Influence of Polymer Ionization Degree on Solute Diffusion in Polyelectrolyte Gels

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ABSTRACT: The ability of an obstruction-scaling model of solute diffusion to account for solute diffusivity in polyelectrolyte gels composed of semiflexible chains is presented. The diffusion of FITC−dextran in poly(acrylic acid) gels was measured at different pH conditions to determine the effect of the ionization degree of the poly(acrylic acid) on the diffusivity of the FITC−dextran. The obstruction-scaling model, as well as a hydrodynamic-based model and a jumping frequency model, was applied to the data. It was determined through regression analysis that the obstruction-scaling approach provided a better fit and could effectively account for the observed effect of the variation in the ionization degree on solute diffusivity.

Introduction

A number of models have been developed to explain the observed behavior of solute movement within gels. These models have taken as a basis enhanced tortuosity or obstruction effects,[1,2] enhanced hydrodynamic drag on the solute molecule,[3−5] a reduction in solvent free volume,[6,7] and a combination of both obstruction and hydrodynamic effects.[8] A recent review of these models has demonstrated that each of these models has limitations.[9]

Recently, a new model has been introduced.[10−12] The model is based on the idea that physical obstruction is the dominant factor governing solute movement through both gels and polymer solutions. Solute mobility within the gel or solution is dependent on the solute encountering an opening between the polymer chains which is larger than its own hydrodynamic radius. Any interaction between solute and the polymer chain is neglected. The average diffusivity of the solute is then determined by the number of openings within the gel greater than this critical limit. The distribution of opening radii within the gel is expressed using the equation derived by Ogston for the distribution of spherical spaces within a random network of infinitely thin straight fibers.[13] This distribution is converted to fibers of finite thickness by incorporating the radius of the polymer chain. Combining these ideas yields the following 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 intragel 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.

The average opening between polymer chains is then defined in terms of scaling relationships. For nonionic polymers, the scaling relationship was determined by considering the gel to exist as a polymer solution at the critical overlap concentration.[10] For this situation, solute diffusivity within the gel is given as

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

in which k_s' is a scaling constant, specific to a given polymer−solvent combination, a is the length of a monomer, ϕ is the volume fraction of polymer in the gel, C is the characteristic ratio of the polymer, and χ is the Flory−Huggins interaction parameter.

For polyelectrolyte gels, a somewhat different approach was taken.[12] The forces governing the swelling of an ionic gel (counterion osmotic activity) and resisting pressure (elastic forces) were equated as was outlined in Skouri et al.[14] This approach yielded the following equation for the situation of low external solution salt concentration,

$$\frac{D_g}{D_0} = \exp\left[-\pi\left(\frac{r_s + r_f}{k_s(\phi a)^{-1/2}(\alpha C)^{-1/4} + 2r_f}\right)^2\right] \tag{3}$$

in which α is the degree of ionization of the polyelectrolyte and k_s is a scaling constant specific to a given polymer−water combination. In high external salt concentration conditions, the electrostatic forces of repulsion along the polyelectrolyte backbone are completely screened, and the nonionic gel equation (eq 2) holds.

The ability of eqs 2 and 3 to account for the influence of polymer volume fraction, solute radius, polymer chain radius, external solution salt concentration, and polymer backbone flexibility has been demonstrated.[9−11,15] However, the model contains a term describing the influence of the degree of ionization that has yet to be verified through application to experimental data. It is the objective of this paper to first demonstrate that the swelling force balance approach and the assumption of a polymer solution at the critical overlap concentration approach for expressing the average opening between polymer chains for polyelectrolyte gels are essentially equivalent and, second, to show that the ionization degree, α, plays an important role.

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Methods

Materials. Acrylic acid, ethylene glycol dimethacrylate, azobis(cylcohexanecarbonitrile), sodium chloride, sodium acetate, boric acid, acetic acid, and FITC−dextran (18 000 Da) were purchased from Aldrich and used as received. De-hibit 200 was obtained from Polysciences Inc.

Hydrogel Preparation. Poly(acrylic acid) gels cross-linked with ethylene glycol dimethacrylate (EGDMA) were prepared by free-radical polymerization in methanol with 20 mol % acrylic acid. The MEHQ inhibitor in the acrylic acid (AA) monomer was removed by passing through a column of De-hibit 200. A molar ratio of 0.8 mol of EGDMA per mole of AA was used to prepare the gels. EGDMA, AA, and 0.1 wt % azobis(cyclohexanecarbonitrile) were combined in a 25 mL flame-dried glass ampule. The solution was deaerated with nitrogen gas. The ampules were then flame-sealed and reacted at 80 °C for 24 h. After reaction, the gels were soaked twice for 4 h each in methanol and then four times in distilled water for 4 h to remove unreacted starting material.

The cylindrical gels obtained were loaded with solute by soaking in a specific buffer containing 0.8 mg/mL FITC−dextran 18 000 for 1 week at room temperature on a shaker bath at 250 rpm. The following buffers were used: for pH 3.3 and 4, an acetic acid, sodium acetate buffer system; for pH 6, a sodium biphosphate, sodium phosphate buffer; and for pH 8, a boric acid, sodium carbonate buffer. The ionic strength of each buffer was equalized to 0.10 M using sodium chloride.

Diffusion Studies. The gel cylinders were removed from the solute baths, wiped dry, and cut into 3 mm thick disks using a razor blade and a cutting guide. The weight and dimensions of each disk were measured and recorded, and the gels then were placed into a 20 mL release medium consisting of the same buffer system in which they were loaded with solute. The beakers were placed on a shaker at 250 rpm and room temperature (23 °C). At frequent sampling times, the release medium was removed and replaced with fresh release medium. The FITC−dextran content of the release medium was determined using a fluorescence spectrometer (Photon Technologies International QuantaMaster model 2) at 495 nm. Each experiment was done in triplicate.

The average diffusivity of the FITC−dextran within the gel was determined by using

$$Q = 1 - \frac{8}{l^2 r_d^{\,2}}\left(\sum_{i=1}^{\infty}\exp(-D_g\alpha_i^{\,2}t)\alpha_i^{\,-2}\right)\left(\sum_{j=0}^{\infty}\exp(-D_g\beta_j^{\,2}t)\beta_j^{\,-2}\right) \quad (4)$$

which describes solute diffusion, in both the radial and longitudinal directions, from a cylinder.[16] In eq 4, l is the disk half-thickness, r_d is the disk radius, Q is the cumulative mass fraction of solute released, t is time, D_g is the average effective intragel 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 4 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. Use of eq 4 assumes that an infinite sink was maintained at all times. As the concentrations of FITC−dextran achieved in the gel were very low, and the solubility of FITC−dextran in water is quite high, this assumption was very reasonable. Boundary layer resistance to diffusion was considered negligible due to the degree of agitation used.

Degree of Ionization, α. The extent to which the backbone monomers on the poly(acrylic acid) gel were ionized was calculated using[17]

$$\mathrm{pH} = 4.25 - 2\log\left(\frac{\alpha}{1-\alpha}\right) \quad (5)$$

Results and Discussion

Before considering the degree to which the obstruction-scaling model agrees with the experimental data, the two approaches to obtaining the scaling relationship will be compared. In the Skouri et al. approach used in the previous paper, a scaling relationship was derived by considering the two main forces at work: the osmotic swelling force and the resisting elastic force of the cross-linked network. Using this analysis, the average distance between polyelectrolyte chains in the network at the equilibrium swelling condition, ξ, is expressed as[14]

$$\xi = k_s(\phi a)^{-1/2}\alpha^{-1/4} \quad (6)$$

This form of the scaling expression assumes that the electrostatic persistence length is much greater than the intrinsic persistence length of the polymer chain.

Now consider the situation in which the gel behaves as a semidilute solution at the overlap concentration, again assuming that the electrostatic persistence length is much greater than the intrinsic persistence length. Each polymer molecule is represented as a chain of electrostatic blobs, and the statistics of the chain inside each blob is governed by the interaction between the uncharged polymer and the solvent. The conformation of the chain is considered to be a rodlike assembly of electrostatic blobs. For this condition, Dobrynin et al. have written the scaling expression originally derived by De Gennes as[18]

$$\xi = k_s(\phi a)^{-1/2}A^{2/7} \quad (7)$$

in which A is the number of monomers between charges on the polyelectrolyte backbone. By definition,

$$A = \alpha^{-1} \quad (8)$$

and so eq 7 becomes

$$\xi = k_s(\phi a)^{-1/2}\alpha^{-2/7} \quad (9)$$

This expression was derived by relating the electrostatic interaction between charges in the electrostatic blobs to the thermal energy and the polymer/solvent interfacial energy.

The two different approaches yield very similar results. There is only a minor difference in the influence of the degree of ionization on the average distance between polymer chains (−2/7 power vs −2/8 power). It should be noted that, in both approaches, the polyelectrolyte is considered to be a semiflexible chain in an essentially salt-free solution. The use of the force balance approach allows for the ready inclusion of the effect of the intrinsic stiffness of the polymer chain. This is accomplished by considering the reference state for the swelling gel to be the Θ condition.[12] This analysis demonstrates that polymer gels can effectively be treated as polymer solutions for scaling purposes.

Equations 6 and 9 describe the influence of the degree of ionization. As the ionization degree of the polymer increases, the polymer chain becomes more extended and stiffer. At the same time, the osmotic pressure within the gel increases due to the presence of a larger number of counterions. The increased osmotic pressure increases the volume of the gel, thereby reducing ϕ. Stiffer chains produce more resistance to solute diffusion than flexible chains by reducing the average opening size between polymer chains,[15] whereas it is well established that greater solute diffusivity results from

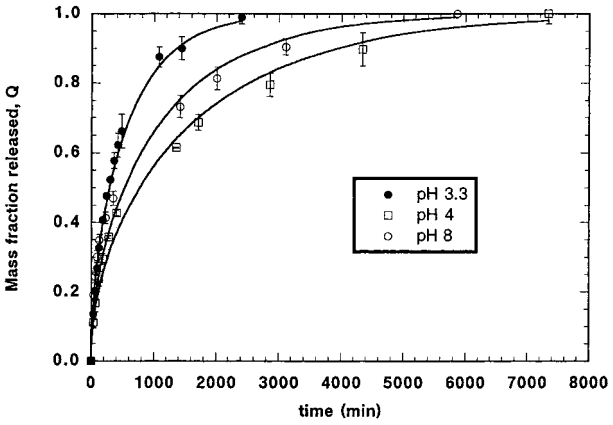

Figure 1. Representative release results showing fits of eq 4 used to determine D_g. The error bars represent standard deviations at each time point.

Table 1. Results of Diffusion Experiments

pH	ϕ	α	D_g/D_0	±	F_{fit}[a]
3.3	0.43	0.273	0.183	0.064	1.09
3.3	0.451	0.273	0.212	0.087	2.00
3.3	0.453	0.273	0.170	0.059	0.36
4	0.19	0.429	0.334	0.059	2.17
4	0.19	0.429	0.301	0.059	2.13
6	0.123	0.882	0.347	0.121	1.71
6	0.122	0.882	0.355	0.034	0.11
8	0.082	0.987	0.513	0.090	2.02
8	0.093	0.987	0.459	0.064	2.16
8	0.084	0.987	0.531	0.086	1.93

[a] F ratio calculated from regression sum of squares of the residuals. F at the 95% confidence interval is 2.39.

a decrease in polymer concentration within the gel. It thus appears that the degree of ionization of the polymer plays a dual and opposing role. To determine whether this influence is actually manifested, we examined the diffusivity of a neutral solute, FITC−dextran, moving through poly(acrylic acid) gels. The gels were prepared such that they all had the same original polymer volume fraction and were then immersed in different pH buffers (3.3, 4, 6, 8) in the presence of the solute and allowed to swell to equilibrium. After swelling equilibrium was achieved, the gels were removed from the solute containing buffers and released into an aqueous buffer of the same pH as that in which they were swollen.

A typical diffusion experiment is illustrated in Figure 1. In the figure, the curves represent fits of eq 4 to the data. The diffusion expression can be seen to provide a good fit to the data. Note that no general trend is immediately observable from this figure, because each gel had different dimensions. The regression results obtained experimentally are given in Table 1, along with the confidence interval for the fit at the 95% confidence interval, ±, the sum of squares of the residuals, SSR, the F value, the volume fraction of the gel, and the degree of ionization of the polyelectrolyte under the pH condition of the experiment. Table 1 illustrates that, as the degree of ionization of the gel increases, the volume fraction of the gel at swelling equilibrium decreases and the diffusivity of the FITC−dextran within the gel increases.

The obstruction scaling approach as described by eq 3 was then fit to the data to determine the effectiveness of the model in accounting for the effect of the degree of ionization. In doing this, the radius of the polymer chain was calculated by assuming that a monomer can

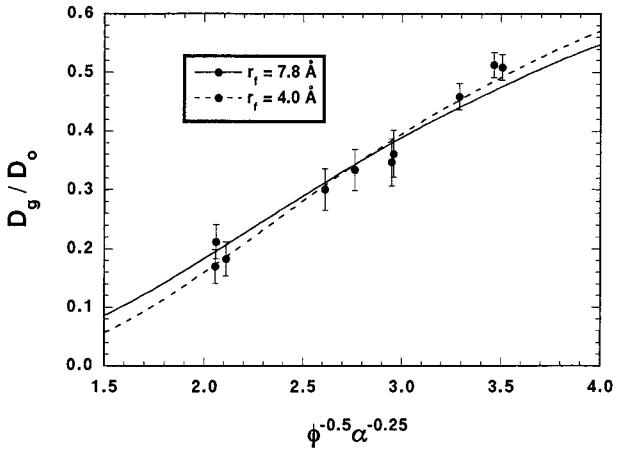

Figure 2. Fit of obstruction scaling model (eq 3) to the diffusivity data showing effect of estimate of r_f on the quality of the fit. The error bars represent the standard deviations (n = 3).

Table 2. Regression Results of Fits of Eq 3 to Data in Table 1[a]

eq for ξ	r_f (Å)	k_s (Å$^{1.5}$)	±	SSR	R^2
6	7.8	35.56	0.57	0.006	0.955
6	4.0	36.39	0.45	0.005	0.968
7	7.8	35.70	0.39	0.008	0.942

[a] ± = the 95% confidence interval for the fitted parameter, k_s. R^2 = the correlation coefficient. SSR = the sum of squares of the residuals.

be considered as a cylinder. In this way, r_f is calculated from

$$r_f = \left(\frac{M_m v}{a\pi N_A}\right)^{0.5} \tag{10}$$

in which M_m is the molecular weight of the monomer, v is the specific volume of the polymer, and N_A is Avogadro's number. b was taken as 1.54 Å, v as 0.648 cm^3/g, and C as 9.[19] To account for the hydration sheath surrounding the polymer chain, the diameter of one water molecule (3.8 Å) was added to the value calculated using eq 10 (4 Å). Thus, r_f was calculated to be 7.8 Å. The solute hydrodynamic radius was taken to be 27.8 Å and its diffusivity in water at 30 °C as 9.96×10^{-7} cm^2/s.[20] The diffusivity at room temperature was calculated from the value at 30 °C and the Stokes−Einstein expression for diffusivity.

To determine whether the value of the chain radius has a significant effect on the degree of fit obtained, both 4 and 7.8 Å were used in fitting eq 3 to the data. The fits can be seen in Figure 2, and the regression results are presented in Table 2. For clarity, the data are plotted as D_g/D_0 vs $\phi^{-0.5}\alpha^{-0.25}$. Furthermore, to determine whether the approach used to derive the scaling relationship for ξ has a significant effect on the fit obtained, the data were also plotted as D_g/D_0 vs $\phi^{-0.5}\alpha^{-2/7}$ in Figure 3. The regression results for this fit are also given in Table 2.

The model provided good agreement to the experimental data, and the value chosen for r_f has little effect on the degree of fit obtained. The sum of squares of the residuals in each case is virtually the same: 0.005 for r_f = 4 Å and 0.006 for r_f = 7.8 Å. The model, then, is not very sensitive to errors in the estimate of the chain radius. Similarly, each scaling expression for ξ gave similar degrees of fit, with a slightly greater sum of

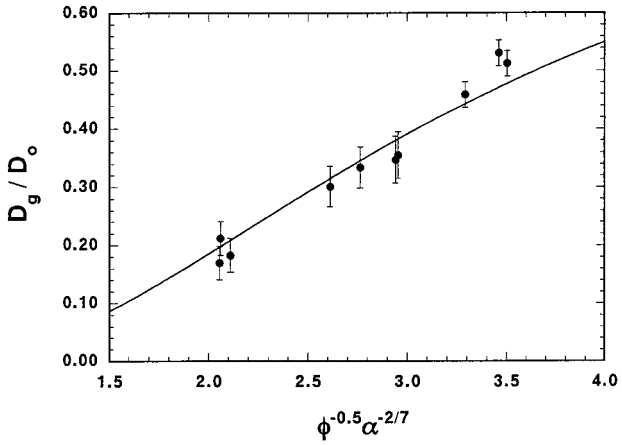

Figure 3. Fit of obstruction scaling model employing eq 7 for ξ.

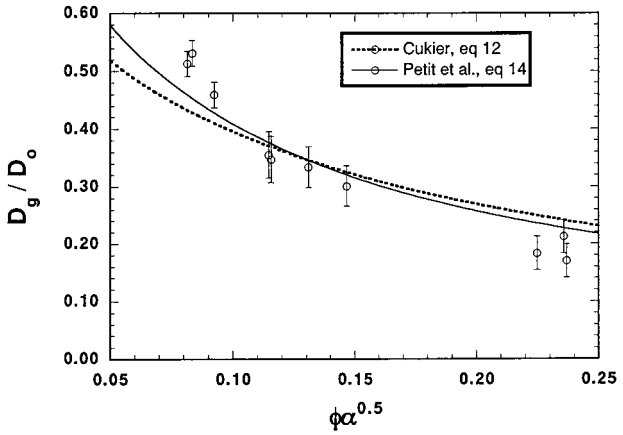

Figure 4. Application of adapted hydrodynamic model (eq 12) and model of Petit et al. (eq 14) to the experimental data.

squares of the residuals resulting from using eq 7 (0.008) over eq 6 (0.006). The value obtained for k_s was consistently 35.6 Å$^{1.5}$. This value can be compared to that obtained for calcium alginate gels, which was 78 Å,[12] or approximately twice as great as that for poly(acrylic acid). In contrast, the k_s value obtained by fitting eq 2 to nonionic gels was consistently approximately unity.[10] Thus, it appears that an a priori estimate of solute diffusivity in a polyelectrolyte gel using this obstruction scaling approach is only possible if the scaling constant has been previously determined.

Many other models have also been developed to explain the retardation in mobility a solute experiences when moving through a gel, some of which also incorporate scaling concepts. One such model is that of Cukier, who explained the reduction in solute mobility in terms of enhanced hydrodynamic drag.[3] His result can be written as

$$\frac{D_g}{D_0} = \exp(-\kappa r_s) \tag{11}$$

wherein κ is the hydrodynamic screening length. Cukier argued that κ is inversely proportional to ξ, and so eq 11 can be written as follows:

$$\frac{D_g}{D_0} = \exp(-k_s(\phi a)^{-1/2}(\alpha C)^{1/4} r_s) \tag{12}$$

Recently, another physical model of solute diffusion in polymer gels was developed by Petit et al.[21] In this approach, solute diffusion is envisioned to occur via jumps of length ξ within the solution. These jumps occur with a frequency k. The polymer contribution to solute transport retardation is considered to arise due to friction, and this friction is determined to be $k\xi^2$. It is assumed further that this frictional contribution is additive to that contributed by the solvent continuum. Their expression for solute diffusivity within a polymer solution is

$$\frac{D_g}{D_0} = \left(1 + \frac{D_0}{k\xi^2}\right)^{-1} \tag{13}$$

Substituting in for ξ results in

$$\frac{D_g}{D_0} = \left(1 + \frac{D_0}{k} k_s(\phi a)(C\alpha)^{1/2}\right)^{-1} \tag{14}$$

Table 3. Regression Results for Fits of Cukier and Petit et al. Models

model	k_s	±	SSR	R^2
Cukier eq 12	0.060	0.004	0.030	0.798
Petit et al. eq 14	3.13[a]	0.199	0.018	0.884

[a] Value contains the terms D_0/k.

Equations 12 and 14 were also fit to the experimental data, and the results of these fits are shown in Figure 4. The regression results are supplied in Table 3.

Both models provide a general agreement with the trend in the data. The model of Petit et al. provides the best fit of the two, with a sum of squares of the residuals of 0.021. This value is greater than the sum of squares of the residuals obtained using the obstruction-scaling model embodied by eq 3, indicating that the data are best described by the obstruction scaling approach, although it provides a reasonable fit to the data. The lack of a description of the influence of solute radius on the jumping frequency factor, k, however, limits the utility of the model.

Limitations of the obstruction-scaling approach merit discussion at this point. As has been pointed out by one reviewer, if the pore size distribution of the gel obeys a power law over a range of concentrations, then the average pore size is not a meaningful number. This situation may occur from gels that result from a fractal distribution of cluster sizes in the pregel state or in gels whose polymer concentration barely exceeds the critical overlap concentration. Thus, this modeling approach would not be valid for these situations. Furthermore, this modeling approach is in effect a mean-field approach in that it does not account for spatial variations in cross-link density and thus pore sizes within the gel.

Conclusions

The work presented demonstrates that the development of a scaling relationship for the distance between polymer chains at swelling equilibrium from either a force balance or a semidilute solution basis provides essentially the same expression. This scaling relationship was incorporated into an obstruction-based model and shown to successfully account for the observed effect of the degree of ionization of the polymer chain on the intragel diffusion of a nonionic solute. The model predicts that, as the ionization degree of the polymer increases, the stiffness of the polymer increases which leads to a greater average opening radius between

polymer chains. This increased average opening results in a greater diffusivity than would be predicted if the ionization degree was not considered. The predictive ability of this obstruction model was compared to the hydrodynamic model of Cukier and the jumping frequency model of Petit et al. and found to provide a better fit to the trend in the data. This model should be useful in areas where the influence of pH on polyelectrolyte gels is important, for example, in the prediction of drug delivery along the GI tract (where the pH varies from 1 to 8[22]) from tablets containing pH-sensitive gel coatings and in the design of such delivery forms.

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