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Research Article

Diffusion in HPMC Gels. I. Determination of Drug and Water Diffusivity by Pulsed-Field-Gradient Spin-Echo NMR

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Purpose. This work describes diffusivity measurements of drug (adinazolam mesylate) and water in a variety of solutions including polymer gels. ***Methods.*** Pulsed-field-gradient spin-echo (PFGSE) NMR methods were employed to measure the diffusivity. ***Results.*** In binary component solutions, adinazolam diffusivity is generally found to exhibit an exponential dependence on the concentration of the viscosity-inducing agent (VIA), which is glucose, lactose, maltoheptaose, hydroxypropyl methylcellulose (HPMC) or drug itself. An increasing obstruction power to drug diffusion from glucose to HPMC is observed, which can be related to the polymerization degree of the VIA. In contrast, adinazolam diffusivity in HPMC gels shows little dependence upon the polymer viscosity grades examined (K100LV, K4M, and K15M). The temperature dependence of adinazolam diffusivity in dilute VIA solutions reveals that the diffusion barrier for the drug is similar to that for self-diffusion of water. ***Conclusions.*** The retarding effect from the VIA for drug diffusion is concluded to be primarily associated with a steric obstruction mechanism. In multicomponent gels with varied concentrations of drug, lactose and HPMC, the drug diffusivity can be approximately described as an exponential function of the summation of the products of the proportionality constant (K_i) and concentration for each VIA component. In contrast, water diffusion behavior shows an universal exponential dependence upon the VIA concentration and small dependence upon the nature of the VIA. The interpretation of the diffusivity data is discussed and compared to two existing diffusion models (Yasuda and Mackie-Meares models).

KEY WORDS: nuclear magnetic resonance spectroscopy; pulsed-field-gradient spin-echo NMR; hydroxypropyl methylcellulose; HPMC; extended release; diffusion; self-diffusion; diffusion coefficient; adinazolam mesylate.

INTRODUCTION

Diffusion is an important subject for research in medical and pharmaceutical applications. One method of achieving sustained drug delivery is by the use of a hydrophilic polymeric matrix, which swells in the presence of water to form hydrogel structures, from which drugs are released by diffusion (1–3). It is of interest to study the diffusional behavior of drug and water molecules in polymer gels in order to develop and optimize sustained release (SR) formulations of such systems. Although a significant amount of research involving a variety of techniques has been conducted on the diffusivity measurement of such systems (3), little work has focused on the systematic evaluation of diffusivity of drug and water as a function of formulation factors. In particular, the conventional techniques of membrane permeation, sorption/desorption, and radiotracers are commonly applied and usually provide an apparent (or averaged) diffusivity through a matrix (3). Besides other technical challenges, it is also difficult to apply these methods for determination of solute diffusivity as a function of the matrix composition. Drug diffusivity is also often estimated from a cumulative release profile using predetermined theoretical models (3,4) which usually either involves assumptions or requires previous knowledge of the system. Furthermore, diffusivity measurement in multicomponent systems is usually complex and has been rarely reported.

Pulsed-field-gradient spin-echo (PFGSE) NMR techniques provide an elegant method of self-diffusion coefficient measurements (5,6). A self-diffusion coefficient is a measure of transport due to the Brownian motion of molecules in the absence of a chemical concentration gradient. Thus self-diffusion can serve as a starting point for probing diffusional process in polymeric systems. With the advent of the Fourier transform version of the PFGSE NMR methods (7), it is possible to measure self-diffusion coefficients of individual components in a complex mixture with high sensitivity (the concentration of species of interest ca. 0.1%) and precision over a broad range of molecular mobilities (10^{-6} to 10^{-9} cm^2/s). This technique provides an independent approach to characterize the diffusion behavior of drug and water molecules in a complex, multicomponent polymeric matrix.

In the present study we report the measurements of the diffusivity of drug and water molecules in hydroxypropyl methylcellulose (HPMC) gels and related media applying

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PFGSE NMR methods. Adinazolam mesylate was selected as a model drug for a systematic study. Particular attention has been given to the examination of drug diffusivity as a function of the concentration of glucose-based viscosity-increasing agents and the degree of polymerization. The interpretation of the diffusivity data will be discussed and compared to two existing diffusion models (Yasuda and Mackie-Meares). The significance and application of the diffusional information to predict the relative drug release rate resulting from a variety of HPMC based sustained release formulations will be discussed in detail in a companion report (8).

MATERIALS AND METHODS

α-D-glucose and maltoheptaose hydrate (90%) were obtained from Aldrich Chemical and used without purification. Lactose was obtained from Foremost Whey Products. D_2O (99.9%) was used as solvent and obtained from ISOTEC. HPMC 2208 polymer was supplied by Dow Chemicals as METHOCEL with viscosity grades of K100LV, K4M, and K15M each having nominal viscosities of 100, 4,000 and 15,000 cps, respectively, in 2% aqueous solution (9). Adinazolam mesylate (ADM) was manufactured by The Upjohn Company.

Glucose, lactose, maltoheptaose, and HPMC solutions containing adinazolam mesylate were prepared with D_2O. All HPMC gels were made according to the preparation procedure described in reference 9. Moderately concentrated HPMC gels (ca. 20% for K100LV and K4M; 10% for K15M) were difficult to load into 5-mm NMR tubes because of their extremely high viscosities and viscoelasticities; therefore the diffusivity measurements were limited to the equilibrium swollen gels with HPMC concentration less than 20%. The partial specific volume of lactose (0.610 ml/g) was calculated using the solution density data reported in ref. 10. The partial specific volume of HPMC (0.717 ml/g) was provided in ref. 9. Volume fractions of lactose, HPMC or water in the solutions were converted from the concentrations (%, w/w) using these partial specific volumes and D_2O density (10).

The self-diffusion coefficients were measured based on the method established by Stejskal and Tanner (11). The pulse sequence consists of a standard 90°-τ-180°-τ echo sequence with two field gradient pulses of duration, δ, during the τ periods. The integrated peak intensity, I, of the species of interest in a FT-NMR spectrum is given (6) by

$$I(G) = I_0 \exp(-2\tau/T_2) \exp -[\gamma^2 G^2 D \delta^2(\Delta - \delta/3)] \quad (1)$$

where I(G) and I_0 are the echo intensities with and without the field gradient, respectively; T_2 is the transverse relaxation time of the species; γ is the magnetogyric ratio of proton; G is the magnitude of the field gradient; and Δ is the time interval between the field gradient pulses (6). Multiple spectra are collected by systematically varying G, while keeping Δ constant. Absorption mode spectra were obtained by applying a symmetric (sinebell squared) window function to each echo data set before Fourier transformation, followed by a magnitude mode calculation (12). The self-diffusion coefficient, D, of the species of interest is determined from the slope of a linear least squares fit of the natural logarithm of its integrated peak intensity, I, against G^2 which is further divided by $[\gamma^2\delta^2(\Delta-\delta/3)]$. The drug examined in this study, adinazolam mesylate, is a salt and dissociates in water. The diffusivity of the adinazolam moiety was extracted utilizing its 7.4 ppm resonance (from the aromatic moiety) while the water diffusivity was extracted utilizing the 4.6 ppm (HDO/H_2O) resonance. The linear least-square fitting of the peak intensities was performed using SigmaPlot 5.1. The self diffusion coefficient will be simply called diffusion coefficient in the following text.

NMR experiments were performed on a Bruker MSL-200 spectrometer equipped with a Bruker ASPECT 3000 computer. A dedicated diffusion measurement probe (Bruker) was used which can impose a magnetic field gradient of 125 gauss/cm across the sample. The probe gradient coil is driven by a Techron 7570 audio power amplifier, which in turn is driven from a computer controlled pulse generator associated with the Bruker imaging accessory of the MSL-200. A selective excitation of the water signal with a Gaussian shaped pulse at the resonance frequency prior to the spin-echo pulse sequence was applied for solvent suppression (13) when adinazolam diffusivity was measured. The multiple spectra (typically a series of 8–16 echoes) were acquired sequentially with an automation program which systematically varied the amplitude of the pulsed field gradient.

Standard 5 mm NMR tubes were used for all measurements. All measurements of diffusivity were conducted at ambient temperature (23 ± 1°C) except the temperature-dependent diffusivity experiments. The temperature of the probe was controlled by an external device (FTS Systems, Model TC-44). The probe temperatures were calibrated with a 100% ethylene glycol standard (Varian) according to the Bruker's manual (14). The gradient magnitudes were calibrated by using samples of pure water and dry glycerol with their known self-diffusion coefficients, 2.40×10^{-5} cm²/s and 1.73×10^{-8} cm²/s, respectively (15).

RESULTS

Adinazolam Diffusivity in VIA Solutions

Results from studies of diffusion coefficient in solutions are often compared to the diffusion coefficient in the absence of the additives, i.e., in the solvent, and reported as the normalized diffusion quotient, D/D° (16). D° is the diffusion coefficient of the solute extrapolated to infinite dilution. Diffusion coefficients of adinazolam were initially examined as a function of its concentration as shown in Figure 1. Plotted in Figure 2 is the natural logarithm of the normalized diffusion quotient of adinazolam vs. the concentration. Denoting D_A as the adinazolam diffusivity, a linear relationship is observed between $\ln(D_A/D_A°)$ and drug concentration, suggesting an exponential dependence of the drug diffusivity upon its own concentration. The diffusion coefficients of adinazolam were similarly examined as a function of HPMC concentration in the equilibrium swollen gels using different viscosity grades. Since the drug concentration is fixed at the level of 0.5% (w/w), these systems are considered as binary component systems (HPMC and water) by ignoring drug presence. The adinazolam diffusivities are plotted against HPMC concentration (%, w/w) and also shown in Figure 1.

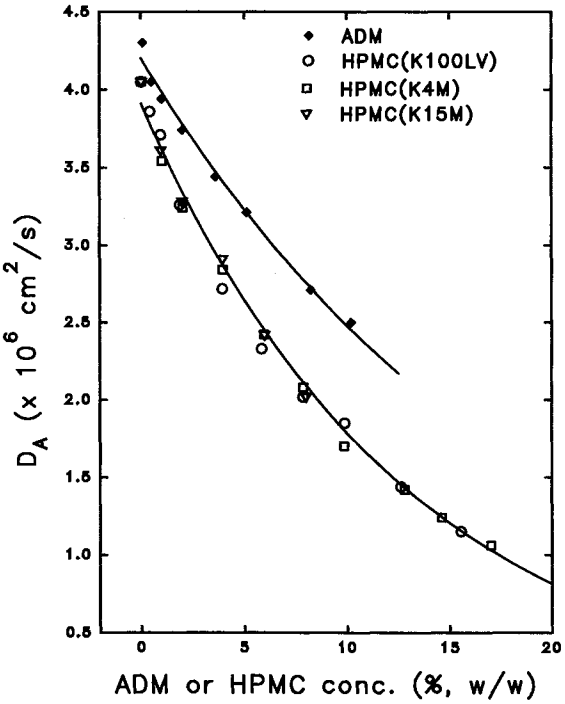

Fig. 1. Diffusion coefficients of adinazolam, D_A, plotted against ADM or HPMC concentration (%, w/w). D_A values were obtained from: (♦) x% ADM; (○) 0.5% ADM + x% HPMC(K100LV); (□) 0.5% ADM + x% HPMC(K4M); and (▽) 0.5% ADM + x% HPMC(K15M). The solid curves were obtained through a non-linear curve fitting of the data using $y = A \exp(-kx)$.

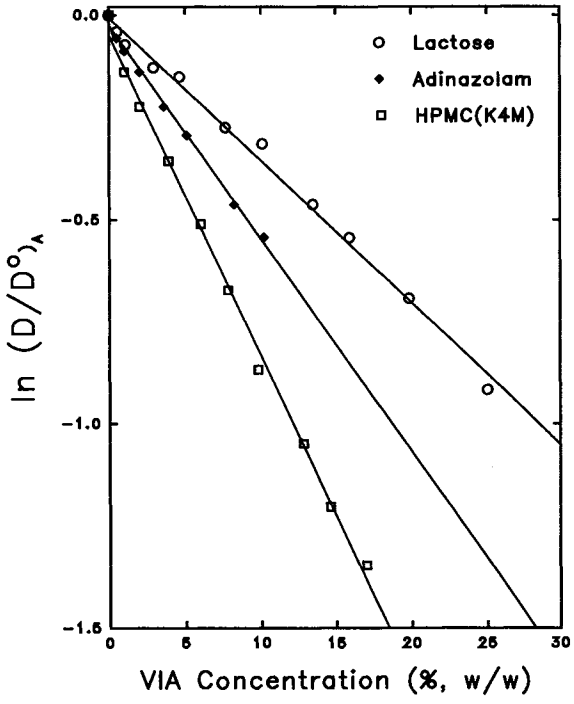

Fig. 2. Natural logarithm of normalized diffusion quotients of adinazolam, ln $(D/D^\circ)_A$, plotted against the VIA concentration (%, w/w). D_A values were obtained from: (♦) x% ADM; (○) 0.5% ADM + x% lactose; and (□) 0.5% ADM + x% HPMC(K4M). The solid lines were obtained through a linear least-squares analysis of the data.

Adinazolam diffusivities in HPMC media show a distinct dependence upon HPMC concentration and appear to be indistinguishable among the three viscosity grades (K100LV, K4M, and K15M) within the concentration range examined. We conclude that adinazolam diffusivity in HPMC solutions is mainly determined by HPMC concentration and essentially independent of HPMC viscosity grade. Adinazolam diffusivity observed in HPMC gels also shows an approximately exponential dependence upon HPMC concentration (represented by the K4M data) as depicted in Figure 2.

Since glucose can be considered as the pseudo-repeating unit of HPMC polymer and lactose is the dimer of glucose, each molecule may be considered as the lower extreme of HPMC polymer chain length. Since lactose is often used as an inert filler in sustained release tablet formulations, it is of interest to study drug diffusivity as a function of glucose or lactose concentration. In order to further examine the dependence of drug diffusivity upon polymer chain length, especially at the lower chain length of HPMC, the diffusion coefficients of adinazolam were also obtained from maltoheptaose (containing seven glucose units) solutions.

Diffusion coefficients of adinazolam obtained from glucose, lactose, and maltoheptaose solutions, respectively, are plotted against their concentrations in Figure 3 in comparison with the drug diffusion coefficients obtained in HPMC gels. For clarity, only the natural logarithms of the normalized diffusion quotients of adinazolam obtained from lactose solutions are plotted against the lactose concentration and shown in Figure 2. Although linear relationships are generally achieved between ln (D_A/D_A°) and the VIA concentration within a wide concentration range, apparent deviations of this relationship are observed at relatively low VIA concentrations (<3%, w/w). For simplicity, adinazolam diffusivity, D_A, is approximately formulated as an exponential function of the VIA concentration:

$$D_A = D_A^\circ \exp(-K_i C_i) \quad (2)$$

where K_i is a proportionality constant and C_i is the concentration of the VIA (%, w/w). These K_i values for adinazolam were obtained through a linear least squares fit of the diffusivity data from these binary component systems and are reported here: K_A(adinazolam) = 5.22; K_G(glucose) = 3.34; K_L(lactose) = 3.48; K_M(maltoheptaose) = 4.22; and K_H(HPMC) = 7.85.

Adinazolam Diffusivity in VIA Mixtures

Adinazolam diffusivity was also examined in equilibrium swollen gels with varied concentrations of drug, lactose and HPMC. For instance, a set of adinazolam diffusivity values was obtained from a series of gels with a fixed lactose concentration of 10% and varied concentrations of HPMC (K100LV). Drug diffusivities are plotted against HPMC concentration and shown in Figure 4. Also plotted in Figure 4 for comparison is the drug diffusivity obtained in HPMC (K100LV) gels without the presence of lactose. Apparently, drug diffusivity is determined by both HPMC and lactose contributions rather than HPMC alone when a multicomponent gel is encountered. The two curves shown in Figure 4 suggest a similar dependence of the drug diffusivity upon

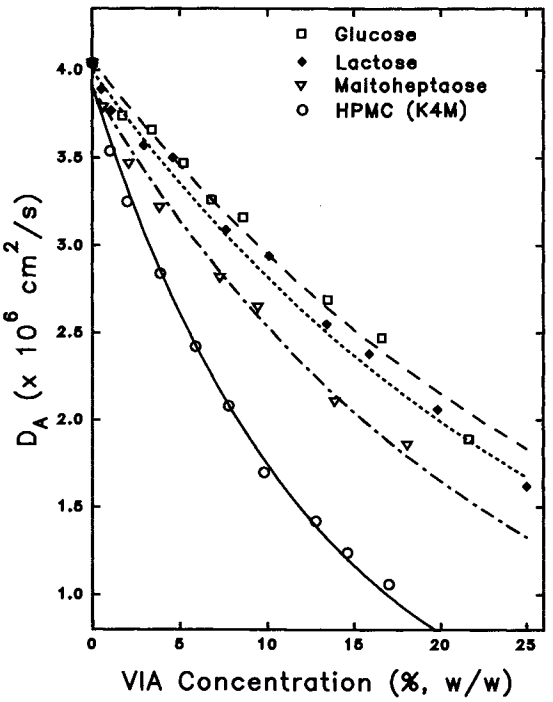

Fig. 3. Diffusion coefficients of adinazolam, D_A, plotted against the VIA concentration (w/w, %). D_A values were obtained from: (□) 0.5% ADM + x% glucose; (◆) 0.5% ADM + x% lactose; (▽) 0.5% ADM + x% maltoheptaose; and (○) 0.5% ADM + x% HPMC(K4M). The curves were obtained through a non-linear curve fitting of the data using $y = A \exp(-kx)$.

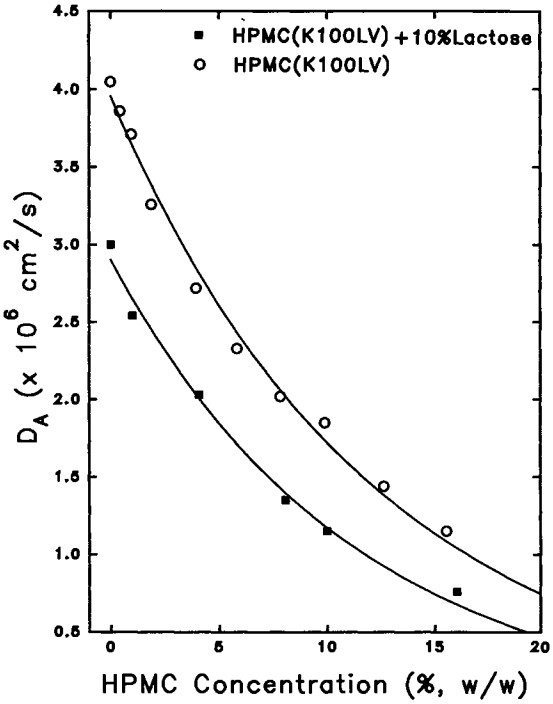

Fig. 4. Diffusion coefficients of adinazolam, D_A, plotted against HPMC concentration (%, w/w). D_A values were obtained from: (○) 0.5% ADM + x% HPMC(K100LV); and (■) 0.5% ADM + 10% lactose + x% HPMC(K100LV). The solid curves were obtained through a non-linear curve fitting of the data using $y = A \exp(-kx)$.

HPMC concentration with the offset between lines attributable to the retarding effect of 10% lactose. This implies that the retarding effect from each individual component, HPMC and lactose, respectively, is additive in nature.

Drug diffusivity data observed from the multicomponent gels, D_A(Obs), are summarized in Table I along with the gel compositions. These results further indicate that the drug diffusivity in a multicomponent gel is affected by all existing components (i.e., adinazolam, HPMC and lactose). Considering an additive retarding effect from these VIA components, Equation 2 is expanded to describe adinazolam diffusivity in a quaternary component gel:

$$D_A = D_A^\circ \exp(-K_H C_H - K_L C_L - K_A C_A) \quad (3)$$

where C_H, C_L and C_A are the concentrations (w/w, %) of HPMC, lactose and drug, respectively. By applying the K_i values determined from the binary component systems and the concentration of each component, the diffusion coefficients of adinazolam in these multicomponent gels were calculated according to Equation 3 and these values are reported in Table I as D_A(Cal). A linear least-square analysis using $y = mx + b$ where $x = D_A$(Cal) and $y = D_A$(Obs) yields $m = 0.958 \pm 0.028$ and $b = 0.005 \pm 0.038$ with the coefficient of determination (R^2) = 0.994. In general, a good agreement is achieved between the observed and calculated adinazolam diffusion coefficients, even at moderately concentrated gels (total VIA concentration up to 31%, w/w) (Table I).

Water Diffusivity

Water diffusivity is also of interest in these systems because the water penetration rate determines the kinetics of the gel layer formation of a sustained release tablet and, therefore, significantly affects drug dissolution and diffusion in the gel. Water diffusivities in glucose, lactose, or HPMC solutions were similarly measured to discern a possible difference in the dependence upon the nature of VIA. The natural logarithms of normalized diffusion quotients of water, ln (D_W/D°_W), are plotted as a function of glucose, or lactose, or

Table I. Comparison Between Adinazolam Diffusion Coefficients Observed in Multicomponent Gels, D_A(Obs), and Calculated, D_A(Cal), Based on the Gel Composition Using Equation 3

Gel Composition			D_A (×10^6) (Obs)	D_A (×10^6) (Cal)
% ADM	% HPMC	% Lactose		
0.5	1.0	10.0	2.54	2.64
0.5	4.1	10.0	2.03	2.06
0.5	8.1	10.0	1.35	1.51
0.5	10.0	10.0	1.15	1.30
0.5	16.0	10.0	0.76	0.81
0.5	15.5	—	1.22	1.19
1.0	14.9	—	1.14	1.18
2.0	14.9	—	1.04	1.12
3.9	14.9	—	0.96	1.05
6.0	14.9	—	0.88	0.91
7.5	14.9	—	0.82	0.84
2.0	8.0	10.0	1.31	1.37
2.0	15.0	10.0	0.84	0.80
3.9	8.0	10.0	1.13	1.24
5.8	15.0	10.0	0.64	0.66

HPMC concentration (w/w, %), respectively, in Figure 5. In contrast to adinazolam, water diffusivity shows essentially the same dependence upon the concentrations of glucose, lactose or HPMC regardless of the nature of the VIA. At low VIA concentrations, significant deviations of the data points from the linear least-squares fit line is consistently observed (Figure 5), suggesting a biexponential behavior. Thus a more significant reduction of water diffusivity is observed by addition of smaller amounts of VIA in the low VIA concentration range.

Water diffusivities in multicomponent HPMC gels were similarly examined. Representative data obtained from the gels with varied concentrations of drug, lactose and HPMC(K4M) are plotted against the total VIA concentration and also shown in Figure 5. Consistent with the observation in binary component systems, these data indicate an approximately linear relationship between ln ($D_W/D°_W$) and the total VIA concentration, especially at relative high VIA concentrations. An additive retarding effect from all VIA components towards water diffusion is also concluded. In general, water diffusivity, D_W, can only be approximately described by Equation 4:

$$D_W = D_W° \exp(-K_W \Sigma C_i) \quad (4)$$

Where $D_W°$ (2.06×10^{-5} cm^2/s) is the water diffusivity extrapolated from the intercept of the linear least-squares fit which significantly deviates from the true water diffusivity (2.40×10^{-5} cm^2/s); K_W (3.53) is a universal constant for those VIAs studied in this report. Notice that the fit of water diffusivity data to Equation 4 is much poorer compared to the fit of drug diffusivity data to Equation 3, especially at the low VIA concentrations (Figure 2).

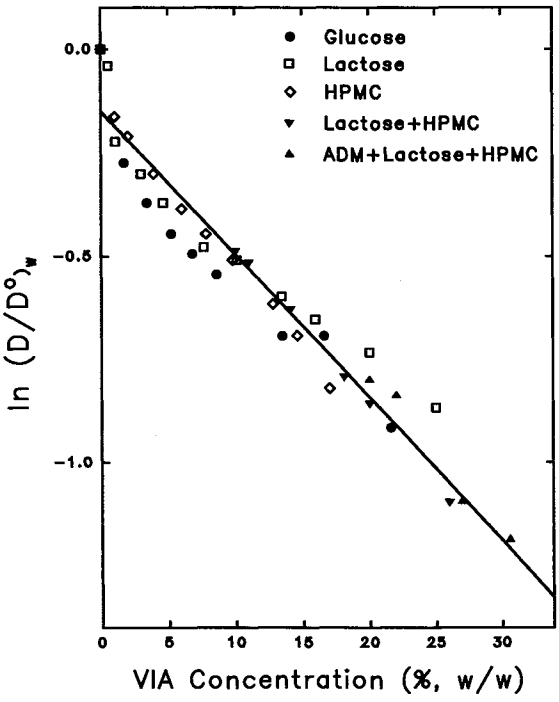

Fig. 5. Natural logarithm of normalized diffusion quotients of water, ln $(D/D°)_W$, plotted against the VIA concentration (○, □, and ◇) (%, w/w) or the *total* VIA concentration (ΣC_i; ▼ and ▲). D_W values were obtained from: (○) 0.5% ADM + x% glucose; (□) 0.5% ADM + x% lactose; (◇) 0.5% ADM + x% HPMC(K4M); (▼) 0.5% ADM + 10% lactose + x% HPMC(K4M); and (▲) x% ADM (x = 2–6%) + y% lactose (y = 8–12%) + z% HPMC(K4M) (z = 8–16%). The solid line was obtained through a linear least-squares analysis of the data.

Diffusivity–Temperature Dependence

The temperature dependence of drug and water diffusion coefficients in these gels/solutions were studied between 10°C and 50°C. The logarithms of adinazolam diffusion coefficients observed in solutions containing a fixed 0.5% adinazolam mesylate with 2% glucose, or 2% lactose, or 2% HPMC, respectively, are plotted versus the reciprocal of absolute temperature in Figure 6; the data are approximately linear, implying Arrhenius behavior. The apparent diffusion activation energies were determined from the slopes of these plots. The apparent diffusion activation energy for adinazolam, E_A, from these solutions are essentially the same (≈5.0 − 5.3 ± 0.4 kcal/mol), as easily judged by the parallel lines in Figure 6, regardless of the nature of VIA, or HPMC viscosity grade (K100LV, K4M and K15M).

A systematic small deviation of the plot of ln D_A versus 1/T is apparent in Figure 6 near 50°C; it was noted that HPMC gels became cloudy at this temperature. These ob-

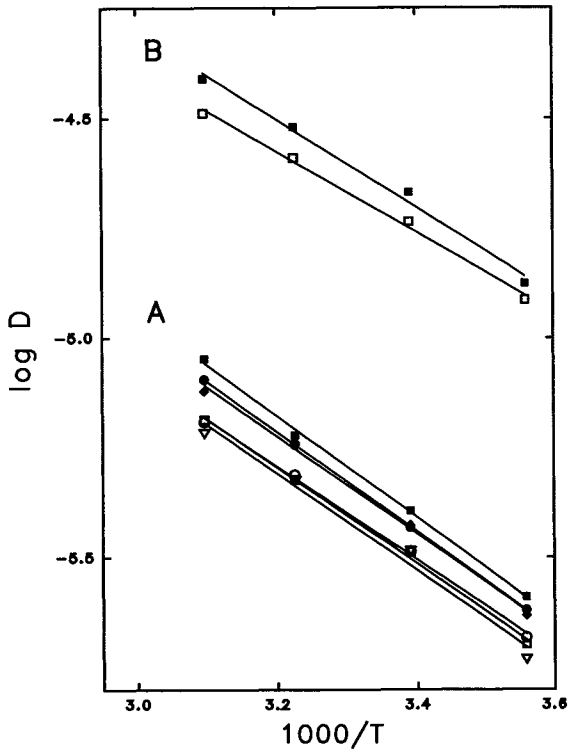

Fig. 6. A) Logarithm of diffusion coefficients of adinazolam, log D_A, plotted against the reciprocal of absolute temperature. D_A values were obtained from: (■) 0.5% ADM; (◆) 0.5% ADM + 1.7% glucose; (●) 0.5% ADM + 2% lactose; (○) 0.5% ADM + 2% HPMC(K100LV); (□) 0.5% ADM + 2% HPMC(K4M); and (▽) 0.5% ADM + 2% HPMC(K15M). B) Logarithm of diffusion coefficients of water, log D_W, plotted against the reciprocal of absolute temperature. D_W values were obtained from: (■) 0.5% ADM; and (□) 0.5% ADM + 2% HPMC(K4M). The solid lines were obtained through a linear least-squares analysis of the data.

servations are presumably due to the thermal gelation process of the polymer solutions (9). This thermal gelation restricts the study of diffusion activation energy in gels at higher temperatures and the study in HPMC gels of higher concentration.

Examination of the dependence of water diffusivity upon temperature was also conducted in the same temperature interval (5–50°C). Representative Arrhenius plots of the water diffusion coefficient observed in 0.5% adinazolam solutions with and without the presence of 2% HPMC (K4M) are displayed in Figure 6 for comparison. The apparent activation energies of water diffusion are essentially the same (≈4.3 –4.6 ± 0.5 kcal/mol) regardless of the presence of 2% HPMC. The apparent activation energies for drug and water diffusion observed in this study are consistent with the similar studies in dilute agarose hydrogels (17) or water itself (18–19) and are comparable to the hydrogen bonding energy of water (20).

DISCUSSION

One goal in the present study is the utilization of the PFGSE NMR methods to study the diffusion behavior of drug and water in a multicomponent gel as a function of the gel composition. There are several fundamental issues that may now be addressed: (a) What is the mechanism of drug and water diffusion in a HPMC gel? (b) What is the nature of the interactions among adinazolam, HPMC and other VIA component in such matrices? (c) What is the influence of polymer molecular weight, or chain length, upon drug diffusion process? (d) What structural information can be deduced for a gel solution? (e) How does our diffusivity data fit with the current diffusional models? We now discuss these and related issues.

Yasuda Model

The Yasuda model has been developed based on the free volume theory and is considered one of the most useful models for describing diffusion of small molecules in moderately swollen gels (21–23). The Yasuda equation is:

$$D_3 = D^\circ_3 \exp\left[-(B\, Q_3/V_{f,1})\,(1/\varphi_1 - 1)\right] \qquad (5)$$

where D and D° are the diffusion coefficients in a polymer gel and in a solvent, respectively; integer subscripts refer to solvent, polymer, and solute, respectively; B is a proportionality constant for a given system; Q_3 is the effective cross section of the diffusing solute; $V_{f,1}$ is the free volume in pure water; and φ_1 is the volume fraction of water in polymer gel (21–23).

A representative set of adinazolam diffusivity data obtained from HPMC(K4M) gels with a fixed concentration of 0.5% adinazolam mesylate is analyzed according to Yasuda model and all related parameters are reported in Table II. The volume fraction of drug is ignored since this model is only applicable to a binary component system. A linear relationship, which is predicted by this model, is observed as the values of ($\ln D_A/D^\circ_A$) for adinazolam are plotted against ($1/\varphi_{HDO} - 1$) and shown in Figure 7.

The solvent is also expected to follow the Yasuda model (21–23). The values of ($\ln D_W/D^\circ_W$) for water obtained from the same gels show an approximately linear relationship versus ($1/\varphi_{HDO} - 1$) in Figure 7 although significant deviations are observed at low VIA concentrations. It is worth noting that the slope of Yasuda plot is proportional to the molecular size of the solute, which has been verified by several studies (21–24). The different slopes obtained for adinazolam and water in Figure 7 are qualitatively consistent with the differences in their molecular sizes.

Table II. Diffusion Quotients of Adinazolam and Volume Fractions of HPMC-K4M (φ_{HPMC}) and Water (φ_{HDO}) in 0.5%ADM + x% HPMC-2208-K4M

$[D/D_0]_A$	$\ln [D/D_0]_A$	W_{HPMC} (%)	φ_{HPMC} (%)	$1/\varphi_{HDO} - 1$
1.00	0	0	0	0
0.87	−0.139	1.0	0.8	0.008
0.80	−0.223	2.0	1.6	0.016
0.70	−0.356	3.9	3.1	0.032
0.60	−0.510	5.9	4.7	0.049
0.51	−0.673	7.8	6.3	0.067
0.42	−0.868	9.8	7.9	0.086
0.35	−1.050	12.8	10.4	0.116
0.30	−1.204	14.6	11.9	0.135
0.26	−1.347	17.0	14.0	0.163

The diffusional behavior of drug and water described by this work, particularly Equation 2, can be related to the Yasuda model through the reasoning given below. The solvent volume fraction, $1/\varphi_1$, can be approximately expressed as

$$1/\varphi_1 = 1/(1 - \varphi_2) = 1 + \varphi_2 + \varphi_2^2 + \ldots \qquad (6)$$

assuming that φ_1 and φ_2 sum to unity (ignoring the drug

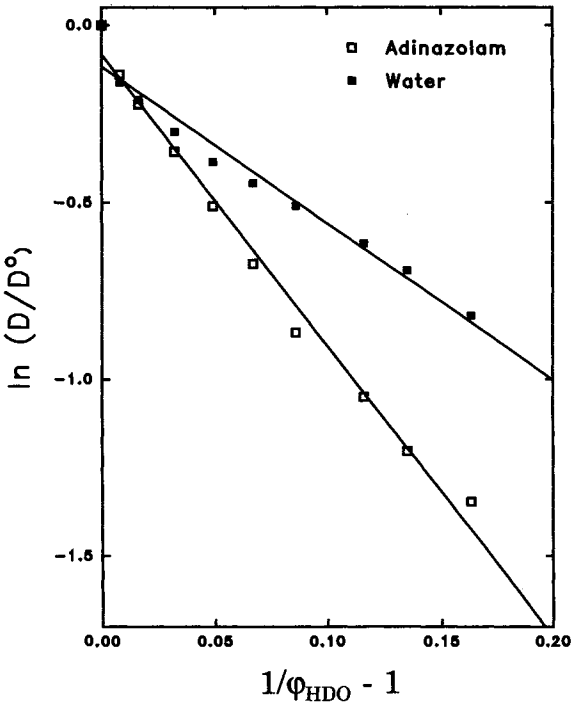

Fig. 7. Natural logarithm of normalized diffusion quotients of both (□) adinazolam and (■) water, obtained from gels of 0.5% ADM + x% HPMC(K4M), are plotted against ($1/\varphi_{HDO} - 1$). The solid lines were obtained through a least-squares analysis.

concentration) and the polymer volume fraction, φ_2, is small ($\varphi_2 \ll 1$). Therefore, φ_2 is a good approximation to $(1/\varphi_1 - 1)$ in dilute gels. Given the proportional relationship between φ_2 and the weight percentage of polymer, or C_H, at least at low polymer concentrations, there is a linear relationship between values of C_H and $(1/\varphi_{HDO} - 1)$ (see columns 3 and 5, Table II). Therefore, Equation 2 is equivalent to Equation 5 when the terms B, Q, and V are combined to a single constant K.

In some reported cases, the solute (usually small molecule) diffusivity has been similarly found to show an exponential dependence on polymer concentration (28–30). However, these data were usually fit to Equation 2 without justification. Given the arguments above, our empirical observations of the approximately exponential dependence of the drug diffusivity upon the VIA concentration in a non-interactive binary component system is inherently linked to the Yasuda model.

More important, we further develop an empirical formula to describe drug and water diffusion behavior in non-interactive multicomponent gels. Nearly all current theories/models as well as experiments are based on (pseudo) binary modeling. Particularly, theoretical works have not yet been properly developed for multicomponent systems (16,25–27). For the ternary and quaternary mixtures examined in this study, drug diffusivity can be adequately predicted using Equation 3 by incorporating the individual VIA contributions (K_iC_i) and assuming an additive obstruction effect from these VIA components. Based upon the relationship between Equations 2 and 5, Equations 3 and 4 are a natural extension of the Yasuda model for describing solute or solvent diffusivity in non-interactive multicomponent gels, respectively. These formulas describe the drug and water diffusivity appropriately even for moderately concentrated gels (up to 31% VIA, due to experimental restraints). Therefore, they are very useful for estimation of drug and water diffusivities in HPMC or related solutions of a similar chemical nature without conducting diffusional measurements. An example dealing with alprazolam diffusivity will be discussed in the companion paper.

Degree of Polymerization

Diffusion coefficients of adinazolam observed in glucose or lactose solutions decrease similarly as the concentration of glucose or lactose increases (Figure 3). Although drug diffusivities obtained from glucose and lactose solutions closely resemble each other, slightly greater dependence of adinazolam diffusivity upon lactose concentration is obvious. However, the dependence of adinazolam diffusivity upon lactose or glucose concentration is dramatically different from its dependence upon HPMC concentration as depicted in Figure 3. Adinazolam diffusivities obtained from maltoheptaose solutions falls between the diffusivity curves obtained from lactose and HPMC solutions. There is a partial substitution of the hydroxyl groups by methyl (22–24%, w/w) and hydroxypropyl (8–10%, w/w) groups in HPMC 2208 polymer (9); nonetheless, glucose, lactose, maltoheptaose and HPMC are essentially chemically similar substances from a simplified point of view, except for the difference in their chain length. Evidently, a gradually increased retarding effect of these VIAs on adinazolam diffusivity is observed from glucose, lactose, maltoheptaose to HPMC; it indicates a distinct dependence of retarding effect upon the degree of polymerization of the VIA molecules. The K value for each VIA determined from their binary component systems (Table I) clearly suggests a trend:

$$K_{glucose} < K_{lactose} < K_{maltoheptaose} < K_{HPMC}$$

Intuitively, these K values are indicative of the relative obstruction power of the VIA molecules for drug diffusion on the same weight basis.

The physical obstruction mechanism we propose for drug diffusion in HPMC gels or related solutions is also supported by the temperature–dependence of the drug diffusivity data. As reported in the Results section, similar apparent activation energies for drug and water diffusion are observed, suggesting a common mechanism. This energy is comparable to the hydrogen bonding energy, which is presumably the minimum diffusion barrier in aqueous solutions assuming no other chemical interactions. Thus drug molecules move through the water filled regime of the gel with little partition in the polymer phase. The diffusion barrier for both adinazolam and water in these solutions is determined solely by the interactions between water molecules. Microscopically, the presence of VIA molecules simply imposes a tortuous diffusional path to drug or water molecule. This is consistent with the free volume theory, which predicts that the solute diffusivity is determined by the interaction of the solvent with its environment (25–27).

As already mentioned, little dependence of adinazolam diffusivity is observed upon the viscosity grade of HPMC polymer (K100LV, K4M, and K15M). This finding is consistent with the conclusion of a recent report (31) which studied the diffusion of verapamil hydrochloride in HPMC media including E4M, E10M and K100M. Since the macroscopic viscosity of HPMC polymer in solution is directly related to its molecular weight or chain length (9), both results suggest that drug diffusion in swollen HPMC gels shows little dependence upon the molecular weight of HPMC. There must be a plateau to this dependence as the polymer chain length elongates. Based on the rapid shift of diffusivity curve with the degree of polymerization (Figure 3) and the lowest polymerization degree of HPMC-K100LV about 150 (32), then, a low degree of polymerization of HPMC is estimated ($n = 30–50$) beyond which a plateau is reached for the drug diffusivity dependence upon the VIA polymerization.

The rapid decrease of adinazolam diffusivity upon the increased degree of polymerization of the VIA molecules, can also be rationalized based on the free volume theory. It is essentially the motion of the polymer segments which determines the solute diffusivity regarding the ease of formation of a solvent "hole" for solute to diffuse. The diffusion of adinazolam definitely requires highly cooperative, correlated motions between the solvent molecule and the surrounding segments of VIA molecules to form such holes. That probability decreases as the polymerization degree of VIA molecules increases, and therefore, the ease of formation of such a "hole" greatly decreases. A decrease of the solute diffusion coefficient is anticipated as the mobility of the polymer chain becomes less appreciable due to the ex-

tension of chain length. A significant decrease of adinazolam diffusivity is thus anticipated along with the increased polymerization degree of the VIA.

Tortuosity and Mackie-Meares Model

Since polymer macromolecules are less mobile than small solute or solvent molecules, the polymer acts as an obstructing stationary phase in the gel solutions. Obstruction theories have been developed to evaluate the degree of tortuosity of polymers (21,24,25). One of the most widely used obstruction theories is the Mackie-Meares model (24,25), which is usually expressed as Equation (7):

$$D/D^0 = (1 - \varphi)^2/(1 + \varphi)^2 \quad (7)$$

where D and D^0 are the same as defined in Equation 5; and φ is the polymer volume fraction. The theoretical dependence of D/D^0 of the solute upon the volume fraction of polymer, φ_2, is shown in Figure 8 using Equation 7. Also depicted in Figure 8 are the diffusion quotients of adinazolam, $(D_A/D_A{}^0)$, obtained from lactose and HPMC solutions, respectively, as a function of the volume fraction of each VIA. As shown in Figure 8, the diffusion quotients of adinazolam obtained from lactose solutions show a reasonably good agreement with the theoretical prediction. However, the diffusion quotients of adinazolam obtained from HPMC solutions deviate significantly from the Mackie-Meares model (Figure 8). Similar observations regarding small molecules diffusing in polymeric matrices are reported in the literature (33).

A directly related, and perhaps clearer interpretation for the large deviations of adinazolam diffusivity in HPMC gels from the Mackie-Meares model is the formation of a three dimensional gel structure in HPMC solution. Mathematical treatment of free volume theory for diffusion in equilibrium swollen gels (34–36) indicates that for uncrosslinked polymers, this three-dimensional network is formed by entangled chains of the polymer. Associated with this network, is a characteristic correlation length of the "mesh size", which is in turn a function of the polymer concentration, polymer chain length, rigidity of the chains, and molecular weight between crosslinks, degree of hydration etc. (34–39). The solute diffusion coefficient in such a network matrix decreases rapidly due to the combined results of (1) an increase in the hydrodynamic drag; (2) steric restriction imposed on the solute by a sieving mechanism; and (3) hydrophobic or other specific interactions between the solute and the polymer network segments. Thus, under such circumstances, the Mackie-Meares model would overestimate a solute diffusivity even at low polymer concentration.

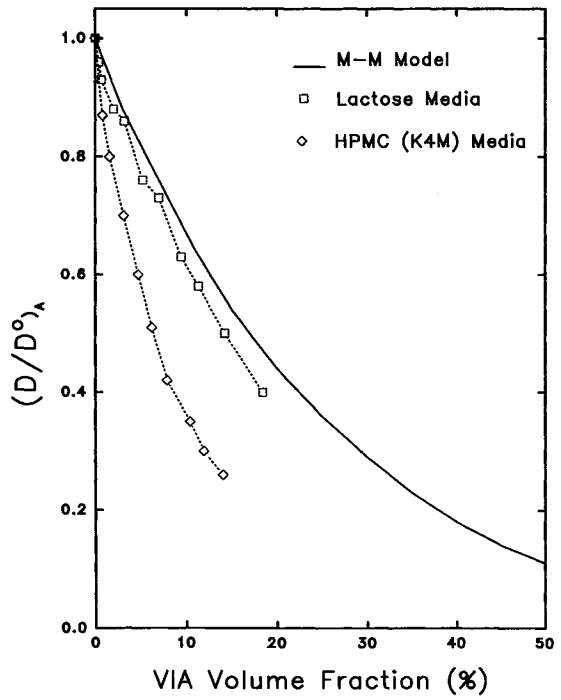

Fig. 8. Normalized diffusion quotients of adinazolam plotted against the VIA volume fraction. D_A values were obtained from: (□) 0.5% ADM + x% lactose; and (◇) 0.5% ADM + x% HPMC(K4M). Theoretical prediction of the Mackie-Meares model is also plotted for comparison.

The distinct dependence of the drug diffusivity upon the degree of polymerization of VIA molecules can also be interpreted by the polymer network structure. Small VIA molecules, such as glucose and lactose, can not possibly form an extensive network in the solution because of their extremely short chains. As the polymerization degree increases, the entanglements of the chains of the VIA molecules in addition to the extensive hydrogen bonding become more important and affect the drug diffusion more effectively, as in maltoheptaose solutions. As the polymerization degree reaches the "plateau value" (as we propose in this work), a "stationary" polymer network is presumably interwoven and mainly responsible for the transport characteristic of solute and solvent. Further extension of the polymer chain length beyond the threshold does not change the microscopic organization of the network structure. Nonetheless, it changes the macroviscosity of the solution dramatically. This explains the independence of the adinazolam diffusivity upon the HPMC viscosity grades. Supporting this argument is the observation that the drug diffusivity shows a more significant deviation from the prediction of the Mackie-Meares model, or from the drug diffusivity in lactose solutions (Figure 8), at relatively higher HPMC concentrations. The extent of the deviation of the experimental data from the Mackie-Meares theory would be expected to increase with increasing polymer concentration, since the "mesh size" of the polymer network in the gels becomes progressively smaller. In contrast, a nearly constant deviation between the drug diffusivity in lactose solutions and the Mackie-Meares theory is observed within a wide range of lactose concentration.

The normalized diffusivity of water plotted versus the HPMC volume fraction is shown in Figure 9, which also deviates from the predictions of the Mackie-Meares model. Water diffusivity appears to be independent of the degree of polymerization of VIA molecules, and is primarily determined by an additive concentration of VIA (Equation 4). A more rapid decrease of water diffusivity at the lower VIA concentration regime is apparent (Figures 5 and 9) in contrast to the drug diffusivity at the same concentration region (Figures 2 and 8). We do not offer an interpretation regarding these observations. Since the water molecule is small, the cooperative motion between obstructing stationary objects

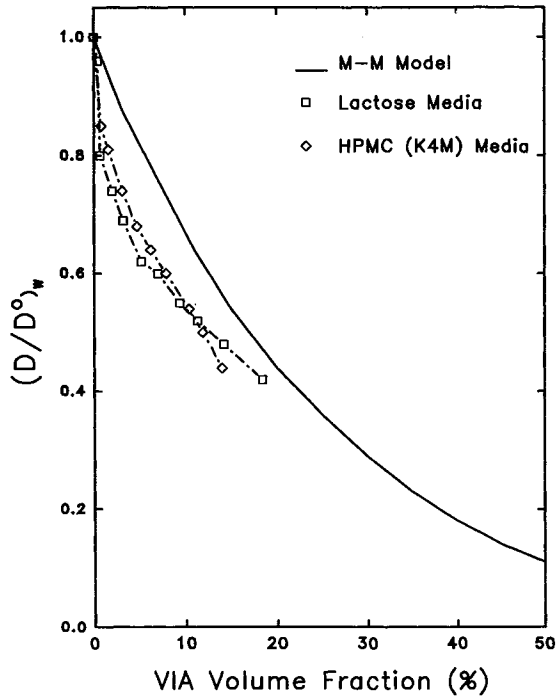

Fig. 9. Normalized diffusion quotients of water plotted against the VIA volume fraction. D_W values were obtained from: (□) 0.5% ADM + x% lactose; and (◇) 0.5% ADM + x% HPMC(K4M). Theoretical prediction of the Mackie-Meares model is also plotted for comparison.

and diffusing species is unlikely as important as for large solute (e.g., drug), and the sieving mechanism of the polymer network is also less operative for water. The deviation of water diffusivity from Mackie-Meares model is probably caused by the extensive interactions (such as hydrogen bonding) between water and these hydroxyl rich VIA molecules. This deviation is not surprising because this model ignores solute-VIA interactions.

CONCLUSIONS

Diffusional behavior of both adinazolam and water in solutions containing glucose based VIA molecules (glucose, lactose, maltoheptaose, and HPMC) have been systematically studied using PFGSE NMR. These results demonstrate that the PFGSE NMR technique is a reliable and appropriate method for accurate determination of the diffusion coefficient of species of interest in a complex multicomponent system. The present work also demonstrates the significant potential of the PFGSE NMR methods for obtaining insight into the diffusion mechanism, kinetics and gel structure. We report for the first time that the drug diffusivity in a non-interactive multicomponent system can be described as an exponential function of an additive contribution from each VIA component. We have also demonstrated a relationship between our empirical formula and the Yasuda model. An Arrhenius type of temperature dependence of the drug and water diffusivity in these systems is observed, and their apparent diffusion activation energies are comparable to the hydrogen bonding energy. Retardation from the VIA components to drug diffusion in these systems is mainly caused by a steric obstruction mechanism. The hypothesis of a three dimensional network of polymer in the gels is generally consistent with the drug diffusion behavior in HPMC gels we observed through this work, which show a significant deviation from the Mackie-Meares model. In contrast, the diffusion coefficient of water is only determined by the VIA concentration and is independent of the nature of the VIA. The deviation of water diffusivity from the Mackie-Meares model is presumably due to its extensive hydrogen bonding interactions with the hydroxyl groups of the VIA.

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