Solute Diffusion within Hydrogels. Mechanisms and Models

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ABSTRACT: Solute diffusion in hydrogels is important in many biotechnology fields. Solute behavior in hydrogels has been explained in terms of reduction in hydrogel free volume, enhanced hydrodynamic drag on the solute, increased path length due to obstruction, and a combination of hydrodynamic drag and obstruction effects. In this article the various mathematical models derived to explain and predict solute diffusion in hydrogels are reviewed and tested against literature data. These models can be divided into those applicable to hydrogels composed of flexible polymer chains (i.e., homogeneous hydrogels) and those composed of rigid polymer chains (i.e., heterogeneous hydrogels). For homogeneous hydrogels it was determined that a scaling hydrodynamic model provided the best explanation for solute diffusion, while for heterogeneous hydrogels obstruction models were more consistent with the experimental data. Both the scaling hydrodynamic model and the most appropriate obstruction model contain undefined parameters which must be clarified in order for these models to gain widespread acceptance.

Introduction

The diffusion of solutes in hydrogels has application in a wide variety of fields. Hydrogels are used in separation processes such as chromatography,[1] for the encapsulation of cells for both biomedical and fermentation purposes,[2] in biosensors,[3,4] and as biomaterials for the delivery of bioactive agents to the body[4−6] and prosthetic applications.[3,4] The one feature of hydrogels that all these applications capitalize upon is the ability of the hydrogel to restrict the diffusive movement of a solute. It is therefore important to have an understanding of the parameters governing solute diffusion within hydrogels as well as the means by which they affect diffusion. For this reason, a number of mathematical expressions have been developed in an effort to model solute diffusion in hydrogels. It is the purpose of this article to examine the most prevalent models and compare them to data taken from the literature, to assess their predictive abilities. Such an examination was undertaken a number of years ago by Muhr and Blanshard;[7] however, a number of models have since been proposed.

Before introducing the different models, it would be beneficial to review the properties of hydrogels. Hydrogels are cross-linked hydrophilic polymers swollen in water or an aqueous environment. Their three-dimensional structure is often described as a mesh, with the spaces between the polymer chains filled with water. The cross-links can be formed by covalent or ionic bonds, van der Waals forces, hydrogen bonds, or physical entanglements.[3,4] The cross-link sites form microregions of local polymer precipitation from solution. The overall structure of hydrogels therefore ranges from homogeneous, where the polymer chains have a high degree of mobility, to heterogeneous, in which there is a great deal of inter-polymer interaction and the polymer chains are virtually immobile at the molecular level.[7] Examples of homogeneous hydrogels include poly(ethylene oxide), poly(acrylamide), and poly(vinyl alcohol). Examples of heterogeneous hydrogels include calcium alginate, agarose, and κ-carrageenan.[3,7]

Solute transport within hydrogels occurs primarily within the water-filled regions in the space delineated by the polymer chains. Any factor which reduces the size of these spaces will have an effect on the movement of the solute. Such factors include the size of the solute in relation to the size of the openings between polymer chains, polymer chain mobility, and the existence of charged groups on the polymer which may bind the solute molecule. Polymer chain mobility is an important factor governing solute movement within the hydrogel. For homogeneous gels, the mesh openings are neither constant in size nor location, whereas for heterogeneous hydrogels the openings between chains can be considered constant in size and location.[7] In general, the diffusivity of a solute through a physically cross-linked hydrogel decreases as cross-linking density increases, as the size of the solute increases, and as the volume fraction of water within the gel decreases.[4,8,9]

As will be shown in the following sections, the polymer chains have been proposed to retard solute movement by reducing the average free volume per molecule available to the solute, by increasing the hydrodynamic drag experienced by the solute, and by acting as physical obstructions thereby increasing the path length of the solute. As well, models have been proposed which combine the effects of increased hydrodynamic drag and the existence of physical obstructions. For succinctness, this review will be restricted to hydrophilic, generally spherical solutes and polymer−solute interaction effects are neglected.

Mechanisms and Models

Free Volume Theory. These models are based on the theory put forward by Cohen and Turnbull to explain the process of solute diffusion in a pure liquid.[10] In this theory, the solute diffuses by jumping into voids formed in the solvent space by the redistribution of the free volume within the liquid. It is assumed that the free volume can be redistributed without any energy change. The voids are pictured as being formed by a general withdrawal of the surrounding liquid molecules due to random thermal motion. These holes are then filled in by the reverse process.[11]

Solute diffusion is dependent on the jumping distance, the thermal velocity of the solute, and the probability

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that there is a hole free volume adjacent to the molecule. At a given temperature, the rate of diffusion is determined by the probability of a void being formed of sufficient volume to accommodate the solute molecule. The diffusion coefficient of the solute in the liquid at infinite dilution, D_0, is then expressed as

$$D_0 \propto V\lambda \exp\left(-\frac{\gamma v^*}{v_f}\right) \tag{1}$$

in which V is the average thermal velocity, λ is the jump length roughly equivalent to the solute diameter, v^* is the critical local hole free volume required for a solute molecule to jump into a new void, γ is a numerical factor used to correct for overlap of free volume available to more than one molecule ($0.5 \leq \gamma \leq 1$), and v_f is the average hole free volume per molecule in the liquid.

Yasuda et al.[12] were the first to apply this theory to solute diffusion in gels. In their derivation, they assumed that only trace amounts of solute were present so that the free volume per molecule within the gel was given by the summation of the free volumes per molecule of the water, $v_{f,w}$, and polymer, $v_{f,p}$, within the gel, written as

$$v_f = (1 - \varphi)v_{f,w} + \varphi v_{f,p} \tag{2}$$

wherein φ is the volume fraction of polymer in the gel. In other words, the available free volume for diffusion in the gel arises not only from the random redistribution of the water molecules but also by the random redistribution of sections of the polymer molecules, called polymer jumping units. The contribution of the polymer chains to the available free volume per molecule is considered to be small, and so the free volume available to the solute is expressed as

$$v_f \approx (1 - \varphi)v_{f,w} \tag{3}$$

Within the gel, in addition to the requirement of finding a sufficient free volume within the liquid, the solute molecule also needs to find an opening between the solute chains large enough to allow its passage. Thus, the diffusivity of a solute in the gel is given by the product of the probabilities of finding a proper free volume and a proper opening within the chains. Using this concept and combining eqs 1−3, yields the following expression for solute diffusion in a gel, D_g:[12]

$$\frac{D_g}{D_0} = P_0 \exp\left(-\frac{Ba^*}{v_{f,w}}\left(\frac{\varphi}{1 - \varphi}\right)\right) \tag{4}$$

In eq 4 P_o is the probability of finding an opening between the polymer chains, a^* is the effective cross-sectional area of the solute molecule, and B is an undefined constant of proportionality. The term P_o represents the sieving action of the polymer chains on the solute molecule. Yasuda et al.[12] chose the solute cross-sectional area as the determining parameter for P_o and examined a number of sieving factor probability functions but did not apply the functions to experimental data.

Variations of eq 4 have been derived by others. For example, Peppas and Reinhart[13] suggested the form

$$\frac{D_g}{D_0} = k_1\left(\frac{\bar{M}_c - \bar{M}_c^*}{M_n - \bar{M}_c^*}\right) \exp\left(-k_2 r_s^2\left(\frac{\varphi}{1 - \varphi}\right)\right) \tag{5}$$

in which k_1 and k_2 are undefined structural constants for a given polymer−solvent system, r_s is the radius of the solute, $\bar{M}_c$ is the number average molecular weight between polymer cross-links, $\bar{M}_n$ is the number average molecular weight of the uncross-linked polymer, and $\bar{M}_c^*$ is a critical molecular weight between cross-links required to allow solute passage. In their derivation, Peppas and Reinhart considered the volume of the solute to be the critical geometrical parameter deciding whether a solute will pass through the polymer chains. In a subsequent paper, Reinhart and Peppas[14] found that a more accurate expression of their model is given as

$$\frac{D_g}{D_0} = k_1\left(\frac{\bar{M}_c - \bar{M}_c^*}{\bar{M}_n - \bar{M}_c^*}\right)^2 \exp\left(-k_2 r_s^2\left(\frac{\varphi}{1 - \varphi}\right)\right) \tag{6}$$

Despite this finding, this research group recently used eq 5 to explain solute diffusion within poly(vinyl alcohol)/poly(acrylic acid) interpenetrating networks,[15] suggesting an inconsistency with this model.

Another version of the free volume theory expression was given by Lustig and Peppas,[16] who introduced the concept of the scaling correlation length between cross-links, ξ. By arguing that a solute will pass through the polymer chains only if its effective radius is smaller than ξ, they assumed that the sieving factor expression should be $(1 - r_s/\xi)$. Applying this argument to the free-volume expression gave

$$\frac{D_g}{D_0} = \left(1 - \frac{r_s}{\xi}\right) \exp\left(-Y\left(\frac{\varphi}{1 - \varphi}\right)\right) \tag{7}$$

where $Y = \gamma\pi\lambda r_s^2/v_{f,w}$. Y is therefore the ratio of the critical volume required for a successful translational movement of the solute molecule and the average free volume per molecule of the liquid. The correlation length is related to polymer volume fraction, the functionality of this dependence varying with polymer volume fraction and polymer−solvent interaction.[17] For example, in the situation where the polymer and the solvent have a high affinity for each other, the polymer chains are just touching and no entanglements occur (i.e., high water fraction in a homogeneous gel), $\xi \propto \varphi^{-0.75}$. Lustig and Peppas also state that for correlation purposes a good approximation for Y is unity. However, again there is some confusion as to the proper form of the sieving factor. The same authors also give $(1 - (r_s/\xi)^2)$ as the appropriate form of the sieving factor.[18,19]

Another version of the free volume theory has been given by Hennink et al.[20] In their model, the reduction in solute diffusivity is given by

$$\ln\left(\frac{D_g}{D_0}\right) = \ln(\Psi) - k_2 r_s^2\left(\frac{\varphi}{1 - \varphi}\right) \tag{8}$$

in which Ψ accounts for the sieving effect. However, these authors assume that the sieving factor is independent of polymer volume fraction. This assumption could only be considered approximately valid at very low polymer volume fractions. As the concentration of polymer chains per given volume increases, the degree of obstruction or sieving a solute experiences will necessarily increase. Therefore, this model is unrealistic.

Hydrodynamic Theory. Hydrodynamic descriptions of solute transport through gels are based on the Stokes−Einstein equation for solute diffusivity. In the Stokes−Einstein derivation, the solute molecule is assumed to be a hard sphere which is large compared to the solvent in which it moves.[21] The solute is considered to move at a constant velocity in a continuum composed of the solvent and is resisted by frictional drag. The diffusivity at infinite dilution, D_o, is expressed as[21]

$$D_o = \frac{k_B T}{f} \tag{9}$$

in which k_B is Boltzmann's constant, T is temperature, and f is the frictional drag coefficient.

Almost all hydrodynamic, and obstruction, models necessarily assume an idealized picture of the polymer structure. Within the hydrogel, the polymer chains are considered to be centers of hydrodynamic resistance, fixed in place relative to the moving solute by entanglements and physical cross-links. The polymer chains enhance the frictional drag on the solute by slowing down the fluid near the polymer chain. Hydrodynamic models of solute diffusion through hydrogels are therefore concerned with describing f.

The frictional coefficient has been calculated by summing the frictional contribution of each chain to the movement of the solute molecule. In this manner, Altenberger et al.[22] derived the expression

$$\frac{D_e}{D_o} = 1 - \alpha_1 \varphi^{1/2} - \alpha_2 \varphi \ldots \tag{10}$$

in which

$$\alpha_1 \propto r_s \sqrt{r_f} \tag{11}$$

and α_2 is a constant determined by the fluctuation of the force of interaction between the polymer chains and the solute molecule. In eq 11 r_f is the radius of the polymer fiber.

Using the same model as a basis, Cukier[23] described the decrease in diffusivity for heterogeneous hydrogels, which have very rigid chains, as

$$\frac{D_e}{D_o} = \exp\left[-\left(\frac{3\pi L_c N_A}{M_f \ln(L_c/2r_f)}\right) r_s \varphi^{1/2}\right] \tag{12}$$

wherein L_c is the length of the polymer chain, M_f is the molecular weight of the polymer chain, and N_A is Avogadro's number. For homogeneous hydrogels, Cukier[23] proposed an equation based on scaling concepts,

$$\frac{D_g}{D_o} = \exp(-k_c r_s \varphi^{0.75}) \tag{13}$$

in which k_C is an undefined constant for a given polymer−solvent system.

Phillips et al.[24] calculated the frictional coefficient by using Brinkman's equation for flow through a porous medium and assuming no slip at the solute surface and constant fluid velocity far from the solute surface. The medium is considered to be composed of straight, rigid fibers, oriented in a random three-dimensional fashion. They thereby obtained the expression

$$\frac{D_e}{D_o} = \left[1 + \left(\frac{r_s^2}{k}\right)^{1/2} + \frac{1}{3}\frac{r_s^2}{k}\right]^{-1} \tag{14}$$

in which k is the hydraulic permeability of the medium. The hydraulic permeability is estimated using a correlation derived by Jackson and James,[25]

$$k = 0.31 r_f^2 \varphi^{-1.17} \tag{15}$$

Although derived differently, Kosar and Phillips[26] have recently demonstrated that eqs 10, 13, and 14 are mathematically equivalent. They therefore can be interpreted in the same manner.

Obstruction Theory. Models based on obstruction theory assume that the presence of impenetrable polymer chains causes an increase in the path length for diffusive transport. The polymer chains act as a sieve, allowing passage of a solute molecule only if it can pass between the polymer chains. Perhaps due to its conceptual appeal, a number of obstruction theory models have been developed.

Mackie and Meares[27] were among the earliest to develop an obstruction expression for solute diffusion in a heterogeneous medium. They assumed a lattice model for the water−polymer hydrogel system, with the polymer blocking a fraction, φ, of the sites. The solute molecule was assumed to be the same size as the polymer segments and solute transport to occur only within the free sites. The expression they derived was

$$\frac{D_g}{D_o} = \left(\frac{1-\varphi}{1+\varphi}\right)^2 \tag{16}$$

Although this expression has been used to analyze transport through hydrogels,[28] it is of limited utility because it does not take into consideration any properties of the hydrogel or of the solute.

The sieving behavior of the polymer chains has also been incorporated into free volume theory. Yasuda et al.[12] used a differential hole distribution function to describe the sieving action of the polymer chains. The reduction in solute diffusivity due to this sieving action was given by

$$p(r_s) = \int_{a^*}^{\infty} f(a)\, \mathrm{d}a \tag{17}$$

in which $p(r_s)$ is the probability of a solute passing through a given hole in the mesh, $f(a)$ is the hole area distribution function, a is the area of the openings between polymer chains, and a^* is the effective cross-sectional area of the solute molecule. These researchers showed the qualitative effects of several distributions, including a Gaussian distribution, but did not apply the distributions to experimental data. Lustig and Peppas[16] assumed that the probability of a solute passing through a given hole in the mesh was

$$p(r_s) = 1 - \frac{r_s}{\xi} \tag{18}$$

This expression is based on the argument that solutes of equal cross-sectional area could have different hydrodynamically equivalent radii.

A more phenomenological approach was taken by Ogston et al.[29] They assumed that solute diffusion in the hydrogel occurs by a succession of directionally

random unit steps and that the unit step does not take place if the solute encounters a polymer chain. The cross-linked polymer is assumed to exist as a random network of straight, long fibers of negligible width, and the solute is considered to be a hard sphere. The unit step is taken to be the root-mean-square average diameter of spherical spaces residing between the fiber network. From such an analysis, they expressed the ratio of the diffusion coefficient in the gel to that in infinite dilution in water as

$$\frac{D_g}{D_o} = \exp\left[-\frac{(r_s + r_f)}{r_f}\sqrt{\varphi}\right] \tag{19}$$

Although conceptually appealing, eq 19 provides only a qualitative agreement to experimental observations.[7,9]

Johansson et al.[30] developed an obstruction model based on the idea that the gel can be viewed as being composed of a number of cylindrical cells. Each cylindrical cell consists of an infinite polymer rod centered in a cylinder of solvent of a given radius. The average diffusivity of the solute within this cell can be found by solving Fick's first law. The global diffusivity of the solute (i.e., throughout the gel) is then calculated by summing up the number of cells having a given radius times the average diffusivity within that cell. The distribution of the cell radii was calculated using an expression for the distribution of spherical spaces within a random network of straight fibers.[31] Their expression for the reduction in solute diffusivity is

$$\frac{D_g}{D_o} = e^{-\alpha} + \alpha^2 e^{\alpha} E_1(2\alpha) \tag{20}$$

where

$$\alpha = \varphi\left(\frac{r_s + r_f}{r_f}\right)^2 \tag{21}$$

and E_1 is the exponential integral.

The model produced a satisfactory agreement to simulation and experimental results for solute diffusion in both polymer solutions and polymer gels. However, the theory predicted diffusivities greater than those found from simulation for large solutes at high polymer volume fractions (>0.01).[32] The Brownian motion simulation data were, however, well-described by the following argument, obtained through a regression to the data:

$$\frac{D_g}{D_o} = \exp[-0.84\alpha^{1.09}] \tag{22}$$

Moreover, as a result of the assumption of an infinite polymer chain, the analytical expression (eq 20) does not work well for the condition where the persistence length of the polymer, which is the average projection of the end-to-end distance of an infinite chain in the direction of the first chain segment, is less than 10 times greater than the solute radius. For this situation, it is necessary to calculate the diffusivity numerically.

The random network of overlapping fibers picture of hydrogel structure has also been invoked as a physical model in the study of transport properties within many types of porous media, whether the transport be thermal, electrical, or diffusional in nature.[33] Each of these processes is mathematically analogous, and so results obtained in one field are applicable in another. Recently, models developed to describe transport properties in random arrays of overlapping fibers have been reviewed and compared to the results of a Brownian motion simulation.[33] The results indicate that, of these models, that of Tsai and Strieder[34] adapted for the diffusive process as

$$\frac{D_g}{D_o} = \left(1 + \frac{2}{3}\alpha\right)^{-1} \tag{23}$$

provided the best agreement to Brownian motion simulation data for cylinder volume fractions less than 0.40. In eq 23, α is as described in eq 21. In the derivation of this equation, the volume fraction of the fiber network excluded to the solute, Φ, was given by Ogston's expression,[31]

$$\Phi = 1 - \exp(-\alpha) \tag{24}$$

Recently, a new obstruction model was developed.[35] In this model, solute movement through the hydrogel is considered to be a stochastic process, with successful movement through the gel determined by the solute molecule finding a succession of openings within the polymer chains large enough to accommodate its hydrodynamic radius. Again, Ogston's expression was used to describe the distribution of openings between straight, randomly oriented polymer fibers.[31] The model is expressed as

$$\frac{D_g}{D_o} = \exp\left(-\frac{\pi}{4}\left(\frac{r_s + r_f}{\bar{r} + r_f}\right)^2\right) \tag{25}$$

in which $\bar{r}$ is the average radius of the openings between the polymer chains. The average radius of the openings between the polymer chains was taken to be one-half of the average end-to-end distance between the polymer chains, ξ. With employment of scaling concepts, this distance is given by[36]

$$\xi = k_s \varphi^{-1/2} \tag{26}$$

where k_s is a constant for a given polymer−solvent system, dependent on the flexibility of the polymer chain. Due to the assumption of straight polymer chains, this model is applicable to diffusion in heterogeneous hydogels, although the use of scaling laws to describe the average distance between polymer chains may make it applicable to homogeneous hydrogels.

Combined Obstruction and Hydrodynamic Effects. Recently, Brady[37] proposed that the obstruction and hydrodynamic influences on solute transport within a gel fiber matrix are multiplicatively related. Johnson et al.[38] used this concept and combined the obstruction expression of Johansson et al.[32] (eq 22) with eq 14, resulting in

$$\frac{D_g}{D_o} = \frac{\exp[-0.84\alpha^{1.09}]}{\left[1 + \left(\frac{r_s^2}{k}\right)^{1/2} + \frac{1}{3}\frac{r_s^2}{k}\right]} \tag{27}$$

where α is given by eq 21.

Equation 27 was shown to be a better predictor of the effect of φ and r_s on solute diffusivity within agarose gels than either the Ogston et al. expression (eq 19) or

the expression of Phillips et al. (eq 14). However, the model consistently underestimated the decrease in relatively small solute diffusivity and provided only a qualitative approximation to the diffusivity data at the highest polymer volume fraction tested.

A more rigorous combined hydrodynamic/obstruction simulation model which does not depend on an effective medium calculation was developed by Clague and Phillips.[39] In this model the hydrodynamic interactions were calculated by representing the solute as a collection of point singularities and accounting for the fibers by using a numerical version of slender-body theory. Clague and Phillips[39] performed simulations at various solute radius to fiber radius ratios and fit a stretched exponential function to these data of the form

$$\frac{D_g}{D_o} = \exp(-a\varphi^{\upsilon}) \tag{28}$$

in which a and υ are fitted parameters and are functions of r_f/r_s. This simulation model was tested against the effect of polymer volume fraction on BSA diffusivity within agarose gels and was shown to provide a closer agreement to the data than that given by the model of Johnson et al.[38] However, the model was only tested against one other solute, myoglobin, and thus its ability to account for the effect of solute radius is as yet unresolved. Unfortunately, the simulation nature of the model does not easily lend itself to comparison.

To use their model it is necessary to have a means of determining a and υ for various r_f/r_s values. However, the exponential nature of the data means that there are multiple possible solutions to this exponential fit. The parameters returned by the fitting algorithm depend on the initial guesses supplied. Reviewing their fitted parameters indicated that the values of a returned were all approximately equal to π. Therefore, their data was refit by fixing $a = \pi$. The results are displayed in Figure 1. The values of υ obtained were then plotted as a function of r_f/r_s (Figure 2). A regression analysis of these data yields the following relationship

$$\upsilon = 0.174 \ln\left(59.6\frac{r_f}{r_s}\right) \tag{29}$$

which provides very good agreement ($R^2 = 0.976$). Thus the hydrodynamic contribution to the reduction in solute diffusivity can be written as

$$\frac{D_g}{D_o} = \exp(-\pi\varphi^{0.174\ln(59.6r_f/r_s)}) \tag{30}$$

Clague and Phillips combined their hydrodynamic term with the obstruction expression of Tsai and Streider (eq 23), and so their model can be written as

$$\frac{D_g}{D_o} = \left(1 + \frac{2}{3}\alpha\right)^{-1} \exp(-\pi\varphi^{0.174\ln(59.6r_f/r_s)}) \tag{31}$$

Due to the assumptions made in the development of this model, it can only strictly apply to solute diffusion in heterogeneous hydrogels composed of very stiff polymers.

Models Summary. The suitability of each of the models described depends to a large extent on the nature of the polymer making up the hydrogel. Diffusion in homogeneous hydrogels could not expected to be aptly described by a model which assumes that the polymer chains are rigid, straight, and motionless, and neither would the converse be expected to be true. The hydrogel class for which each of the models discussed above is suitable is listed in Table 1, along with the form of the model equation which will be used for comparison to literature data.

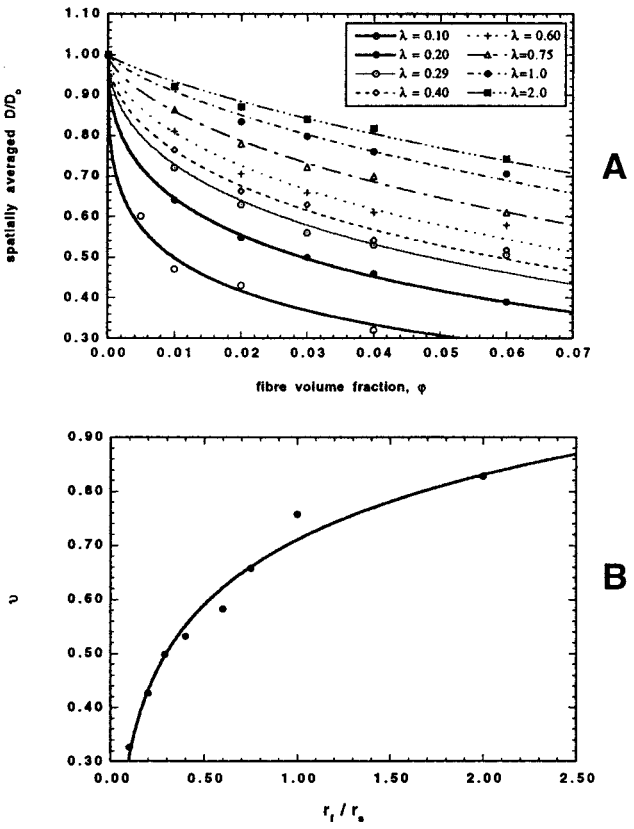

Figure 1. Clague and Phillips simulation results of hydrodynamic effects on spherical solute diffusion through a random network of cylindrical fibers.[39] (A) Effect of fiber volume fraction, fiber radius, and solute radius. In the legend, $\lambda = r_f/r_s$. The lines represent the regression results of eq 28 with $a = \pi$. (B) Relationship between fitted values of υ and r_f/r_s. The line represents the regression result given by eq 29.

Methods

Data for solute diffusion in hydrogels were taken from a number of sources.[9,20,28,35,40−47] These sources are listed in Table 2, along with the polymer and solute(s) used. In order for the literature source to be considered useful the following information had to be provided: the volume fraction of polymer in the hydrogel (given or readily calculated based on literature data) and the diffusivity of the solute in aqueous medium used in the study. The method used for determining diffusivity in the gel and the classification of the hydrogel as either homo- or heterogeneous are also listed in Table 2. It is beyond the scope of this paper to compare methods of determining diffusivity. The values obtained in the literature were accepted as accurate. The interested reader can see Westrin et al.[48] for a comparison of the estimated accuracy's of these methods. A final criteria for use of the data was that more than three data points be provided in the study.

As all the models require an estimation of the solute radius, the Stokes−Einstein hydrodynamic radius of the

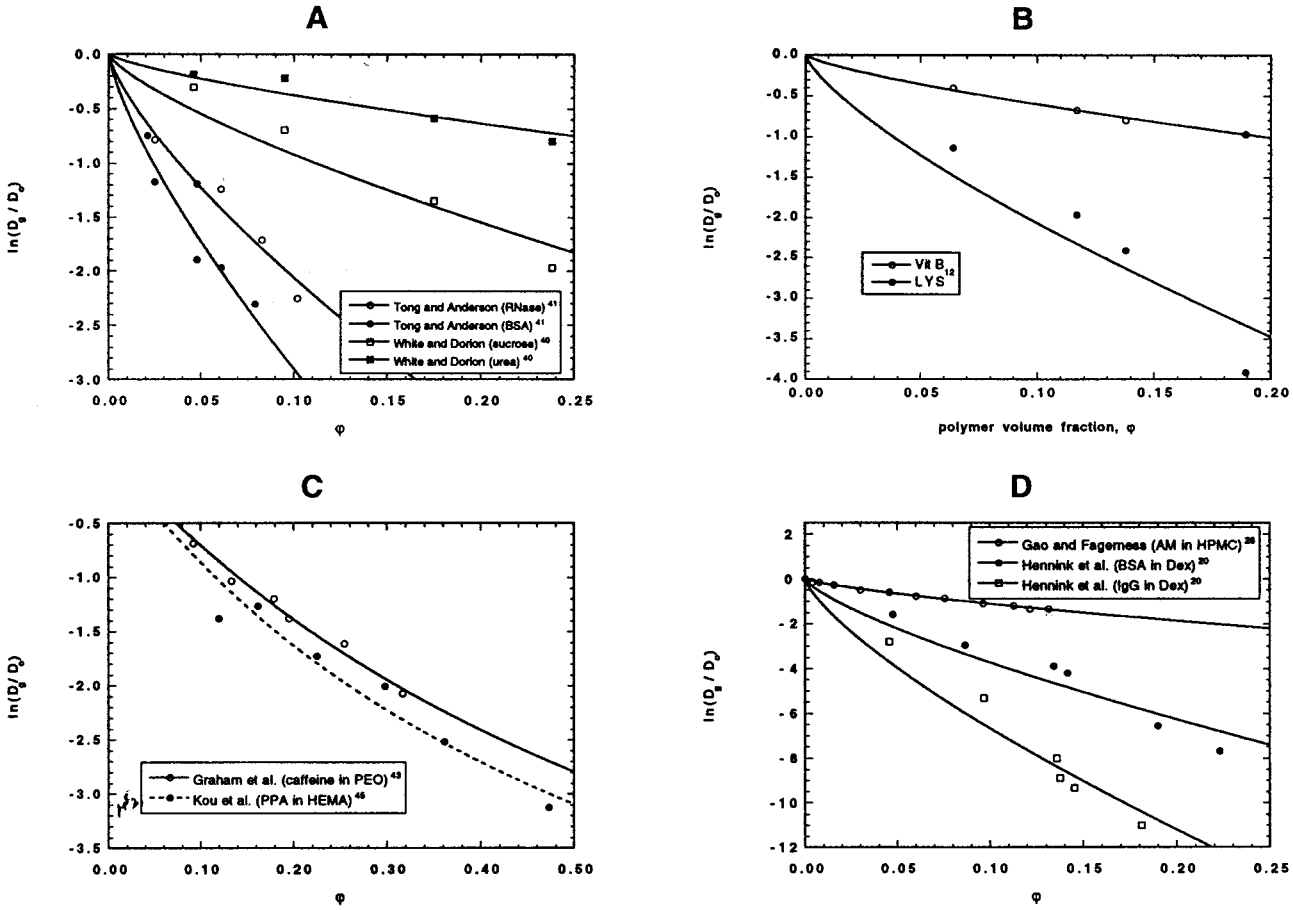

Figure 2. Application of the Cukier hydrodynamic-scaling model[23] to literature data showing the effect of polymer volume fraction on solute diffusivity within various homogeneous hydrogels: (A) polyacrylamide gels; (B) poly(vinyl alcohol) gels;[42] (C) poly(ethylene oxide) (PEO) and poly(hydroxyethyl methacrylate) gels (HEMA); (D) dextran (Dex) and hydroxypropyl methylcellulose (HPMC) gels. The lines represent regression results.

Table 1. Summary of Diffusion Models and the Hydrogels for Which They are Suited

model	expression	ref	hydrogel class
free volume theory	$\frac{D_g}{D_0} = (1 - k_1 r_s \varphi^{0.75}) \exp\left(-k_2 r_s^2 \left(\frac{\varphi}{1-\varphi}\right)\right)$	Lustig and Peppas[16]	homogeneous
hydrodynamic	$\frac{D_g}{D_o} = \exp(-k_C r_s \varphi^{0.75})$	Cukier[23]	homogeneous
hydrodynamic	$\frac{D_g}{D_o} = \left[1 + \left(\frac{r_s^2}{k}\right)^{1/2} + \frac{1}{3}\frac{r_s^2}{k}\right]^{-1}$	Phillips et al.[24]	heterogeneous
obstruction	$\frac{D_g}{D_o} = \exp\left[-\frac{(r_s + r_f)}{r_f}\sqrt{\varphi}\right]$	Ogston et al.[31]	heterogeneous
obstruction	$\frac{D_g}{D_o} = \exp(-0.84\alpha^{1.09})$	Johansson et al.[30]	heterogeneous
obstruction	$\frac{D_g}{D_o} = \left(1 + \frac{2}{3}\alpha\right)^{-1}$	Tsai and Streider[34]	heterogeneous
obstruction	$\frac{D_g}{D_o} = \exp\left[-\pi\left(\frac{r_s + r_f}{k_s \varphi^{1/2} + r_f}\right)^2\right]$	Amsden[35]	heterogeneous
combined	$\frac{D_g}{D_o} = \frac{\exp[-0.84\alpha^{1.09}]}{\left[1 + \left(\frac{r_s^2}{k}\right)^{1/2} + \frac{1}{3}\frac{r_s^2}{k}\right]}$	Johnson et al.[38]	heterogeneous
combined	$\frac{D_g}{D_o} = \left(1 + \frac{2}{3}\alpha\right)^{-1} \exp(-\pi\varphi^{0.174\ln(59.6 r_f/r_s)})$	Clague and Phillips[39]	heterogeneous

solute was used, as calculated from[21]

$$r_s = \frac{k_B T}{6\pi\eta D_o} \tag{32}$$

in which k_B is Boltzmann's constant, T is temperature, and η is the viscosity of water at T. The radii obtained for the solutes examined are listed in Table 3, along with the literature source used to obtain D_o. The exception to this definition of effective solute radius was the radius of gyration, r_g, used for the poly(ethylene glycol) (PEG) solutes. The radius of gyration was used for these

Table 2. Literature Sources Used

polymer	solute(s)[a]	φ	method	ref
		Homogeneous		
poly(acrylamide)	sucrose, urea	0.046−0.238	diffusion into slab	White and Dorion[40]
poly(acrylamide)	RNase, BSA	0.021−0.138	FRAP[b]	Tong and Anderson[41]
poly(vinyl alcohol)	TPL, α-LA, LYS, vit B_{12}	0.043−0.189	permeation across membrane	Matsuyama et al.[42]
poly(ethylene oxide)	caffeine	0.092−0.317	release from slab	Graham et al.[43]
poly(ethylene oxide)	LYS, vit B_{12}, CHY, OVA	0.062, 0.084	diffusion into slab	Merrill et al.[44]
poly(hydroxyethyl methacrylide)	PPA	0.19−0.60	release from slab	Kou et al.[45]
hydroxypropylmethyl cellulose	AM	0.000−0.131	PFSGE-NMR[c]	Gao and Fagerness[28]
dextran	LYS, BSA, IgG	0.048−0.227	release from cylinder	Hennink et al.[20]
		Heterogeneous		
calcium alginate	dextrans, CHY, BSA	0.003	laser light scattering	Sellen[58]
calcium alginate	glucose, α-LA, BSA, IgG, FBG	0.012	release from spheres	Tanaka et al.[46]
calcium alginate	β-LG, OVA, PEP, BSA	0.005−0.050	release from slab	Amsden[35]
agarose	BSA, MYO, $C_{12}E_8$ and $C_{12}E_{10}$ micelles	0.010−0.050	holographic interferometry	Kong et al.[47]
κ-carageenan	PEG 326, 678, 1118, 1822, 2834, 3978	0.005, 0.010	slab-sectioning	Johansson et al.[9]

[a] Solute abbreviations: AM, adinazolam mesylate; BSA, bovine serum albumin; CHY, chymotrypsinogen; FBG, fibrinogen; IgG, immunoglobulin G; α-LA, α-lactalbumin; β-LG, β-lactoglobulin; LYS, lysozyme; MYO, myoglobin; OVA, ovalbumin; PEG, poly(ethylene glycol); PEP, pepsin; PPA, Phenylpropanolamine; RNase, ribonuclease; vit B_{12}, vitamin B_{12}. [b] FRAP: fluorescence recovery after photobleaching. [c] PFSGE-NMR: pulsed field gradient spin−echo nuclear magnetic resonance.

Table 3. Diffusivity and Radius of the Solutes Examined

solute	D_o ($\times 10^6$ cm^2/s)	temp (°C)	radius (Å)	ref
urea	18.1	37	1.9	White and Dorion[40]
glucose	6.4	23	3.6	Tanaka et al.[46]
theophylline	6.54	25	3.8	Matsuyama et al.[42]
sucrose	6.97	37	4.8	White and Dorion[40]
caffeine	6.3	37	5.3	Graham et al.[43]
adinazolam mesylate	4.30	23	5.4	Gao and Fagerness[28]
phenylpropanolamine	5.51	37	6.0	Kou et al.[45]
vitamin B_{12}	3.79	37	8.7	Colton et al.[61]
PEG 326	4.9	25	7.5	Johansson et al.[9]
PEG 678	3.5	25	10.5	
PEG 1118	2.8	25	13.1	
PEG 1822	2.2	25	16.7	
PEG 2834	1.8	25	20.4	
PEG 3978	1.5	25	24.5	
ribonuclease	0.131	20	16.3	Tyn and Gusek[62]
myoglobin	0.113	20	18.9	
lysozyme	0.112	20	19.1	
α-lactalbumin	0.106	20	20.2	
chymotrypsinogen	0.095	20	22.5	
pepsin	0.090	20	23.8	
ovalbumin	0.073	20	29.3	
bovine serum albumin	0.060	20	36.3	
β-lactoglobulin A	0.042	20	51.0	
immunoglobulin G	0.040	20	56.3	
fibrinogen	0.020	20	107.0	
$C_{12}E_8$ micelle	0.08	21	27.4	Kong et al.[47]
$C_{12}E_{10}$ micelle	0.069	21	31.7	Kong et al.[47]

solutes because it was reported to be a better estimate of the effective radius of the solute than the hydrodynamic radius.[30]

The literature models were applied to the data and analyzed via a nonlinear regression procedure (Levenberg−Marquardt nonlinear regression algorithm using KaleidaGraph software). In some cases, the diffusivity data were plotted as $\ln(D_g/D_o)$ versus either polymer volume fraction, φ, or solute radius, r_s. The natural logarithm of the diffusivity ratio was used to provide a more robust regression procedure. The success of the respective model was determined by an analysis of both the value of the fitted parameter(s) returned, their confidence intervals, and the sum of squares of the residuals (χ^2) obtained by the fit. In the majority of the cases, estimates of experimental error were not given, and so confidence intervals were determined using the sum of squares of the residuals divided by the degrees of freedom as an estimate of the variance.

Table 4. Regression Results of Application of Hydrodynamic Model of Cukier[23] to Solute Diffusion in Homogeneous Hydrogels (Eq 13)[a]

polymer	solute	r_s, Å	k_c	±SE	χ^2	R^2	data ref
PAAM	urea	1.9	1.12	0.11	0.255	0.874	White and Dorion[40]
	sucrose	4.75	1.06	0.09	0.116	0.929	
PAAM	RNase	16.3	0.55	0.025	0.070	0.945	Tong and Anderson[41]
	BSA	36.3	0.45	0.020	0.116	0.929	
Dextran	LYS	19.1	0.57	0.020	0.26	0.921	Hennink et al.[20]
	BSA	36.3	0.58	0.034	2.52	0.903	
	IgG	56.3	0.66	0.027	3.17	0.921	
PVA	vit B_{12}	8.7	0.619	0.050	0.500	0.874	Matsuyama et al.[42]
	LYS	19.1	0.398	0.013	0.007	0.960	
PEO	caffeine	5.25	0.883	0.020	0.030	0.974	Graham et al.[43]
PHEMA	PPA	6.0	1.10	0.06	2.36	0.904	Kou et al.[45]
HPMC	AM	5.4	1.16	0.009	0.006	0.998	Gao and Fagerness[28]

[a] SE = standard error (95% confidence interval). χ^2 = sum of squares of the residuals. R = correlation coefficient.

Results and Discussion

The results of the application of the various descriptive models to the literature data will be discussed as follows. The models found to be best at describing the entirety of the data will be presented first, with the less successful models discussed after.

Homogeneous Hydrogels. Of the models derived to predict solute diffusion in homogeneous hydrogels, the hydrodynamic-scaling model of Cukier[23] provided the best fit to the literature data. This model (eq 13) was applied to the D_g/D_o versus polymer volume fraction data shown in Figure 2a−d. The regression results are listed in Table 4. The free volume model expression derived by Lustig and Peppas (eq 7) was applied to the D_g/D_o versus polymer volume fraction data shown in

Table 5. Regression Results of the Application of the Lustig and Peppas[16] Free Volume Model to Solute Diffusion in Homogeneous Hydrogels (eq 7)[a]

polymer	solute	r_s, Å	k_1	±SE	k_2	±SE	χ^2	R^2	data ref
PAAM	urea	1.9	0.070	0.491	0.728	0.337	0.0080	0.970	White and Dorion[40]
	sucrose	4.75	0.066	0.050	0.263	0.014	0.0005	0.998	
PAAM	RNase	16.3	0.143	0.605	0.043	0.097	0.0976	0.924	Tong and Anderson[41]
	BSA	36.3	0.071	1.486	0.019	0.115	0.3550	0.783	
Dextran	LYS	19.1	0.082	1.02	0.031	0.120	0.945	0.726	Hennink et al.[20]
	BSA	36.3	0.061	0.087	0.017	0.004	0.403	0.984	
	IgG	56.3	0.026	0.073	0.016	0.024	0.986	0.978	
PVA	vit B_{12}	8.7	0.176	0.977	0.026	0.246	0.0126	0.925	Matsuyama et al.[42]
	LYS	19.1	0.158	0.005	0.022	0.002	0.0130	0.996	
PEO	caffeine	5.25	0.260	1.36	0.129	0.53	0.0081	0.904	Graham et al.[43]
PHEMA	PPA	6.0	0.175	1.10	0.059	0.298	3.07	0.878	Kou et al.[45]
HPMC	AM	5.4	0.391	0.862	0.193	0.419	0.076	0.970	Gao and Fagerness[28]

[a] SE = standard error (95% confidence interval). χ^2 = sum of squares of the residuals. R^2 = correlation coefficient.

Table 6. Regression Results of the Application of the Free Volume Model without a Preexponential Sieving Term to Solute Diffusion in Homogeneous Hydrogels (eq 33)[a]

polymer	solute	r_s (Å)	k_2	±SE	χ^2	R^2	data ref
PAAM	urea	1.9	0.774	0.039	0.0080	0.970	White and Dorion[40]
	sucrose	4.75	0.281	0.002	0.0010	0.998	
PAAM	RNase	16.6	0.060	0.003	0.121	0.904	Tong and Anderson[41]
	BSA	36.3	0.023	0.002	0.399	0.755	
dextran	LYS	19.4	0.038	0.003	1.08	0.677	Hennink et al.[20]
	BSA	36.3	0.021	0.0005	0.433	0.984	
	IgG	56.5	0.016	0.0004	1.024	0.978	
PVA	vit B_{12}	8.7	0.061	0.005	0.051	0.719	Matsuyama et al.[42]
	LYS	19.4	0.044	0.003	0.255	0.937	
PEO	caffeine	5.25	0.179	0.011	0.208	0.819	Graham et al.[43]
PHEMA	PPA	6.0	0.081	0.006	4.87	0.803	Kou et al.[45]
HPMC	AM	5.4	0.338	0.0125	0.122	0.952	Gao and Fagerness[28]

[a] SE = standard error (95% confidence interval). χ^2 = sum of squares of the residuals. R = correlation coefficient.

Figure 3a−d. This expression was chosen over eq 6 because it contains parameters for which data is readily obtainable from other literature sources. The results of the nonlinear fitting procedure to the data are given in Table 5.

What is immediately noticeable about the values of the fitted parameters obtained using the free volume model of Lustig and Peppas,[16] is that in the vast majority of the cases neither k_1 nor k_2 is statistically significant. In other words, the confidence interval for each parameter is greater than the value of the parameter, indicating that zero is as likely a value for the parameter as the returned value. This result implies that the structural parameters are highly correlated; that is, there is some functional dependence of one of the parameters on the other. As neither of the structural parameters has been defined in any way, the fact that they are correlated demonstrates that further refinement to this model is required if it is to be considered a viable explanation for solute transport in homogeneous hydrogels.

By removal of the sieving term from eq 7, the fitted values for k_2 become statistically relevant (Table 6). The fitting equation used was

$$\ln\left(\frac{D_g}{D_o}\right) = -k_2 r_s^2\left(\frac{\varphi}{1-\varphi}\right) \qquad (33)$$

The lines in Figure 3a−d are the resultant curves from fitting eq 33 to the data. An examination of the χ^2 and R values in Table 6 suggests that eq 33 provides a reasonably good fit to the data. However, the χ^2 values obtained using the hydrodynamic-scaling model were, in most cases, lower than those obtained using the free volume models indicating that the hydrodynamic expression is a better model. Also, the k_c values obtained using the hydrodynamic-scaling model are all statistically significant. Furthermore, since k_c is defined as a constant for a given polymer−solvent condition, the fitted values for this parameter should be statistically equal for situations where more than one solute was investigated in a particular hydrogel. An examination of Table 6 shows that, with the exception of the results from the data of Matsuyama et al.,[42] this is indeed the case. The fitted values for k_c are either consistent or statistically equal. Thus, it appears at this point that the hydrodynamic-scaling model of Cukier[23] is a better model to use for homogeneous hydrogels than the free volume models.

Further support for this conclusion comes from a mathematical analysis of the two model equations. The free volume model as expressed by eq 33 is an analytic function whereas the hydrodynamic model (eq 13) is not. Analytic functions represent a small class of possible functions and so place a restriction on the type of function required to represent the phenomena. Expanding eq 33 for φ results in

$$\frac{D_g}{D_o} = 1 - k_2 r_s^2 \varphi - \frac{k_2 r_s^2}{2}\varphi^2 - \frac{k_2 r_s^2}{6}\varphi^3 \ldots \qquad (34)$$

For $\varphi < 0.10$, eq 34 reduces to just the first two terms, and so an analytic function is unnecessary. This result indicates that free volume theory cannot represent diffusion in hydrogels of low volume fraction. The hydrodynamic-scaling model does not pose this type of restriction and thus can represent diffusion in hydrogels of a wider polymer volume fraction range.

The finding that hydrodynamic phenomena are important comes in contradiction to the findings of a recent paper[19] which compared the predictions of the hydrodynamic model of Anderson and Quinn[49] and the predictions of free volume theory to the diffusion of solutes in polyacrylamide gels. On the basis of this comparison, it was concluded that hydrodynamic models do not describe solute diffusion well. However, the model of Anderson and Quinn is not a valid model for diffusion in hydrogels, and was not considered in this review, because it assumes that the hydrogel is a porous membrane where the pores are long, cylindrical, and connect both surfaces of the membrane. This depiction

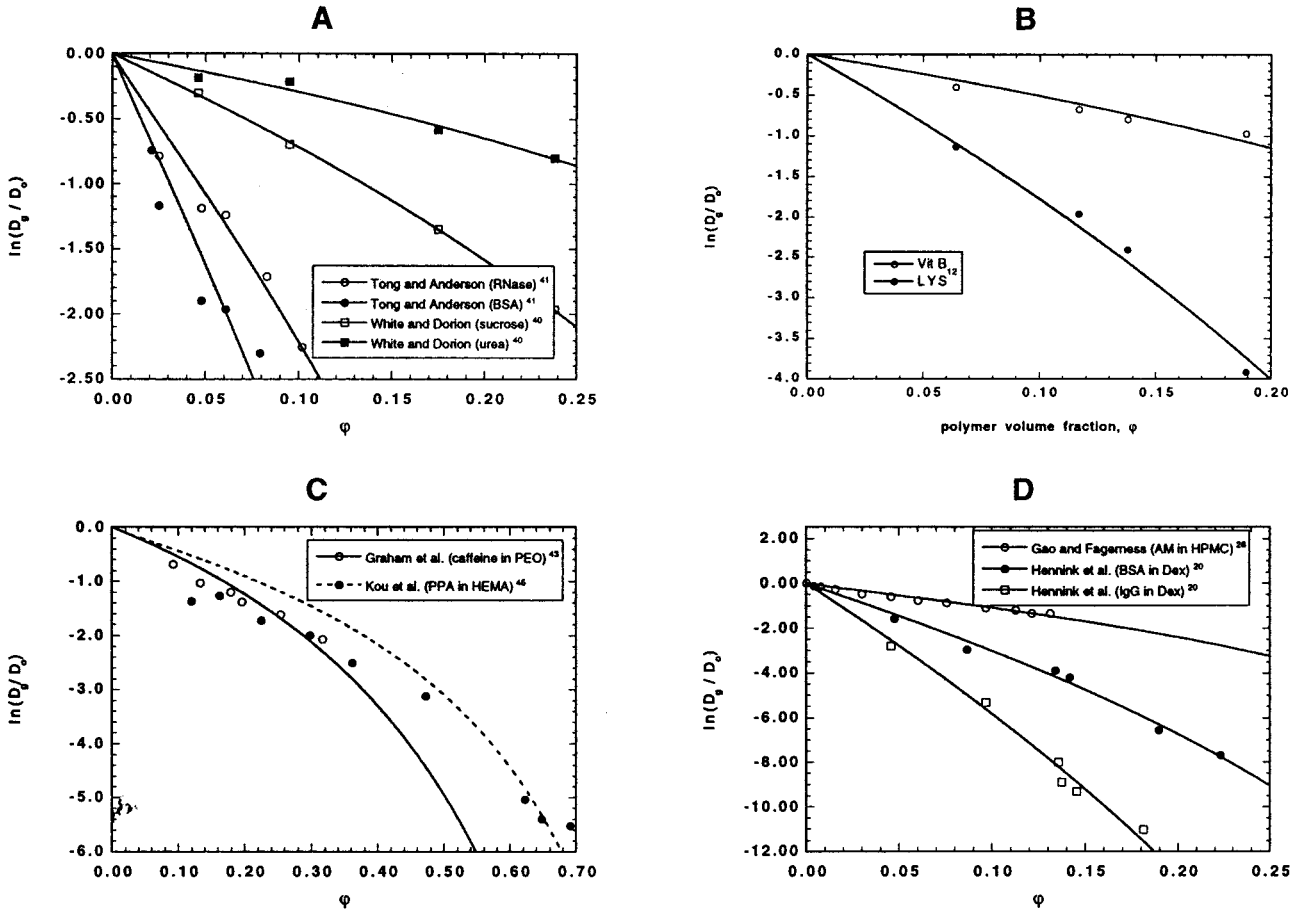

Figure 3. Application of free volume theory models to literature data showing the effect of polymer volume fraction on solute diffusivity within various homogeneous hydrogels: (A) polyacrylamide gels; (B) poly(vinyl alcohol) gels;[42] (C) poly(ethylene oxide) (PEO) and poly(hydroxyethyl methacrylate) gels (HEMA); (D) dextran (Dex) and hydroxypropyl methylcellulose (HPMC) gels. The lines represent regression results.

of hydrogel morphology is unrealistic, and so their conclusion that hydrodynamic effects are not a viable explanation for the observed decrease in solute diffusion is unwarranted.

Thus far, the hydrodynamic model has been applied only to data for which the range of solute size is relatively narrow. The model was therefore applied to literature data in which the solute size ranges from 3.8 to 36.3 Å (Figure 4). The regression results are displayed in Table 7.

From this rather limited data, it appears that the hydrodynamic model provides an adequate fit. Further support for the model comes from the result that the k_c parameters obtained for the Merrill et al. data[44] at two different polymer volume fractions are statistically identical. The k_c parameter reflects polymer−solvent interaction and thus would be expected to be constant for a given polymer−solvent system. However, the data in Figure 4, particularly that of Merrill et al., suggest some convex curvature that is not accounted for by the hydrodynamic model. Hence, the dependence of $\ln(D_g/D_o)$ on solute size seems to be at least a weak power function and not simply the linear dependence suggested by the hydrodynamic model. This dependence has also been noted by other researchers.[9,50] To verify this observation a study needs to be done to find the diffusivities of solutes of a wide size range using a well-characterized homogeneous hydrogel.

A few additional comments on the free volume model are warranted at this point, particularly because of its

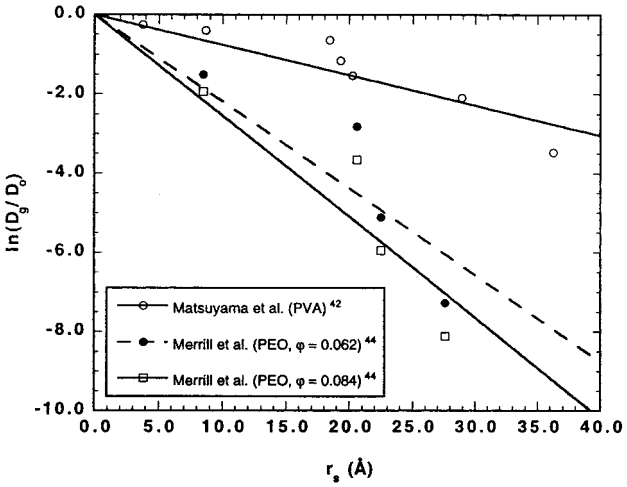

Figure 4. Regression results of the implementation of the Cukier hydrodynamic-scaling model[23] (eq 13) to literature data showing the effects of solute radius on diffusivity within homogeneous hydrogels. The lines represent the regression results.

popularity in the field of controlled drug delivery. Examination of the data in Table 6 indicates that k_2 is statistically relevant in all cases. What needs to be ascertained is whether the values for k_2 make sense physically. Comparing the fitted values obtained for cases where the polymer and solvent used were identical and the solvent varied shows that, in each case, the value of k_2 decreased as the solute size increased.

Table 7. Regression Results for Application of Obstruction Models to D_g/D_o versus Solute Radius Literature Data for Heterogeneous Hydrogels

	model											
	Johansson et al.[30]				Tsai and Streider[34]				Amsden[a,35]			
polymer (ref)	r_f fit (Å)	±SE	χ^2	R^2	r_f fit (Å)	±SE	χ^2	R^2	k_s fit (Å)	±SE	χ^2	R^2
alginate[35]	3.46	0.05	0.001	0.992	2.10	0.26	0.029	0.801	5.63	0.24	0.005	0.964
alginate[46]	7.31	0.46	0.013	0.974	5.13	0.50	0.019	0.962	13.02	1.05	0.020	0.960
alginate[58]	7.28	0.40	0.036	0.931	5.68	0.55	0.065	0.878	13.62	0.87	0.043	0.918
carageenan[9] ($\varphi = 0.005$)	2.66	0.08	0.001	0.964	2.38	0.04	0.001	0.992	6.56	0.25	0.001	0.951
carageenan[9] ($\varphi = 0.010$)	3.72	0.13	0.004	0.912	3.08	0.07	0.001	0.974	7.31	0.10	0.001	0.987

[a] Regression done using $r_f = 8.0$ Å. SE = standard error (95% confidence interval). χ^2 = sum of squares of the residuals. R = correlation coefficient.

The structural parameter k_2, as defined, is equal to $\gamma\pi\lambda/v_{f,w}$. The average free volume of bulk water, $v_{f,w}$, is constant for a given temperature, and so the effect of solute size cannot be explained by changes in its value. It would be unreasonable to expect that the overlap in free volume parameter, γ, would be a function of solute size and so it too can be discounted. What remains is the jump length, λ, of the solute molecule moving from one free volume to another. One would expect that the larger the molecule, the greater the length required in order for a successful translational jump to occur. Therefore, the result that k_2 actually decreases as solute size increases is in direct contradiction to the underlying theory.

Another fundamental weakness of the free volume approach is the use of eq 3 to describe the contributions of both the water and the polymer to the total free volume of the system. In order for this equation to be valid, the specific volume and molecular weights of the polymer jumping units and water must be equal.[11] At polymer concentrations near unity, these conditions may be approximated, depending on the polymer, but they cannot hold over a wide range of polymer volume fractions. The models derived to date based on free-volume theory are thus strictly valid *only* for polymer−diluent systems with large polymer volume fractions.[7] Despite this limitation, the theory has been applied to hydrogels of high water content.[11,13−16,20,42,51−53] The basis for this widepsread use of the free volume models is the generally linear relationship which typically results from a plot of $\ln(D_g/D_o)$ versus $\varphi/(1 - \varphi)$. However, the fact that such a functional dependence is predicted by the theory does not necessarily mean the theory is accurate. Other models, such as the obstruction models and hydrodynamic models derived for heterogeneous hydrogels, also predict a similar functional dependence and yet are derived using a completely inappropriate basis.

Finally, the Cohen and Turnbull free volume model of solute transport in simple liquids[10] is known to be an improper model of the mechanism involved.[54,55] The free volume model also cannot adequately explain solute diffusivity in situations where the solute molecule is larger than the solvent molecule, a situation commonly encountered in applications of hydrogels.[56,57] Since the free volume model fails to explain aqueous solution diffusivities, there is no reason to expect it to be extendable to hydrogels.

Heterogeneous Hydrogels. There are a relatively large number of mechanistic models which have been derived to describe solute diffusion in heterogeneous hydrogels (Table 1). It would therefore appear to be a lengthy task to determine which of these models is most applicable. However, the task can be reduced by examining the effect of solute size on diffusivity in a heterogeneous hydrogel system first. Figure 5 displays such a dependence for various solutes in calcium alginate. An examination of the experimentally observed relationship between solute radius and the diffusivity ratio D_g/D_o reveals that the diffusivity ratio displays a Gaussian dependence on solute radius, such as would be given by an $\exp(-r_s^2)$ function. This result immediately rules out the applicability of the Ogston et al. obstruction expression (eq 19) and the hydrodynamic models represented by eq 14. The remaining models were applied to the data shown in Figure 5 and other literature data for solute diffusion in both calcium alginate and κ-carageenan. The calcium alginate data reflects two different types of alginate, a high guluronic acid residue content[35] and a low guluronic acid residue content.[46,58] The high guluronic acid residue alginate has very stiff polymer chains, while the low guluronic acid residue alginate has more flexible chains.[59]

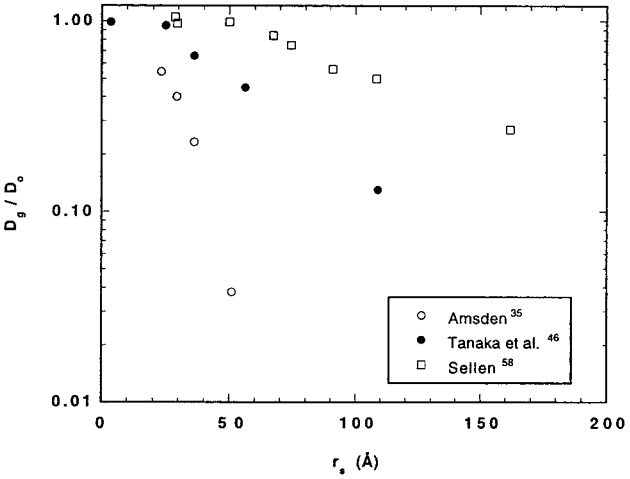

Figure 5. Literature data showing the effect of solute radius on diffusivity within heterogeneous (calcium alginate) hydrogels.

The remaining models, with the exception of the Amsden obstruction model, were fit to the literature data by considering the polymer radius, r_f, to be an adjustable parameter. The values returned by the regression procedure were then compared to available literature data. For calcium alginate, which gels through an electrostatic attraction for two guluronic acid residues on opposing polymer chains for the divalent calcium ion, the polymer chain radius was estimated to be 4.2 Å. This value is a number average of the radius of the unreacted residues which make up about $^2/_3$ of the hydrogel chains (3.6 Å) and that of the radius of two electrostatically bonded guluronic acid residues (5.4 Å).[60] To account for the strongly bonded water molecules which hydrate the polymer, to this average

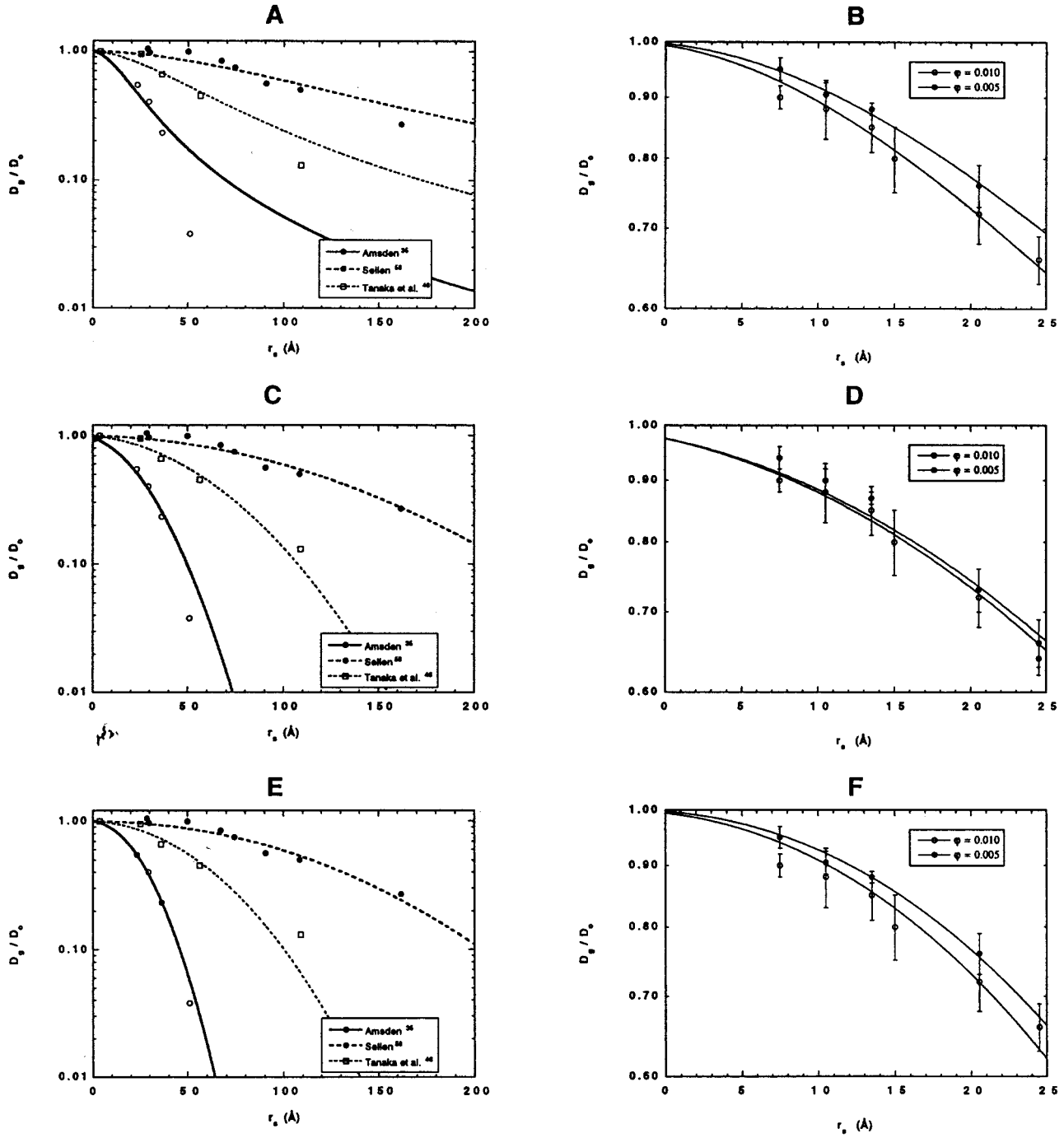

Figure 6. Implementation of obstruction models to literature data showing the relationship between solute radius and solute diffusivity within heterogeneous hydrogels: (A) model of Tsai and Streider[34] (eq 23) versus solute diffusion in calcium alginate gels; (B) model of Tsai and Streider[34] (eq 23) versus solute diffusion in κ-carageenan; (C) model of Amsden[35] (eq 25) versus solute diffusion in calcium alginate gels; (D) model of Amsden[35] (eq 25) versus solute diffusion in κ-carageenan; (E) model of Johansson et al.[30] (eq 22) versus solute diffusion in calcium alginate gels; (F) model of Johansson et al.[30] (eq 22) versus solute diffusion in κ-carageenan.

chain radius can be added the diameter of a water molecule (3.8 Å). This results in an effective polymer radius of 8.0 Å. For κ-carageenan, which in the gel state has some of its chains in an aggregated double helix (radius 5.1 Å), the average polymer radius used was 4.2 Å. This value represents the situation where half of the polymer chains are in the aggregated state.[30] Again, the hydrated polymer chain radius would be 8.0 Å. The regression results are illustrated in Figures 6 and 7 and listed in Tables 7 and 8.

Examination of the figures shows that the obstruction models provided the best fits to the data (Figure 6). All the obstruction models are consistent with the observed Gaussian trend in the data. This result indicates that the obstruction models have potential for wide range application. The polymer radius values obtained (Table 7) were reasonable and consistent for both the Johansson et al. expression[30] and the Tsai and Streider model,[34] but were unrealistically small for the Tsai and Streider model applied to the high guluronic acid alginate and the carageenan hydrogels. This result, coupled with the fact that it produced the greatest χ^2 values, implies that this model is the weakest of the obstruction models. The Johansson et al. expression

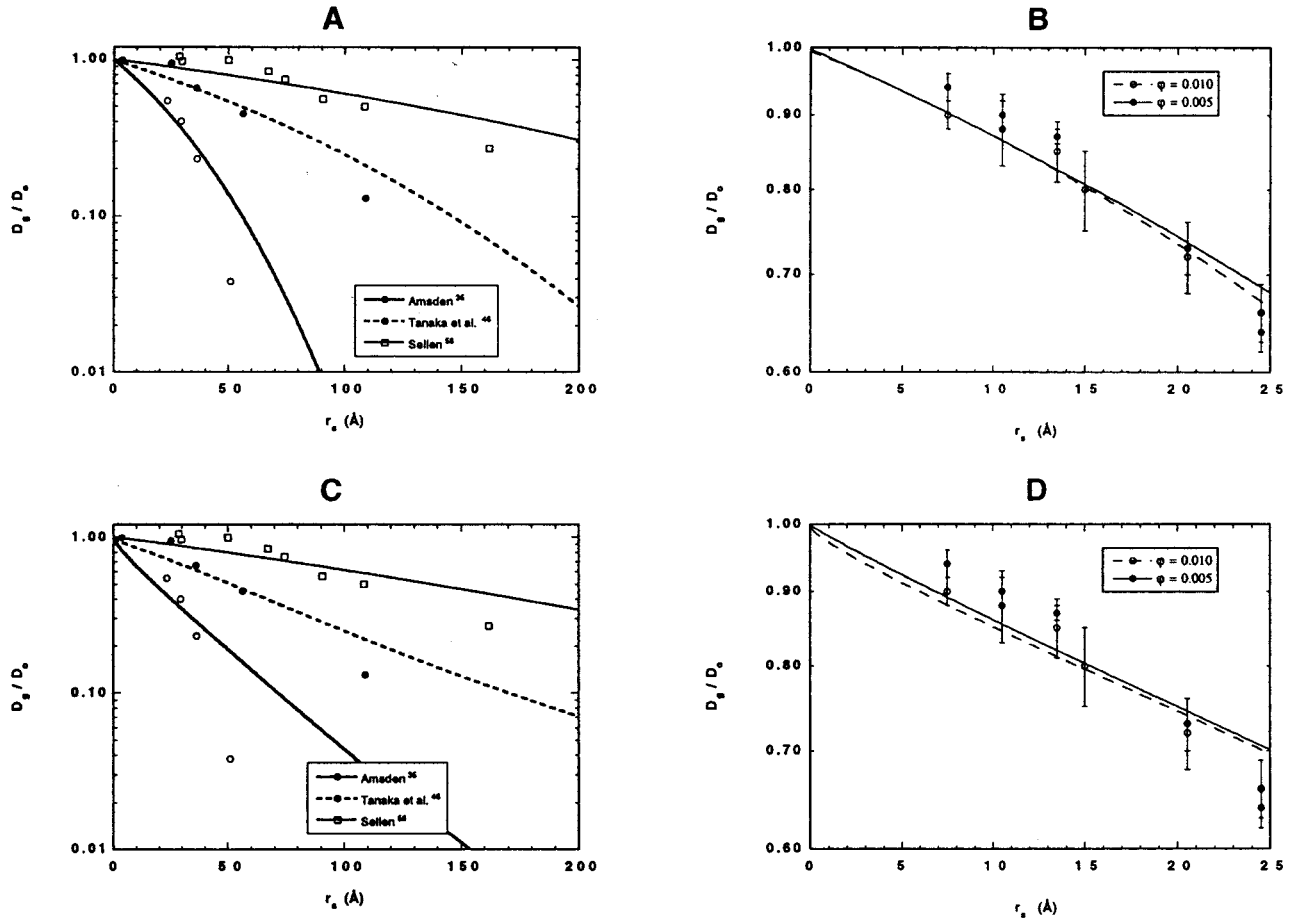

Figure 7. Implementation of combined hydrodynamic and obstruction models to literature data of the relationship between solute radius and solute diffusivity within heterogeneous hydrogels: (A) model of Johnson et al.[38] (eq 27) versus solute diffusion in calcium alginate gels; (B) model of Johnson et al.[38] (eq 27) versus solute diffusion in κ-carageenan gels (data from Johansson et al.[9]); (C) model of Clague and Phillips[39] (eq 31) versus solute diffusion in calcium alginate gels; (D) model of Clague and Phillips[39] (eq 31) versus solute diffusion in κ-carageenan gels (data from Johansson et al.[9]).

Table 8. Regression Results for Application of Combined Hydrodynamic and Obstruction Models to D_g/D_o versus Solute Radius Literature Data for Heterogeneous Hydrogels

	model[a]							
	Johnson et al.[38]				Clague and Phillips[39]			
polymer (ref)	r_f fit (Å)	±SE	χ^2	R^2	r_f fit (Å)	±SE	χ^2	R^2
alginate[35]	5.44	0.50	0.018	0.872	4.09	0.58	0.032	0.780
alginate[46]	13.95	1.81	0.033	0.937	11.15	2.15	0.055	0.893
alginate[58]	14.87	2.35	0.121	0.774	13.72	2.20	0.120	0.774
carageenan[9] ($\varphi = 0.005$)	8.00	0.66	0.002	0.912	7.21	0.69	0.002	0.891
carageenan[9] ($\varphi = 0.010$)	9.56	0.39	0.002	0.956	8.73	0.60	0.004	0.904

[a] SE = standard error (95% confidence interval). χ^2 = sum of squares of the residuals. R = correlation coefficient.

produced a smaller polymer radius estimate for the high guluronic acid content alginate hydrogel than for the low guluronic acid residue hydrogels. This is a reflection of the assumed polymer chain stiffness.

The results from the regression of the Johnson et al.[38] and the Clague and Phillips[39] combined hydrodynamic and obstruction models to the literature data can be seen in Figure 7 and are listed in Table 8. The χ^2 values for each model are very close, with the Johnson et al. expression providing slightly lower values. Examination of Table 8 shows that the obtained fitted values for r_f for diffusion in the same polymer (i.e., for the Tanaka et al.[46] and Sellen[58] alginates and the κ-carageenan of Johansson et al.[9]) were consistent. The r_f values obtained from the regression to the calcium alginate data of Tanaka et al.[46] and Sellen[58] appear somewhat high but can be rationalized by the possibility of the electrostatic interaction of more than 2 alginate chains. Also, neither model matches the observed Gaussian trend in the data. This lack of fit for the lower r_s values indicates that these models are perhaps best suited for situations where the solute size approaches the average opening size in the hydrogel. Therefore, these models appear to be applicable only to the diffusion of large molecules (r_s greater than approximately 20 Å) in very stiff hydrogels of relatively high polymer fraction.

On the basis of these results, the models of Johansson et al. and Amsden were then applied to literature data describing the effect of polymer volume fraction on solute diffusivity for two hydrogels, calcium alginate and agarose (Figure 8). The regression results are listed in Table 9. Both the models provide good agreement with the data, as indicated by the low χ^2 values returned.

Table 9. Regression Results for Application of Obstruction Models to D_g/D_0 versus Polymer Volume Fraction Literature Data for Heterogeneous Hydrogels

		model[a]							
		Johansson et al.[30]				Amsden[b,35]			
polymer (ref)	solute (radius, Å)	r_f fit (Å)	±SE	χ^2	R^2	k_s fit (Å)	±SE	χ^2	R^2
alginate[35]	BSA (36.3)	3.48	0.05	0.018	0.951	5.73	0.11	0.018	0.940
agarose[47]	MYO (18.9)	6.02	0.23	0.005	0.960	11.63	1.39	0.030	0.776
agarose[47]	BSA (36.3)	7.9	0.50	0.033	0.753	12.45	0.31	0.003	0.978
agarose[47]	$C_{12}E_8$ micelle (27.4)	6.26	0.50	0.023	0.284	10.19	0.36	0.003	0.939
agarose[47]	$C_{12}E_{10}$ micelle (31.7)	6.24	0.31	0.010	0.876	9.72	0.64	0.009	0.908

[a] SE = standard error (95% confidence interval). χ^2 = sum of squares of the residuals. R = correlation coefficient. [b] Regression done using $r_f = 8.0$ Å.

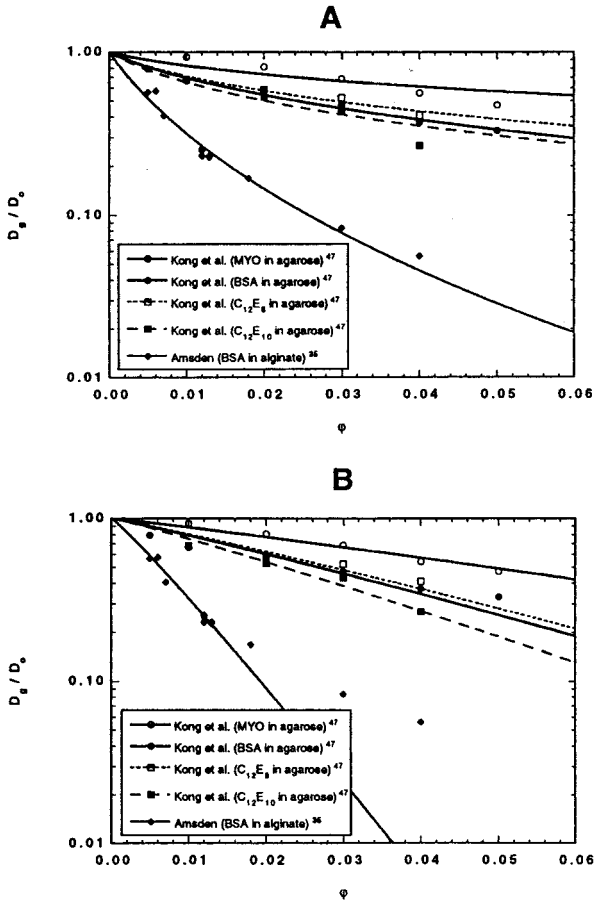

Figure 8. Application of obstruction models to data displaying the dependence of solute diffusivity on polymer volume fraction in heterogeneous hydrogels: (A) model of Amsden[35] (eq 25); (B) model of Johansson et al.[30] (eq 22).

The Johansson et al. expression again produces r_f estimates which are consistent for the agarose data. However, the estimated values of about 6 Å are much lower than the average value given in the literature. Agarose gels by forming physically cross-linked fiber bundles of α-helical chains. As reported by Johnson et al.[38] the distribution of the sizes of these bundles is bimodal, with 87% having a radius of 15 Å and 13% having a radius of 45 Å. Thus, the average polymer chain radius for agarose is taken to be 19 Å. This value was used in applying the Amsden model. The k_s values which were obtained for agarose were very consistent, as predicted by the model.

On the basis of these comparisons, it appears that the obstruction model of Amsden provides the most consistent explanation for solute diffusion in heterogeneous hydrogels. However, the model contains a parameter which is as yet undefined and must be for the model to become completely verifiable.

Conclusions

Models for solute diffusion in hydrogels can be divided into those applicable to hydrogels composed of flexible polymer chains (i.e., homogeneous hydrogels) and those composed of rigid polymer chains (i.e. heterogeneous hydrogels). Of those used to describe solute diffusion in homogeneous hydrogels, the model most consistent with the data and with its physical parameters was the hydrodynamic scaling model of Cukier.[23] This model however, suffers from containing an undefined polymer−solvent interaction parameter. The free volume models, which are generally invoked, are typically applied to situations for which the assumptions made in their derivation are not valid and are not physically consistent. Of those models derived to explain solute diffusion in heterogeneous hydrogels, the obstruction models were best at providing agreement to the experimental data taken from the literature. The combined hydrodynamic and obstruction effect models appeared to be limited in applicability to situations of large solute diffusion in relatively high polymer fraction hydrogels. In terms of accounting for variation due to polymer chain flexibility, the best obstruction model was that of Amsden. Like the Cukier model, which is also based on scaling concepts, this model contains an as yet undefined polymer−solvent interaction parameter. For these models to be considered truly predictive, a means of calculating these parameters must be derived.

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