An Obstruction-Scaling Model for Diffusion in Homogeneous Hydrogels

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Received June 11, 1998; Revised Manuscript Received November 19, 1998

ABSTRACT: A mathematical description of the restricted movement a solute experiences while diffusing in a homogeneous hydrogel is presented. The model is based on the premise that physical obstruction effects dominate the diffusive process, and a scaling law expression is incorporated to describe the distance between cross-links in the polymer network. The model was compared to experimental data taken from literature sources and found to provide good agreement to the effects of both polymer volume fraction and solute size on the diffusivity of a solute within the hydrogel.

Introduction

Hydrogels can be classified in terms of their structure as ranging from homogeneous, or nonporous, to heterogeneous, or macroporous.[1−3] The differences in structure arise as a result of the manner in which the polymer chains interact with the aqueous environment. In homogeneous hydrogels, the polymer chains have a high affinity for the surrounding water, form one phase, and are highly mobile. Heterogeneous hydrogels, on the other hand, have local regions where the polymer chains and the water form two distinct phases.

As a result of hydrogel structure, solute movement in hydrogels is restricted to a much greater extent than in an aqueous medium. This nature of hydrogels has led them to be used in a number of biomedical and biotechnological fields.[2−4] As a necessary component of designing products made from hydrogels, it is important to have an understanding of the factors that affect solute movement through hydrogels. A number of phenomenological models have been proposed to explain the restriction to solute movement in homogeneous hydrogels. These models include those based on free volume theory,[5,6] physical obstruction,[7−9] and enhanced hydrodynamic drag on the solute molecule.[10, 11]

Recently, these models have been reviewed and compared to literature data of solute diffusion in homogeneous hydrogels.[12] The results of this review indicated that, for homogeneous hydrogels, although it is invoked most often as an explanation, free volume theory is not physically consistent with the data. To reconcile free volume theory with restricted solute movement in hydrogels, it was determined that the jump length of the solute molecule in the hydrogel must decrease as solute size increases. This scenario seems unlikely, since larger molecules would be expected to have a longer jump length. A more consistent model, in terms of fitting the data adequately and providing physically reasonable fitted parameters, was the hydrodynamic-scaling model put forward by Cukier.[11] This hydrodynamic-scaling expression can be written as follows:

$$\frac{D_g}{D_0} = \exp\left(-k_c \frac{r_s}{\xi}\right) \tag{1}$$

in which k_c is a constant for a given polymer−solvent system, r_s is the radius of the solute molecule, ξ is the distance between polymer cross-links, D_g is the diffusion coefficient of the solute in the gel, and D_0 is the diffusion coefficient of the solute in water. This model, however, contains an undefined parameter (k_c) and does not account well for the effect of solute size on its diffusivity within a hydrogel. The issue, then, of which model can account for all the available experimental data is still unresolved.

The objectives of this paper are to derive an obstruction-scaling model and show that it is consistent with experimental observations of solute diffusion in homogeneous hydrogels. To accomplish these goals, data of solute diffusion within homogeneous hydrogels will be taken from the literature, to which will be applied the newly developed obstruction-scaling model.

Model Development

The obstruction-scaling model to be derived is similar in basis to a model derived earlier for solute diffusion in heterogeneous hydrogels.[9] The model is based on the premise that a solute moves through a hydrogel by encountering a series of openings between the polymer chains whose radius is greater than the hydrodynamic radius of the solute. In other words, the reduction in diffusivity is due to the solute encountering polymer chain obstacles. Thus, the diffusivity of the solute is expressed as the probability of encountering a series of these openings, or

$$\frac{D_g}{D_0} = \int_{r^*}^{\infty} g(r)\, dr \tag{2}$$

where $g(r)$ is the distribution function describing the distribution of the radii of openings between polymer chains, and r^* is the critical limiting radius required to permit solute passage. Ogston[13] derived an expression for the distribution of radii of spherical spaces between random networks of straight fibers of negligible width. This distribution function is

$$g(r) = \frac{\pi r}{2R^2} \exp\left(-\frac{\pi}{4}\left(\frac{r}{R}\right)^2\right) \tag{3}$$

where R is the mean radius of this distribution. Although the polymer chains comprising the homogeneous hydrogels are definitely not straight, this distribution function will be assumed to hold true for flexible

10.1021/ma980922a CCC: $18.00

polymer chains as well. Substituting this expression into eq 2 and carrying out the integration results in

$$\frac{D_g}{D_0} = \exp\left[-\frac{\pi}{4}\left(\frac{r^*}{R}\right)^2\right] \tag{4}$$

To account for the finite thickness of the polymer chains, eq 4 is rewritten as

$$\frac{D_g}{D_0} = \exp\left[-\frac{\pi}{4}\left(\frac{r_s + r_f}{\bar{r} + r_f}\right)^2\right] \tag{5}$$

in which $\bar{r}$ is the average radius of the openings between the polymer chains and r_f is the radius of a polymer chain.

The average opening radius will be defined by using scaling methods to characterize the gel. de Gennes has proposed that, for a polymer in a good solvent, the gel state is equivalent to the condition in which polymer chains in solution begin to overlap.[14] The distance between cross-links, ξ, is given by the following scaling relationship[15]

$$\xi \propto a\phi^{-0.75}C_\infty^{-0.25}(1 - 2\chi)^{-0.25} \tag{6}$$

in which a is the equivalent bond length of the monomer, ϕ is the volume fraction of polymer in the hydrogel, C_∞ is the characteristic ratio of the polymer, and χ is the Flory–Huggins polymer/solvent interaction parameter. In using eq 6, it was assumed that (1) the gel represents a semidilute solution, (2) there are only binary contacts between the monomer units, (3) water is a good solvent for the polymer, (4) the polymer persistence length is less than the distance between cross-links, and (5) the polymer chains are fully swollen.

The average radius of the openings can be defined as $\xi/2$ by assuming that, in an idealized state, the polymer chains in the gel form a square lattice, a reasonable assumption for gels that form tetrafunctional cross-links. Using this definition, the diffusivity within the hydrogel with respect to diffusivity in the aqueous medium becomes

$$\frac{D_g}{D_0} = \exp\left[-\pi\left(\frac{r_s + r_f}{k_s a\phi^{-0.75}C_\infty^{-0.25}(1 - 2\chi)^{-0.25} + 2r_f}\right)^2\right] \tag{7}$$

in which k_s is a constant of proportionality. By definition, the value of k_s is constant for a given polymer–solvent system. Equation 7 represents the new obstruction-scaling model.

Methods

Data of solute diffusion in homogeneous hydrogels were collected from the literature. These literature sources, the polymers comprising the hydrogels, and the method used to determine diffusivity within the hydrogel are listed in Table 1. The physical properties of the polymers making up the hydrogels are listed in Tables 2 and 3, along with the reference from which the values were obtained. The polymer chain radius, r_f, listed in Table 2 was calculated from the following relationship[8]

$$r_f = \left(\frac{M_m v}{l\pi N_A}\right)^{1/2} \tag{8}$$

Table 1. Sources for Experimental Data, the Polymer Investigated, and the Method Used To Determine the Diffusivity within the Hydrogel

polymer	method of determining D_g	ref
poly(ethylene oxide)	diffusion into a slab	28
poly(ethylene oxide)	diffusion from a slab	29
poly(acrylamide)	nuclear magnetic resonance	30
poly(acrylamide)	diffusion into a slab	31
poly(vinyl alcohol)	diffusion across a membrane	32
dextran[a]	diffusion from a slab	33

[a] Cross-linked with glycidyl methacrylate (low cross-link density).

Table 2. Physical Properties of Polymers Examined

polymer	M_m (g/mol)	v (cm^3/g)[a]	l (Å)[b]	a (Å)	r_f (Å)[c]
poly(ethylene oxide)	44	0.830	3.60	1.54	2.32
poly(vinyl alcohol)	44	0.765	2.51	1.54	2.70
poly(acrylamide)	71	0.700	2.51	1.54	3.23
dextran	142	0.625	5.14	5.14	3.02

[a] From ref 34. [b] Calculated from bond angles and bond lengths, except dextran for which the value for alginate was assumed (see text). [c] Calculated using eq 7.

Table 3. Flory–Huggins Interaction Parameter, χ, and Characteristic Ratio, C_∞, Values for Polymers Examined

polymer	C_∞	T (°C)	χ[a]	ref
poly(ethylene oxide)	4.0	25		35
		20	0.45	36
		25	0.46	36
		30	0.463	36
		40	0.48	36
		25	0.47	37
	4.8			22
	5.2	25		21
poly(vinyl alcohol)		25	$0.48 + 0.4\phi$[b]	25
	8.9	25		35
		30	0.485–0.495	23
	8.5 ± 1			38
	8.3	30		34
poly(acrylamide)		25	0.466	39
	14.6–15.8	21		40
	14.8	30		34
dextran	9[c]	25		41
		37	0.47	18
			0.43	16

[a] Un-cross-linked polymer–water values. [b] For a poly(vinyl alcohol) hydrogel. [c] Calculated from sedimentation coefficient data taken from reference.

Table 4. Characteristic Ratio and Flory–Huggins Interaction Parameter Values Used in This Work

polymer	C_∞	χ
poly(ethylene oxide)	5.2	0.46
poly(vinyl alcohol)	8.5	0.49
poly(acrylamide)	15.2	0.466
dextran	9.0	0.473

in which l is the length of the monomer unit, M_m is the molecular weight of the monomer, v is the specific volume of the polymer, and N_A is Avogadro's number. The characteristic ratio and Flory–Huggins interaction parameters chosen for this work are given in Table 4.

The solutes used and their hydrodynamic radii, calculated from the Stokes–Einstein equation,

$$r_s = \frac{kT}{6\pi\eta D_0} \tag{9}$$

are listed in Table 5. In eq 9 k is Boltzmann's constant, T is the temperature at which D_0 was determined, and

Table 5. Hydrodynamic Radii of Solutes Used in Literature Data

solute	radius (Å)	diffusion study ref
water	1.9	30
urea	2.0	31
theophylline	3.8	32
sucrose	4.8	31
caffeine	5.3	29
vitamin B12	8.7	28, 32
ribonuclease	16.3	32
lysozyme	19.1	28, 32
α-lactalbumin	20.2	32
chymotripsinogen	22.5	32
ovalbumin	29.3	28, 32
bovine serum albumin (BSA)	36.3	28, 32, 33
imunnoglobulin G (IgG)	53.5	33

η is the water viscosity at the temperature at which D_0 was determined.

The model was fit to the literature data using a Levenberg–Marquardt nonlinear regression algorithm incorporated into a computer graphing software package (KaleidaGraph). The applicability of the model was determined by analysis of the sum of squares of the residuals (SSR), the correlation coefficient (R^2), and the physical consistency of the returned value of the fitted parameter. The confidence interval (±) of the returned value, at the 95% confidence limit, was calculated using the sum of squares of the residuals as an estimate of the variance in the data.

Results and Discussion

Before examining the results of applying the model (eq 7) to the data, a short discussion of the physical property values used is warranted. Table 3 shows that, for the most part, the literature values for polymer characteristic ratio and Flory–Huggins interaction parameter are in good agreement with each other. One discrepancy is the value given for the Flory–Huggins parameter of dextran, which varied from 0.43 to 0.47. The 0.43 value is given by Evans and Needham,[16] who determined χ for dextran fraction of molecular weight ranging from 3330 to 94 300. These authors found that χ was constant with increasing molecular weight, but work with other polymers has demonstrated that χ increases slightly as molecular weight decreases, particularly at low molecular weights.[17] In the work of Gekko,[18] who examined dextran molecular weight fractions ranging from 618 to 8980, the value of χ decreased from 0.742 to a plateau value of 0.47 for the higher molecular weight fractions. As these results were in better agreement with results for other polymer–solvent systems, the value of 0.47 was chosen for dextran. Another source of controversy has been the value used for the length of a monomer unit for dextran. Literature values ranged from 3.9[8] to 6.5 Å.[16] An intermediate value of 5.14 Å was used, based on the length of a monomer unit of alginate.[19] This value for the length of the monomer unit has also been used by another group working with celluloses.[20] Finally, a value of 5.2 was used for the characteristic ratio of poly(ethylene oxide)[21] because of its agreement with other, recently published, values.[22]

The results of fitting the obstruction-scaling model relationship (eq 7) to the experimental diffusivity data taken from the literature are displayed in Figure 1A,B (effect of polymer volume fraction) and Figure 2 (effect of solute radius). The scaling parameters, k_s, obtained by the nonlinear regression procedure are listed in Table 6. Table 6 also includes the sum of squares of the residuals, confidence intervals for k_s, and the correlation coefficient for the regressions.

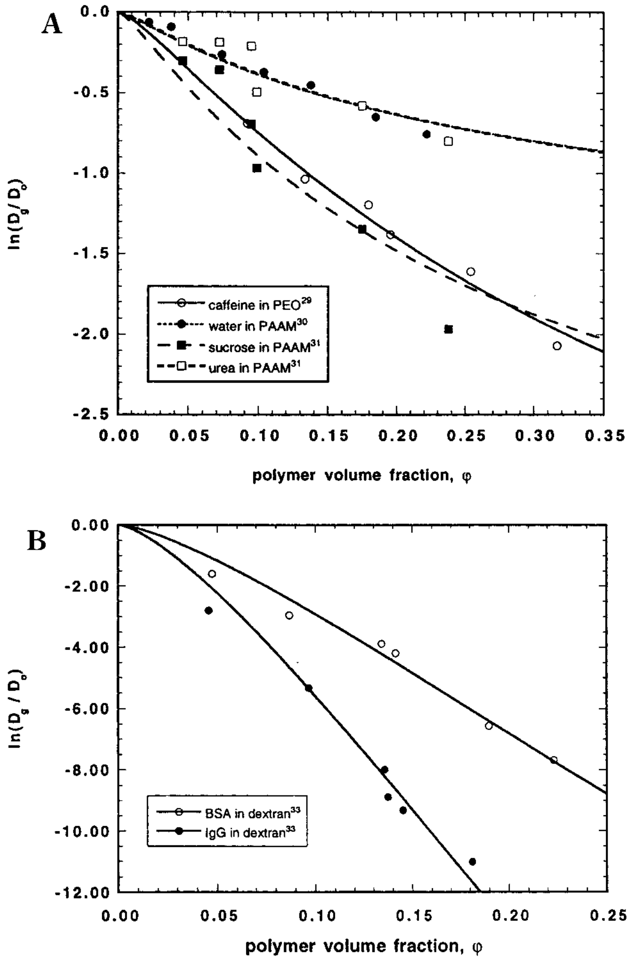

Figure 1. Regression of obstruction-scaling model to literature data of the effect of polymer volume fraction on solute diffusion. The lines in the figure represent the regression results. (A) Synthetic polymer hydrogels, (B)dextran hydrogels.

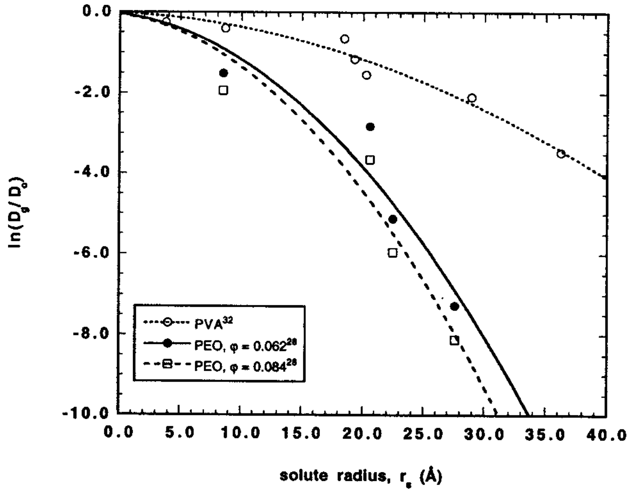

Figure 2. Application of obstruction-scaling model to literature data of the effect of solute radius on solute diffusion. The lines in the figure represent the regression results.

An examination of Figure 1A,B and Figure 2 clearly indicates that the obstruction-scaling provides good agreement to the experimental data. Not only does the model provide a good fit to the effect of polymer volume

Table 6. Results of Regression of Obstruction-Scaling Model to Literature Data of the Effect of Both Polymer Volume Fraction and Solute Radius on Diffusivity within a Homogeneous Hydrogel

ref	polymer[a]	k_s	±[b]	SSR	R^2
effect of ϕ					
33 (BSA)	dextran	1.03	0.02	0.770	0.970
33 (IgG)	dextran	1.08	0.021	1.62	0.964
29	PEO	1.01	0.02	0.025	0.979
30	PAAM	1.02	0.05	0.017	0.958
31 (sucrose)	PAAM	1.09	0.10	0.247	0.878
31 (urea)	PAAM	1.07	0.11	0.056	0.828
effect of r_s					
32	PVA	1.10	0.03	0.330	0.958
28 ($\phi = 0.062$)	PEO	1.01	0.06	2.170	0.888
28 ($\phi = 0.084$)	PEO	1.05	0.05	2.10	0.90

[a] PEO = poly(ethylene oxide), PAAM = poly(acrylamide), and PVA = poly(vinyl alcohol). [b] 95% confidence interval for fitted value of k_s.

Table 7. Results of Regression of Hydrodynamic-Scaling Model to Literature Data of the Effect of Solute Radius and Polymer Volume Fraction on Diffusivity within a Homogeneous Hydrogel

ref	polymer[a]	k_c'	±[b]	SSR	R^2
effect of ϕ					
33 (BSA)	dextran	3.56	0.21	2.52	0.900
33 (IgG)	dextran	4.27	0.17	3.18	0.929
29	PEO	1.69	0.04	0.030	0.973
30	PAAM	1.73	0.08	0.022	0.948
31 (sucrose)	PAAM	1.47	0.12	0.255	0.874
31 (urea)	PAAM	1.57	0.14	0.056	0.828
effect of r_s					
28 ($\phi = 0.062$)	PEO	3.38	0.45	4.53	0.766
28 ($\phi = 0.084$)	PEO	3.19	0.34	3.82	0.824
32	PVA	2.21	0.23	1.27	0.836

[a] PEO = poly(ethylene oxide), PAAM = poly(acrylamide), and PVA = poly(vinyl alcohol). [b] 95% confidence interval for fitted value of k_s.

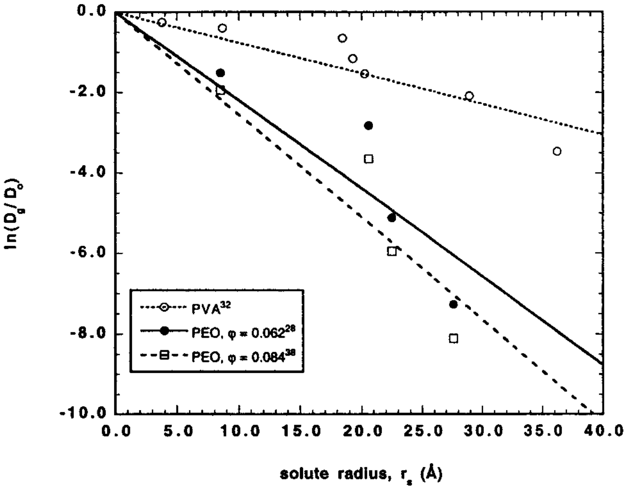

Figure 3. Fit of the hydrodynamic-scaling model of Cukier[11] to literature data of the effect of solute radius on solute diffusion. The lines in the figure represent the regression results.

fraction on a solute's diffusivity within a homogeneous hydrogel (Figure 1A,B), but it is also in accordance with the experimentally observed trend in the diffusivity vs solute radius data (Figure 2). For comparison, the hydrodynamic-scaling model of Cukier[11] is fit to the same data showing the effect of solute radius. By using eq 6 to define ξ, the hydrodynamic-scaling model can be written as follows:

$$D_g/D_0 = \exp(-k_c' r_s a^{-1} C^{0.25} (1 - 2\chi)^{0.25} \phi^{0.75}) \quad (10)$$

The results of the fits of eq 10 to the effect of solute radius data are displayed in Figure 3 and listed in Table 7. Figure 3 illustrates that the hydrodynamic-scaling model does not accurately reflect the dependence of a solute's diffusivity within the hydrogel on its size. This observation is supported by the much lower sum or squares of residuals which results from the fit of the obstruction-scaling model to the same data (Tables 6 and 7).

For further comparison, the hydrodynamic model was also fitted to the data showing the effect of polymer volume fraction. The regression results are also listed in Table 7. Although the hydrodynamic expression provides a good agreement to the data, the newly developed model still produces a lower sum of squares of the residuals (Table 6). The sum of squares of residuals produced by the obstruction model is only slightly better for most cases where relatively small molecules are investigated. However, the obstruction model does provide a significant improvement for the fit to the data of Hennink et al., in which proteins are diffusing in cross-linked dextran. Therefore, the obstruction model appears to be better than the hydrodynamic model, particularly when large solute molecules are involved.

On the basis of these comparisons, it can be said that the obstruction-scaling model provides a more consistent reflection of the observed trends in the data than the model based on hydrodynamic effects. It can be argued that hydrodynamic effects (i.e., enhanced solute drag) would not be expected to be significant for small molecules diffusing in relatively low polymer volume fraction hydrogels. However, the success of the obstruction effect-based model to account for the solute size effect over a wide solute size range, and the failure of the hydrodynamic model over these conditions, infers that enhanced hydrodynamic drag effects may not become significant until much higher polymer volume fractions are reached.

Examination of the k_s values obtained by the regression procedure reveals that they are all virtually statistically equivalent and equal to unity. This result implies that a "universal" model for solute diffusion in homogeneous hydrogels can be written as

$$\frac{D_g}{D_0} = \exp\left[-\pi\left(\frac{r_s + r_f}{a\phi^{-0.75} C_\infty{}^{-0.25} (1 - 2\chi)^{-0.25} + 2r_f}\right)^2\right] \quad (11)$$

Nevertheless, the obstruction-scaling model has only been applied to data for four flexible polymer hydrogel systems, and the universality of the expression would have to be verified by application to many more homogeneous hydrogel systems.

Although the model has been demonstrated to be statistically adequate, the model is only valid within the realm of acceptability of its assumptions. In the derivation of the model a number of assumptions have been made: (1) Water is a good solvent for the polymer (i.e., $\chi < 0.5$). (2) The polymer chain distance between cross-links is greater than the persistence length of the polymer; therefore, scaling concepts can be applied. (3) The polymer chains are fully swollen, and the monomer interaction between polymer chains is a strong two-body effect. (4) χ can be considered constant at low polymer volume fractions. (5) The distribution of spherical spaces between polymer chains in a homogeneous hydrogel is equivalent to the distribution of spherical spaces between a random distribution of straight fibers. (6) The polymer physical properties in the gel state are equivalent to its physical properties in the solution state. (7) Any interactions between the solute and the polymer, such as electrostatic attraction and repulsion or hydrophobic bonding, are negligible. Assumptions 1−3 are readily met by any flexible, water-soluble polymer that has been been rendered into a hydrogel having a relatively low polymer volume fraction. The assumption that χ is constant at low polymer volume fractions is not strictly true. In reality, χ increases as polymer volume fraction increases, but this dependence is generally weak at low polymer concentrations,[23−26]so that this assumption is justified and will not result in significant deviations from the model predictions. From the data examined, it appears that this assumption is useful for polymer volume fractions in the hydrogel up to about 0.30 (Figure 1A). At higher polymer volume fractions, the dependence of χ on polymer volume fraction would have to be considered, along with the fact that ternary monomer contacts will occur. Schaefer[15] has also developed scaling models describing the distance between cross-links in a polymer chains for the situation where ternary contacts exist, which may prove useful for applying the new obstruction-scaling model to those conditions. With respect to the assumption that the physical properties of the polymer (i.e, C_∞ and χ) in the hydrogel state are equivalent to those in the solution state, it has been demonstrated that χ_{gel} is greater than χ_{solution} for poly(vinyl alcohol).[25] Nonetheless, the difference in the values was small, and χ_{gel} was only a weak function of polymer volume fraction. Also, there is no reason to expect C_∞ to change appreciably. Therefore, this assumption can be considered valid.

The next assumption to consider is that of the function describing the distribution of spherical spaces between polymer chains. The distribution function that was used was derived to describe the distribution of openings between straight chains and has been applied to describe the spaces between flexible chains. As any model would have to assume an idealized geometry in order to obtain a theoretical description of the distribution of openings between flexible polymers, the use of a straight chain geometry seems suitable as a first approximation, and indeed, this picture of the hydrogel structure has been used in order to estimate the pore radii distributions for poly(acrylamide) gels from NMR relaxation measurements.[27] In view of the rather good agreement attained between the obstruction-scaling model and the data, the use of this distribution function appears valid.

The last assumption is that the solute has no significant attraction for the polymer. Reduced or enhanced solute diffusivity may result due to hydrophobic attraction and electrostatic repulsion and attraction of the solute for the polymer chains. The data used in this paper were taken from experiments in which these interactions were insignificant. For situations in which attraction or repulsion forces are significant, it will be necessary to add a kinetic term to eq 7 to account for these effects.

Finally, the sensitivity of the model to the values of the most significant parameters needs to be addressed.

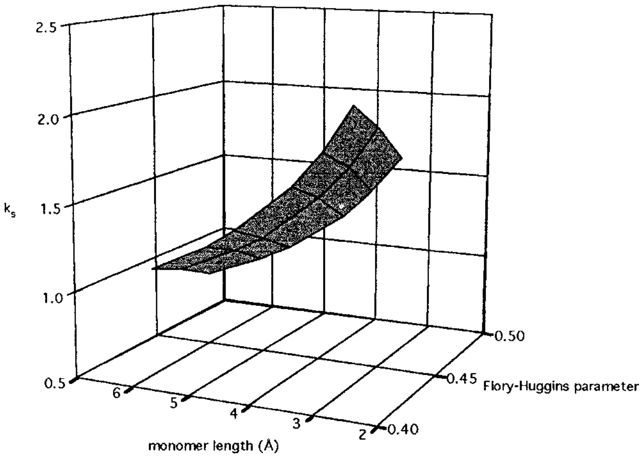

Figure 4. Sensitivity analysis of obstruction-scaling model. The surface represents the results of a Monte Carlo determination of the value of k_s using randomly chosen values for the interaction parameter and the monomer length.

Examination of eq 7 indicates that the model is most sensitive to the values of the length of the monomer unit, which in turn affects the polymer chain radius and the Flory−Huggins interaction parameter. These two parameters are a source of controversy, particularly with respect to dextran. Therefore, a Monte Carlo simulation was performed in which values of χ and l for dextran were varied randomly between 0.43 and 0.47 for χ and 3.0 to 6.5 Å for l. These ranges represent the upper and lower extremes of the literature values. The value of k_s was then determined via regression using the randomly chosen values of χ and l. The result of this analysis is shown in Figure 4, which demonstrates that the value of k_s is most sensitive to the value chosen for the length of the monomer unit. The effect of χ on k_s is more pronounced at lower l values and becomes progressively less important as l increases. The value for k_s approaches unity as l becomes greater than 5 Å. Since the most widely accepted value for the length of the monomer unit for polysaccharides is typically greater than 5, the use of unity for k_s as a means of estimating the diffusivity of a solute in a homogeneous hydrogel is justified.

Conclusions

A model describing the restricted movement experienced by a solute moving through a homogeneous hydrogel has been developed. The model is based on the idea that the factor controlling solute movement is the physical obstruction of the polymer chains producing a increased diffusional path length. This effect is described in terms of the probability of a solute molecule encountering an opening between polymer chains during its random walk which is greater than or equal to its effective hydrodynamic radius. The model accounts for polymer flexibility by employing scaling concepts. The derived obstruction-scaling model was applied to experimental data taken from the literature and found to provide good agreement to the observed effects of both polymer volume fraction and solute radius on solute diffusivity within a hydrogel. The obstruction-scaling model can be considered valid for the following conditions: (1) hydrogels composed of flexible polymers for which water is a good solvent, (2) polymer volume fractions in the hydrogel up to approximately 0.30, and (3) situations in which any interaction between solute and polymer can be considered insignificant.

Acknowledgment. This work was supported by a grant from the National Science and Engineering Research Council of Canada (Grant RGPIN203278-98 AMSD).

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MA980922A