Diffusion in Polyelectrolyte Hydrogels: Application of an Obstruction-Scaling Model to Solute Diffusion in Calcium Alginate

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ABSTRACT: An obstruction-scaling model of the diffusion of solute molecules within polyelectrolyte gels is presented. Two release medium conditions are considered: low ionic strength and high ionic strength. The model is tested against experimental data of protein diffusion in calcium alginate hydrogels. The model provides very good agreement to the experimental results, successfully predicting the effects of polymer concentration, release medium ionic strength, and polymer chain flexibility.

Introduction

In many applications of practical importance, hydrogels are utilized for their ability to retard the movement of a solute. There are a number of manipulatable factors governing the extent to which the transport rate of a solute within the hydrogel is retarded. These factors include polymer concentration, solvent conditions, and choice of polymer (i.e., polymer physical properties). Furthermore, we recently reported on the influence of polymer backbone flexibility on solute diffusion within calcium alginate hydrogels.[1] It was determined through protein release experiments that isotropic hydrogels prepared with alginate of greater mannuronic acid content, and therefore greater backbone flexibility, posed a greater restriction to solute movement than hydrogels prepared using a greater guluronic acid content alginate.

To effectively design devices that employ hydrogels, it is important to be able to predict how altering each of these factors affects the degree of restriction a solute experiences in a given hydrogel. There are a number of models available for predicting intra-gel solubility; however, each has its limitations in terms of predicting the effects of varying polymer and solute properties.[2] For this reason, an obstruction-scaling model was devised and shown to be effective in predicting solute diffusivities in homogeneous, nonionic hydrogels.[3] In this approach, solute movement through the hydrogel structure is considered to be primarily governed by the probability of the solute finding an opening between the polymer chains large enough to permit its passage. The model has the following general expression:

$$\frac{D_g}{D_0} = \exp\left(-\frac{\pi}{4}\left(\frac{r_s + r_f}{\bar{r} + r_f}\right)^2\right) \tag{1}$$

where D_g is the solute intra-gel diffusivity, D_0 is the diffusivity of the solute in the aqueous medium, r_s is the solute hydrodynamic radius, r_f is the radius of the polymer chain, and $\bar{r}$ is the average radius of the openings between the polymer chains. $\bar{r}$ is defined using scaling relationships that are specific for the given polymer−solvent conditions.

A form of this model has previously been developed for polyelectrolyte hydrogels and shown to accurately reflect the influence of both polymer volume fraction and solute radius on the intra-gel diffusivity of a solute in hydrogels prepared from calcium alginate, agarose, and carageenan.[4] That model is represented by eq 2,

$$\frac{D_g}{D_0} = \exp\left(-\pi\left(\frac{r_s + r_f}{k_s\phi^{-0.5} + 2r_f}\right)^2\right) \tag{2}$$

in which k_s is a scaling constant.

It is the objective of this paper to expand the obstruction-scaling expression to further clarify the scaling constant of eq 2. This will be done for both high and low ionic strength release medium conditions. Further, the newly defined model expression will be used to provide a theoretical framework for the effect of polymer backbone flexibility on intra-gel solute diffusion in polyelectrolyte hydrogels. The model equations will be tested against experimental data of the diffusion of a globular protein within calcium alginate hydrogels. Protein diffusion in hydrogels is an area gaining increasing attention due to its impact on drug delivery technologies, modeling of solute transport in human tissue, and downstream purification methods in biotechnology. The protein solute probe examined is bovine serum albumin (BSA). The diffusivity of BSA within the alginate gels is determined via release into sink conditions. Since BSA is a highly charged molecule at neutral pH, release studies were done at pH 6 and the isoelectric point of BSA (pH = 4.8) to ascertain whether any electrostatic effects influenced the solute transport properties.

Model Derivation

In the following derivation it is assumed that the polymer chains between cross-links behave as if they were present as individual chains of the same molecular weight in a solution of the same polymer concentration. Moreover, it is assumed that there are no interactions between the approximately spherical solute molecule and the polymer.

To define $\bar{r}$, a scaling relationship between the average distance between cross-links in the hydrogel must be found. Polyelectrolyte hydrogels differ from nonionic gels in that they possess long-range Coulombic interactions and have within them small counterions which

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maintain electric neutrality. As a result of the osmotic activity of the counterions, water is drawn into the interior and the hydrogel swells. This swelling is balanced by the elastic nature of the cross-linked network.[5−7]

The extent of swelling, and the conformation of the polyelectrolyte chains, is determined by the concentration of ions in the solution and the degree of ionization of the monomers. At low solution ion concentration, a combination of electrostatic repulsion and osmotic expansion results in moderate degrees of swelling, and the polymer chain is stretched. Under these conditions, a Gaussian distribution of end-to-end distances of the polymer chains between cross-links can reasonably be assumed, as has been demonstrated from predicted variations in shear modulus with respect to equilibrium degree of swelling.[8,9] For high degrees of swelling (for example, highly charged, intrinsically stiff chains at very low salt concentrations), the polymer chains become almost entirely stretched and are better represented as rigid rods.[10] This discussion is limited to the case of solute diffusion in gels undergoing moderate degrees of swelling.

In concentrated salt solutions, counterions completely screen the monomer electrostatic repulsion forces, and the degree of swelling is reduced. The polyelectrolyte chains effectively behave as if they were nonionic.[9] The model derivation is therefore divided into each of these salt concentration extremes.

Low Salt Concentration Regime. To develop a scaling expression, the relevant free energies of the process must be stated. For polyelectrolytes, the free energies of mixing of solvent and polymer are not significant, as long as polymer concentration is low.[8] This leaves only the free energy changes due to elastic deformation of the network and to the osmotic effects of the counterions.

The following derivation follows that of Skouri et al.[9] For a perfect network without entrapped entanglements, the elastic resisting pressure of the network can be written as follows:[7]

$$\Pi_{el} = A\frac{k_B T \phi R^2}{N R_0^{\,2}} \tag{3}$$

In eq 3 R and R_0 are the mean-square end-to-end distances of the polymer chain between cross-links within the swollen hydrogel and in its reference state, respectively, k_B is the Boltzmann constant, T is temperature, and N is the number of statistical units between cross-links. The constant A accounts for the assumed type of fluctuations of the interchain junctions. The polymer chain is considered to be a coiled wormlike chain, and thus R_0 is defined as

$$R_0^{\,2} = 2qNa \tag{4}$$

in which q is the persistence length of the polymer and a is the monomer length. The intrinsic persistence length of the polymer chain is given by

$$q_p \sim Ca \tag{5}$$

wherein C is the polymer characteristic ratio. Combining all these definitions, the elastic pressure term becomes

$$\Pi_{el} \sim \frac{\phi R^2}{CN^2 a^2} \tag{6}$$

It remains to define the osmotic expansion energy. In the limit of low salt concentration, the osmotic expansion pressure is given by[11]

$$\Pi_{os} \sim \phi\alpha \tag{7}$$

in which α is the degree of ionization of the polymer chain. Finally, once swollen to equilibrium, the polymer concentration in the hydrogel can be written as

$$\phi \sim NR^{-3} \tag{8}$$

Equating eqs 6 and 7 and using eq 8 yields

$$R \sim (\phi a)^{-1/2}(\alpha C)^{-1/4} \tag{9}$$

To complete the derivation, R is considered the correlation length of the hydrogel and $\bar{r}$ is defined as $R/2$. Therefore, the final relationship between the solute diffusivity in the hydrogel and its diffusivity in the aqueous medium becomes

$$\frac{D_g}{D_0} = \exp\left[-\pi\left(\frac{r_s + r_f}{k_s(\phi a)^{-1/2}(\alpha C)^{-1/4} + 2r_f}\right)^2\right] \tag{10}$$

in which k_s is a scaling constant, specific to a given polymer−water combination.

High Salt Concentration ($\phi \ll \phi_{salt}$). In the presence of a large volume fraction of salt in the gel, the polyelectrolyte behaves as if it were neutral.[9] Under these conditions, for a polymer in a good solvent above the critical overlap concentration, R has been given by[12]

$$R \sim a\phi^{-0.75}C^{-0.25}(1 - 2\chi)^{-0.25} \tag{11}$$

To complete the derivation, $\bar{r}$ is again defined as $R/2$. The final relationship between the solute diffusivity in the hydrogel and its diffusivity in the aqueous medium then becomes

$$\frac{D_g}{D_0} = \exp\left[-\pi\left(\frac{r_s + r_f}{k'_s a\phi^{-0.75}C^{-0.25}(1 - 2\chi)^{-0.25} + 2r_f}\right)^2\right] \tag{12}$$

in which k'_s is the high salt concentration scaling constant, specific to a given polymer−solvent combination, and χ is the Flory−Huggins interaction parameter for the neutral alginate in water condition.

Equations 10 and 12 predict that solute transport within a hydrogel is influenced by the size of the solute molecule and polymer properties such as backbone flexibility, concentration within the hydrogel, and chain radius. The effects of polymer volume fraction and solute radius have been clearly demonstrated in a previous study.[4] However, as far as could be determined, there is little information on the effects of the flexibility of the polymer backbone or on the concentration of salt in the gel. The model equations also predict that the dependence of the solute diffusivity on polymer volume fraction will change depending on the ionic strength of the external medium.

Materials and Methods

Sodium alginate (Protanal LF 10/60) was kindly donated by Pronova, Drammen, Norway. Other reagents used were

sodium chloride, calcium chloride, bovine serum albumin, acetic acid, sodium acetate, and poly(ethylene glycol) 8000, all from Aldrich Chemicals, USA.

Hydrogel Preparation. Protein-loaded, isotropic calcium alginate gels were prepared by adapting the method of Skjåk-Braek et al.[13] Varying amounts of sodium alginate were dissolved in a 0.2 M NaCl solution. The alginate solution was poured into dialysis tubing (Spectrapor 11.5 mm diameter, molecular weight cutoff 3500) which was clipped at both ends. The filled dialysis tubing was immersed in a 0.2 M NaCl, 0.1 M $CaCl_2$ solution which contained poly(ethylene glycol) 8000. The poly(ethylene glycol) was used to balance the osmotic pressure on both sides of the dialysis tubing. The alginate was allowed to gel for 24 h at room temperature. The 11 mm diameter hydrogel cylinder formed was cooled to 5 °C and then cut into approximately 3 mm disk segments using a razor blade. Four disks of approximately the same dimensions were incubated with stirring for 24 h in a 5 w/v % bovine serum albumin (BSA) in 0.25 w/v % (low ionic strength) or 20 w/v % $CaCl_2$ solution (high ionic strength condition). For experiments in which the pH of the release medium was 4.8, an acetic acid/sodium acetate buffer of low ionic strength (1.6×10^{-3} M) to which calcium chloride was added to bring the ionic strength to 0.25 w/v % $CaCl_2$ was used as the incubating medium. The disks were then removed, wiped with a Kimwipe, and weighed, and their dimensions were measured using calibrated calipers both before and after solute release. The amount of solute in the disks was confirmed via a mass balance of the solute depleted disks after the release study.

Diffusion Studies. The protein diffusion studies for the high ionic strength condition and the effect of pH at low ionic strength were performed as described elsewhere.[1] Briefly, the protein loaded alginate disks were placed in 15 mL of an aqueous solution containing 0.02 w/v % sodium azide as a bacteriostatic agent and either 0.25 w/v % (low salt concentration) or 20 w/v % (high salt concentration) $CaCl_2 \cdot 2H_2O$ in a scintillation vial. The vials were placed on a rotator maintained at 25 °C. At frequent sampling times the release solution was removed and replaced with fresh solution. The BSA concentration of the release solution was measured using UV absorption at 280 nm. Protein diffusion studies were also done in a pH 4.8 acetate buffer containing 0.25 w/v % $CaCl_2 \cdot 2H_2O$.

The average effective diffusivity of the protein within the gel was determined using eq 13,[14] which describes solute diffusion, in both the radial and longitudinal directions, from a cylinder:

$$Q = 1 - \frac{8}{l^2 r_d^{\,2}} \left(\sum_{i=1}^{\infty} \exp(-D_g \alpha_i^{\,2} t) \alpha_i^{\,-2}\right) \left(\sum_{j=0}^{\infty} \exp(-D_g \beta_j^{\,2} t) \beta_j^{\,-2}\right) \tag{13}$$

In eq 13 l is the disk half-thickness, r_d is the disk radius, Q is the cumulative mass fraction released, t is time, D_g is the average effective intra-gel diffusivity, α_i are the roots of $J_0(r_d\alpha_i) = 0$, J_0 is the zero-order Bessel function, and $\beta_j = (2j + 1)\pi/2l$. D_g was determined from a least-squares fit of eq 13 to the experimental release data. Thirty terms in each summation series were used. The variance for each release study was estimated by pooling the variance at each time point in the release data. The significance of the curve fitting procedure was determined using an F-ratio test. The reduction in BSA diffusivity within the gel is expressed as the ratio of its diffusivity in the gel to its diffusivity in water, D_g/D_0.

Calculation of Volume Fraction Alginate. The volume fraction of alginate in the hydrogels was determined from a mass balance. The low salt concentration release BSA-depleted hydrogels were placed in vacuo in the presence of a desiccant at 40 °C for at least 24 h and the dry weights measured. This dry weight was multiplied by the partial specific volume of calcium alginate (0.60 cm^3/g [15]) to obtain the initial volume of calcium alginate in the hydrogel. Dividing the volume of alginate by the volume of the initial protein-loaded hydrogel disk yielded the volume fraction of alginate in the disk. For the high salt concentration release studies, the BSA-depleted gels were incubated in a series of volumes of deionized water to remove calcium chloride before being dried in vacuo.

Determination of BSA Hydrodynamic Radius. The model requires that the hydrodynamic radius of the solute be known. The diffusivity, and thus the hydrodynamic radius, of BSA is known to vary with pH and ionic strength.[16,17] A Precision Detectors dynamic light scattering detector PDLS 2020 was therefore used to determine the hydrodynamic radius of BSA in each of the solvent conditions examined. The 5 mg/mL solutions of BSA were prepared in each of the solvents, and the monomer fraction was separated using a BIOSEP 3000S SEC column running at 0.8 mL/min and 35 °C. The hydrodynamic radius was determined via the light scattering software provided which measures the diffusivity of the protein and calculates the hydrodynamic radius using the Stokes–Einstein equation.

Results and Discussion

The obstruction-scaling models were fit to the experimental data using $r_f = 8$ Å. The r_f value was calculated assuming the polymer chain to possess a tightly bound water layer, one water molecule thick. The pH of the release media was 4.8 and 6.0. The degree of ionization of the alginate in either solution approaches one ($\alpha = 0.96$ at pH 6 and $\alpha = 0.92$ at pH 4.8 as measured by titration; these results are consistent with literature data for sodium alginate in solution[18]). The monomer length was assumed to be constant for both polymers and equal to 5.14 Å.[19] To ensure that the time allowed for BSA ingress into the gels was sufficient to produce a homogeneous BSA concentration within the gels, the case of diffusion only through the faces of the disks was considered. For this situation, the concentration profile within the disk viewed as a slab is given by[20]

$$\frac{C - C_0}{C_1 - C_0} = 1 - \frac{4}{\pi^2} \sum_{n=0}^{\infty} \frac{(-1)^n}{2n+1} \exp\left[-\frac{D_g \pi^2 t (2n+1)^2}{4l^2}\right] \cos\left(\frac{(2n+1)\pi x}{2l}\right) \tag{14}$$

in which C is the concentration of BSA within the slab at time t and position x, C_0 is the concentration of BSA initially in the slab, C_1 is the concentration at the surface of the slab, and l is the slab half-thickness (0.15 cm). C_0 is zero, and C_1 is assumed to be constant. For the condition where $C/C_1 = 0.95$ at x approaches zero (i.e., the concentration everywhere in the gel is within 95% of that at the surface), the dimensionless parameter

$$\frac{D_g \pi^2 t}{4l^2} = 2.0 \tag{15}$$

Under these conditions ($t = 24$ h, $l = 0.15$ cm) the diffusivity in the gel must be 7.6×10^{-4} cm^2/h. For the highest alginate concentration used in the incubation method (0.05), the diffusivity of BSA in the gel was 8.6×10^{-4} cm^2/h. Thus, even neglecting radial diffusion, the concentration of BSA within the gel before the release studies can be considered homogeneous.

The hydrodynamic radii of BSA determined using dynamic light scattering are listed in Table 1. Also given in Table 1 is the hydrodynamic radius of BSA in pH 6 and 0.1 M NaCl solution. These latter conditions were used to verify the values obtained in the calcium chloride solutions. Under these conditions, the hydro-

Table 1. BSA Hydrodynamic Radii and Diffusivity at 25 °C Determined Using Light Scattering

solvent	r_s (Å)	±SD	D^a (cm²/s) × 10^7
0.1 M pH 6 NaCl	36.5	0.4	6.77
0.25 w/v % pH 6 $CaCl_2$	39.5	1.3	6.24
0.25 w/v % pH 4.8 $CaCl_2$	36.4	1.2	6.77

[a] At 25 °C.

Table 2. Physical Properties of the Sodium Alginates Used[1]

alginate	mol % guluronic acid	$\bar{M}_w$ (g/mol)	C
LF 10/60	70.0	320 000	26.0
LF 10/60 LS	40.0	253 000	21.2

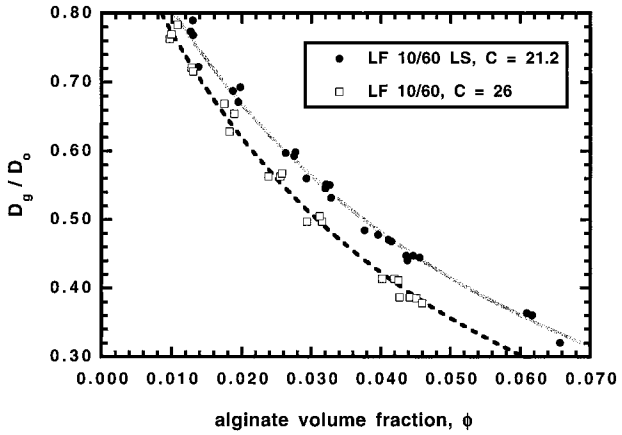

Figure 1. Verification of obstruction-scaling model for conditions of low salt concentration in the release media (eq 10). The lines represent the fit of the obstruction-scaling model to the data. The results demonstrate the effect of polymer backbone flexibility on intra-gel solute diffusivity.

dynamic radius of BSA has been reported to be 36.3 Å,[21] which is in good agreement with the value of 36.5 ± 0.4 Å obtained in this study. The hydrodynamic radius of BSA in calcium chloride solutions at pH 6 is somewhat larger (39.5 Å) while at the isoelectric point in calcium chloride the hydrodynamic radius is similar to that in pH 6 sodium chloride solution. The larger radius at pH 6 in calcium chloride can be attributed to the binding of calcium ions to the surface of the BSA molecule. At the isoelectric point, there are fewer negative charges on the BSA surface than at pH 6 conditions, and so few ions would bind to the surface and thus it presents a smaller frictional cross-sectional area. These radii values were used in the regression procedure to determine the applicability of the models.

Low Ionic Strength Release Medium. The obstruction-scaling model was tested against previously reported experimental data of bovine serum albumin diffusion within calcium alginate hydrogels,[1] corrected here for the measured hydrodynamic radius of BSA at these conditions. The properties of the two forms of alginate, determined in the previous report,[1] are given in Table 2. The experimental data of the diffusion of bovine serum albumin (BSA) in calcium alginate gels are displayed in Figure 1.

The model accurately reproduces the effect of polymer volume fraction on solute diffusivity, a result that has been noted in a previous publication.[4] Listed in Table 3 are the regression values for k_s. The theory upon which the model is built states that k_s should be a constant for a given polymer−solvent condition. The scaling constant values obtained are virtually statistically

Table 3. Regression Results for BSA Diffusion in a Low Ionic Strength Medium

alginate	k_s (Å$^{1.5}$)	±SE[a]	r^2 [b]	F_{fit}	F_{table}	SSR[c]
LF 10/60	76.5	0.5	0.988	1.43	2.39	0.004
LF 10/60 LS	79.9	0.4	0.978	1.67	2.35	0.005

[a] Standard error (95% confidence interval). [b] Correlation coefficient. [c] Sum of squares of the residuals.

equivalent, indicating that the model is consistent with the expected physical situation.

The obstruction-scaling model predicts that the intra-gel diffusivity should decrease as the flexibility of the polymer backbone decreases. This prediction is substantiated by the experimental data shown; the more flexible form of the alginate (LF 10/60-LS, $C = 21.2$) provided less restriction to the intra-gel transport of the protein molecule. The lines in Figure 1 represent the regression results of fitting eq 10 to the data. The regression was done using KaleidaGraph software which employs the Levenberg−Marquardt nonlinear regression algorithm. The equation provides a very good fit, as is indicated by the F-ratios of the regressions being much less than tabulated F-ratios at the 95% confidence level and correlation coefficient listed in Table 3. It should be noted that in these experiments the volume fraction of calcium chloride in the hydrogels was, on average, 0.003, and so the condition of low salt concentration used in the model derivation is valid.

Using the obstruction-scaling model, the experimental results for the effect of polymer backbone flexibility can be attributed to variations in the nature of the hydrogel. The contribution of polymer flexibility to polymer structure can be traced to eq 6, which describes the resisting elastic deformation pressure. The equation indicates that the more flexible the polymer, and thus the smaller the value of C, the greater the elastic deformation of the gel under an applied stress. What this means in terms of the obstruction model is that the distance between cross-links will be greater, and thus the solute molecule is more likely to find an opening between the polymer chains that is large enough to allow its passage. Therefore, solute diffusivity within a hydrogel made of a more flexible polymer will, in general, be greater than that within a hydrogel of a less flexible polymer.

High Ionic Strength Release Medium. The effect of polymer volume fraction of the hydrogel on BSA diffusivity in a high ionic strength release medium is shown in Figure 3. Plotted in the figure as lines are fits of both eq 10 and eq 12 to the data. In fitting eq 12, the fitted parameter was $k_s'(1 - 2\chi)^{-0.25}$. The results are given in Table 4. The data in Table 4 and Figure 2 clearly show that a change in volume fraction dependence of the solute diffusivity occurs when the gel is immersed in a high ionic strength solution. Further, eq 12 provides a very good fit to the data, producing a lower sum of squares of the residuals, indicating the utility of the obstruction-scaling model approach.

In a previous paper a model for predicting solute diffusion in neutral hydrogels was described.[3] In the analysis of the data it was determined that, for the various polymers examined, the scaling constant was approximately unity. Using this value for the scaling constant and the fitted parameter determined for alginate in high ionic strength solutions, a χ parameter value of 0.495 can be calculated, which is very close to

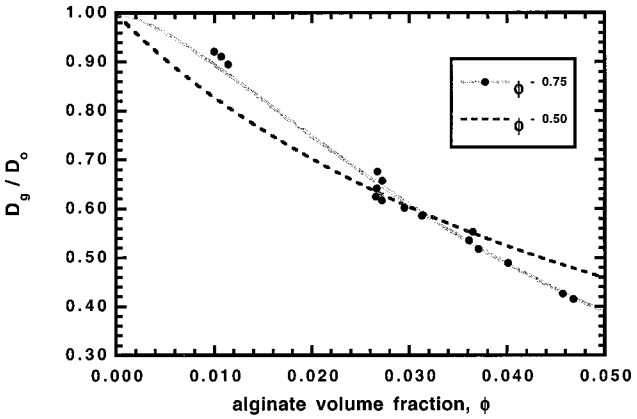

Figure 2. Application of high salt concentration obstruction-scaling model (eq 12). For comparison, the data were also fit using the model for a low ionic strength release medium (eq 10). The alginate used is LF 10/60.

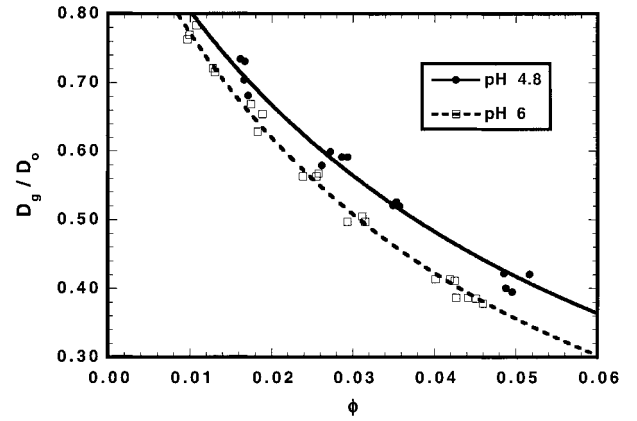

Figure 3. Significance of the charge on the BSA molecule on its intra-gel diffusivity. The hydrodynamic radius of BSA at pH 4.8 is 36.4 Å while that at pH 6 is 39.4 Å (Table 1). The alginate used in both cases is LF 10/60.

Table 4. Regression Results for BSA Diffusion in a High Ionic Strength Medium

model	$k_s'(1-2\chi)^{-0.25}$	±SE[a]	r^2 [b]	F_{fit}	F_{table}	SSR[c]
eq 10	86.9	2.3	0.89	25.8	3.2	0.05
eq 12	3.30	0.04	0.98	2.48	3.2	0.005

[a] Standard error (95% confidence interval). [b] Correlation coefficient. [c] Sum of squares of the residuals.

that of a similar, but uncharged, polysaccharide, dextran, in water (0.473).[22]

Influence of Solute−Polymer Interactions. To verify the assumption that no interactions exist between solute and polymer, the degree of diffusion restriction of BSA within alginate gels loaded and released in a pH 4.8 (the isoelectric point of BSA) medium was compared to that obtained under pH 6 conditions. The results are displayed in Figure 3. At first glance, it appears that solution pH has an effect, with the lower pH solution producing less restriction to solute movement. However, the hydrodynamic radius of BSA at the isoelectric point is smaller than at pH 6, a result implied in other studies examining the diffusivity of BSA under varying pH and ionic strength conditions.[16,23,24] Furthermore, as noted at the beginning of this section, the degree of ionization of the alginate at each pH is very close, and thus α is not expected to play a significant role. When the obstruction-scaling model is applied, using the hydrodynamic radii obtained using light scattering, to the data, the scaling constants are statistically equivalent (Table 5). It can then be concluded that there are no electrostatic interaction effects influencing the movement of BSA through the hydrogel.

Table 5. Regression Results for BSA Diffusion in a Low Ionic Strength Medium under Varying pH Conditions

solution pH	k_s (Å$^{1.5}$)	±SE[a]	r^2 [b]	F_{fit}	F_{table}	SSR[c]
4.8	78.0	0.7	0.98	2.85	3.23	0.004
6.0	76.5	0.5	0.99	1.43	2.39	0.004

[a] Standard error (95% confidence interval). [b] Correlation coefficient. [c] Sum of squares of the residuals.

Conclusions

The obstruction-scaling model for solute diffusion in hydrogels has been further developed by incorporating a scaling relationship for the average distance between cross-linked polymer chains in polyelectrolyte hydrogels. The new model accurately accounts for the observation that polymer backbone flexibility has a significant influence on intra-gel solute diffusivity, with solute diffusivity increasing as the flexibility of the backbone chain increases. The model is also applicable to conditions of variable ionic strength, as demonstrated by the ability of the model to reflect the change in polymer volume fraction dependence of the solute diffusivity.

The application of the obstruction-scaling model to homogeneous hydrogels indicated that, for each of the polymers examined, $k_s \approx 1.0$.[3] Thus, for homogeneous hydrogels, an a priori estimate of intra-gel solute diffusivity is possible. The k_s results for alginate imply that such a straightforward application of the obstruction-scaling model for polyelectrolyte gels may not be possible. Further work with other polyelectrolyte hydrogels that have been well characterized with respect to ionization degree, polymer volume fraction, and characteristic ratio will be necessary in order to compare and evaluate k_s values. There are very few examples in the literature of investigations into the effect of polymer flexibility on solute permeation in polyelectrolyte gels.

It should be noted that the characteristic ratio of the cross-linked alginate was assumed to be equivalent to its pre-cross-linking value. This may not be a good assumption as the cross-linking reaction produces long sections of the polymer backbone which have a large degree of order and so will possess a greater rigidity. Thus, the characteristic ratio will be greater in the gel form than in solution form. This issue and its implications on the model will need to be addressed in the future.

Polyelectrolyte gels are currently being extensively investigated as a means of controlling drug delivery in response to external conditions such as pH and ionic strength.[25] Most of the studies have focused on demonstrating control of drug release capabilities of the systems, without examining in detail how to predict drug release rates. The scaling model proposed in this work should provide a framework from which such models could be developed.

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References and Notes

(1) Amsden, B.; Turner, N. *Biotechnol. Bioeng.* **1999**, *65*, 605−610.
(2) Amsden, B. *Macromolecules* **1998**, *31*, 8382−8395.
(3) Amsden, B. *Macromolecules* **1999**, *32*, 874−879.
(4) Amsden, B. *Polym. Gels Networks* **1998**, *6*, 13−43.
(5) Katchalsky, A.; Michaeli, I. *J. Polym. Sci.* **1955**, *15*, 69−86.
(6) Katchalsky, A.; Lifson, S.; Eisenberg, H. *J. Polym. Sci.* **1951**, *7*, 571−574.
(7) Flory, P. J. *Principles of Polymer Chemistry*; Cornell University Press: Ithaca, NY, 1953.
(8) Nisato, G.; Schosseler, F.; Candau, S. J. *Polym. Gels Networks* **1996**, *4*, 481−498.
(9) Skouri, R.; Schosseler, F.; Munch, J.; Candau, S. *Macromolecules* **1995**, *28*, 197−210.
(10) Barenburg, T. M. A. O. M.; Smit, J. A. M.; Bedeaux, D. *Polym. Gels Networks* **1995**, *3*, 331−373.
(11) Joanny, J.; Pincus, P. *Polymer* **1980**, *21*, 274−278.
(12) Schaefer, D. W. *Polymer* **1984**, *25*, 387−394.
(13) Skjak-Braek, G.; Grasdalen, H.; Smidsrod, O. *Carbohydr. Polym.* **1989**, *10*, 31−54.
(14) Fu, J. C.; Hagemeir, C.; Moyer, D. L. *J. Biomed. Mater. Res.* **1976**, *10*, 743−758.
(15) Cook, W. H.; Smith, D. B. *Can. J. Biochem. Physiol.* **1954**, *32*, 227−239.
(16) Raj, T.; Flygare, W. H. *Biochemistry* **1974**, *13*, 3336−3340.
(17) Anderson, J. L.; Rauh, F.; Morales, A. *J. Phys. Chem.* **1978**, *82*, 608−616.
(18) Schiewer, S.; Volesky, B. *Environ. Sci. Technol.* **1997**, *31*, 1863−1871.
(19) Smidsrod, O. *Carbohydr. Res.* **1970**, *13*, 359−372.
(20) Crank, J. *The Mathematics of Diffusion*; Oxford University Press: New York, 1975.
(21) Tyn, M. T.; Gusek, T. W. *Biotechnol. Bioeng.* **1990**, *35*, 327−338.
(22) Gekko, K. Solution properties of dextran and its ionic derivatives. In *Solution Properties of Polysaccharides*; Brant, D. A., Ed.; American Chemical Society: Washington, DC, 1981.
(23) Minton, A. P.; Edelhoch, H. *Biopolymers* **1982**, *21*, 451−458.
(24) Phillies, G. D. J.; Benedek, G. B.; Mazer, N. A. *J. Chem. Phys.* **1976**, *65*, 1883−1892.
(25) Hoffman, A. S. Intelligent Polymers. In *Controlled Drug Delivery. Challenges and Strategies;* Park, K., Ed.; American Chemical Society: Washington, DC, 1997.

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