	10.12 (0.01)
0.8	Microviscosity							
	Microspheres	3.77 (0.13)	6.03 (0.28)	6.34 (0.32)	4.47 (0.18)	15.98 (1.07)	13.28 (0.76)	18.50 (0.81)
	Theophylline	0.77 (0.06)	4.83 (0.12)	4.77 (0.12)	4.75 (0.12)	17.15 (1.15)	16.37 (1.17)	37.54 (1.84)
	Macroviscosity	6.64 (0.01)	10.83 (0.01)	10.17 (0.01)	8.49 (0.03)	53.52 (0.02)	57.10 (0.03)	77.46 (0.12)
1.2	Microviscosity							
	Microspheres	6.27 (0.31)	13.48 (0.88)	11.40 (0.78)	10.36 (0.73)	34.09 (1.36)	38.16 (2.40)	44.99 (3.20)
	Theophylline	2.56 (0.10)	8.17 (0.56)	7.45 (0.45)	7.35 (0.35)	52.58 (2.58)	52.23 (2.32)	132.2 (3.22)
	Macroviscosity	16.70 (0.01)	28.65 (0.05)	22.69 (0.04)	22.57 (0.05)	233.8 (0.89)	238.4 (0.20)	344.8 (0.14)

[a] Values shown are means (S.D.) for six determinations. In the determination of microviscosity, D_0 was 1.716×10^{-6} cm^2/min and η_0 was 0.707 mPa·s.

4). Similar results were obtained by Smidt et al. (1991), who investigated the diffusion of theophylline in low-concentration ($< 0.25\%$) dispersions of a hydroxypropylmethylcellulose with nominal viscosity of 4000 mPa·s. The fact that behaviour of this type was not observed in the latex-microsphere diffusion tests can be attributed to the greater diameter of these particles, 162 nm, versus a value of equivalent spherical solute radius of 0.356 nm for theophylline molecules, estimated according to the Stokes equation (Stringer and Peppas, 1996).

The microviscosities of the HPC dispersions, calculated from the theophylline diffusion coefficients and shown in Table 5, were in all cases clearly lower than the macroviscosities. Again, there is a clear power relationship between micro- and macroviscosity (Fig. 6), though goodness-of-fit is markedly improved when the Klucel GF data are excluded ($a = 0.751$, $b = 0.847$, $r^2 = 0.9726$). When the lower-molecular-weight HPCs are considered, the microviscosity values estimated in the latex-microsphere diffusion tests are higher than the values estimated from theophylline diffusion coefficients; when the higher-molecular-weight HPCs are considered, the opposite is true (Table 5). The differences between microviscosities as estimated by the two methods were more marked in the case of the Klucel varieties, which may be partially attributable to the more intense polymer–surfactant interactions observed with these varieties. The difference in size between the latex microspheres and the theophylline molecules may also be relevant: the smaller the molecular diameter, the lower the resistance to diffusion offered by the medium, so that microviscosity is reduced (Phillies et al., 1985; Smidt and Crommelin, 1991; Phillies and Lacroix, 1997).

4. Conclusions

In general, the diffusion coefficient for theophylline in HPC dispersions declines exponentially with increasing polymer concentration. In the case of Klucel GF (molecular weight

Table 6
Theophylline diffusion coefficients in dispersions of the different HPCs at the concentrations indicated[a]

% Polymer	Diffusion coefficient (cm^2/min)						
	KGF	MBJ	MDC	MJD	HBJ	HJE	KMF
0.2	1.076×10^{-3} (1.394×10^{-5})	6.847×10^{-4} (2.654×10^{-5})	6.668×10^{-4} (2.621×10^{-5})	6.999×10^{-4} (2.049×10^{-5})	4.114×10^{-4} (8.078×10^{-6})	4.335×10^{-4} (2.467×10^{-6})	5.145×10^{-4} (4.582×10^{-6})
0.4	1.120×10^{-3} (2.551×10^{-5})	4.402×10^{-4} (9.675×10^{-6})	4.287×10^{-4} (7.144×10^{-6})	4.501×10^{-4} (6.108×10^{-6})	1.147×10^{-4} (1.047×10^{-5})	1.285×10^{-4} (8.729×10^{-6})	1.079×10^{-4} (1.181×10^{-5})
0.8	9.884×10^{-4} (6.511×10^{-5})	1.583×10^{-4} (6.228×10^{-6})	1.603×10^{-4} (1.126×10^{-5})	1.609×10^{-4} (3.848×10^{-6})	4.461×10^{-5} (2.250×10^{-6})	4.673×10^{-5} (1.503×10^{-6})	2.038×10^{-5} (1.474×10^{-6})
1.2	2.982×10^{-4} (2.061×10^{-6})	9.366×10^{-5} (8.192×10^{-6})	1.026×10^{-4} (3.197×10^{-6})	1.040×10^{-4} (9.315×10^{-7})	1.455×10^{-5} (8.795×10^{-7})	1.465×10^{-5} (1.504×10^{-6})	5.787×10^{-6} (3.868×10^{-7})
1.6	1.773×10^{-4} (3.806×10^{-7})	2.785×10^{-5} (6.683×10^{-7})	3.008×10^{-5} (3.439×10^{-6})	3.390×10^{-5} (1.850×10^{-6})	5.570×10^{-6} (2.835×10^{-7})	5.313×10^{-6} (2.139×10^{-7})	2.371×10^{-6} (1.200×10^{-7})
2.0	9.685×10^{-5} (3.120×10^{-6})	9.399×10^{-6} (3.432×10^{-7})	9.603×10^{-6} (1.197×10^{-7})	1.032×10^{-5} (2.622×10^{-7})	2.222×10^{-6} (1.000×10^{-7})	2.082×10^{-6} (1.000×10^{-7})	3.510×10^{-7} (1.221×10^{-8})

[a] Values shown are means (S.D.) of six determinations. $D_0 = 1.069\times10^{-3}$ cm^2/min.

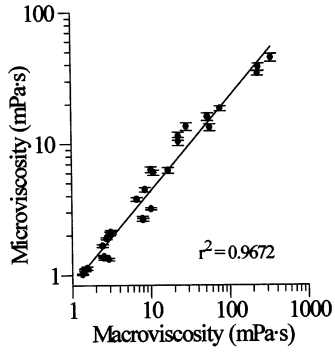

Fig. 3. Relationship between microviscosity (as estimated by DLS with latex microspheres) and macroviscosity (as estimated by capillary viscometry) of HPC dispersions. Each point represents the mean (six determinations of both variables; vertical bars show S.D. of microviscosity) for a given concentration of a given HPC variety ($\eta_{micro} = 0.851 + \eta_{macro}^{0.711}$; $F_{1,26} = 765.2$; $\alpha < 0.01$).

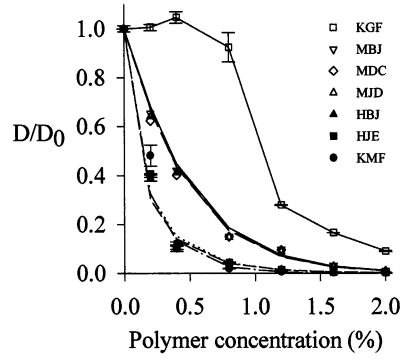

Fig. 4. Relationship between the relative diffusion coefficient (D/D_0) for theophylline and HPC concentration. Each point represents the mean of six determinations of diffusion; vertical bars show S.D.

479 000), the diffusion coefficient remains more or less constant over a considerable part of the polymer concentration range, probably because of its high entanglement concentration. The microviscosity of the dispersions, as evaluated with DLS using latex microspheres, predicts the resistance of gels to theophylline diffusion with reasonable accuracy, particularly in the case of the more hydrophilic polymers. Inclusion in the dispersions of a surfactant that does not interact significantly with these HPCs (Triton X-100, i.e. polyethyleneglycol *tert*-octylphenyl ether) prevented the aggregation of latex microspheres, and minimized error in the estimation of diffusion coefficients and microviscosities by this technique. Macroviscosities determined by capillary viscometry were markedly higher than microviscosities (whether determined by DLS with latex microspheres or on the basis of theophylline diffusion), though the power relationship observed between macro- and microviscosity means that the former may be of some value for predicting diffusion rates.

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Table 7
Mean values (S.D.) of the parameters obtained by fitting Eq. (3) (Phillies et al., 1985) to the theophylline diffusion data (2 and 28 d.f.; $\alpha < 0.05$ in all cases)

Parameter	KGF	MBJ	MDC	MJD	HBJ	HJE	KMF
α	0.08 (0.16)	2.22 (0.08)	2.19 (0.09)	2.14 (0.10)	3.77 (0.08)	3.74 (0.07)	4.43 (0.16)
v	4.95 (3.10)	1.07 (0.06)	1.06 (0.08)	1.07 (0.08)	0.71 (0.03)	0.74 (0.03)	0.82 (0.06)
r^2	0.6769	0.9941	0.9908	0.9911	0.9956	0.9967	0.9907
F	10.54	1084	696.2	711.1	1876	2394	712.0

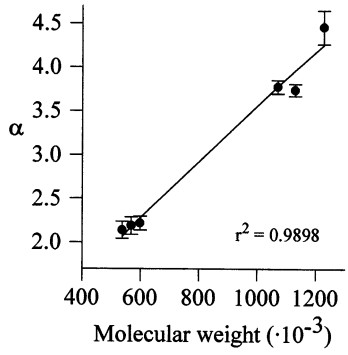

Fig. 5. Relationship between the parameter α, estimated by fitting Fig. 3 (Phillies et al., 1985) to the theophylline diffusion data, and molecular weight. Each point represents the mean value of α (six determinations of diffusion; vertical bars show S.D.) for a given HPC variety ($\alpha = -0.190 + 4.514 \times 10^{-5}$ $M^{0.82}$; $F_{1,4} = 196.0$; $\alpha < 0.01$).

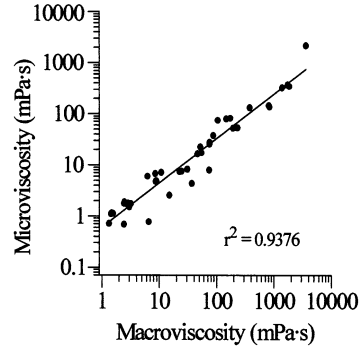

Fig. 6. Relationship between microviscosity (as estimated from the theophylline diffusion data) and macroviscosity (as estimated by capillary viscometry) of HPC dispersions. Each point represents the mean (six determinations of both variables) for a given concentration of a given HPC variety ($\eta_{micro} = 0.595 + \eta_{macro}^{0.870}$; $F_{1,39} = 558.7$; $\alpha < 0.01$).

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