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An assessment of the ability of the obstruction-scaling model to estimate solute diffusion coefficients in hydrogels

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ABSTRACT

The ability to estimate the diffusion coefficient of a solute within hydrogels has important application in the design and analysis of hydrogels used in drug delivery, tissue engineering, and regenerative medicine. A number of mathematical models have been derived for this purpose; however, they often rely on fitted parameters and so have limited predictive capability. Herein we assess the ability of the obstruction-scaling model to provide reasonable estimates of solute diffusion coefficients within hydrogels, as well as the assumption that a hydrogel can be represented as an entangled polymer solution of an equivalent concentration. Fluorescein isothiocyanate dextran solutes were loaded into sodium alginate solutions as well as hydrogels of different polymer volume fractions formed from photoinitiated cross-linking of methacrylate sodium alginate. The tracer diffusion coefficients of these solutes were measured using fluorescence recovery after photobleaching (FRAP). The measured diffusion coefficients were then compared to the values predicted by the obstruction-scaling model. The model predictions were within ±15% of the measured values, suggesting that the model can provide useful estimates of solute diffusion coefficients within hydrogels and solutions. Moreover, solutes diffusing in both sodium alginate solutions and hydrogels were demonstrated to experience the same degree of solute mobility restriction given the same effective polymer concentration, supporting the assumption that a hydrogel can be represented as an entangled polymer solution of equivalent concentration.

1. Introduction

Solute diffusion within a hydrogel is an important phenomenon in a number of research fields, including pharmaceutics and regenerative medicine. For the rational design of controlled release devices [1,2], as well as for the assessment of drug distribution within tissue or intracellularly following release or upon administration [3–5] and for the survival and function of encapsulated cells implanted as artificial organs [6,7] or for regenerative purposes [8,9], it would be highly useful to have a mathematical expression that provides reliable estimates of solute diffusion coefficients within hydrogels and that relies solely on physical property measurements of the solute and the polymer. A number of mathematical expressions have been derived for this purpose [10,11], yet no model is capable of providing a priori predictions of the solute diffusion coefficient without relying on fitted parameters. A mathematical expression based on obstructive effects has been shown to predict the influence of solute size as well as polymer properties, such as chain flexibility, degree of ionization, and chain radius, on the solute diffusion coefficient within both nonionic and charged hydrogels [12–14]. Thus, it was posited that the model could be adapted to provide a priori predictions for solute diffusion coefficients within hydrogels.

The model is based on the premise that solute diffusion is controlled by the ability of the solute to find a series of openings between the polymer chains large enough to allow its passage, a mechanism initially proposed by Yasuda et al. [15]. The diffusion coefficient of the solute within the swollen hydrogel, D, is given by,

$$D = D_o \exp\left[-\pi\left(\frac{R + r_f}{\xi + 2r_f}\right)^2\right] \quad (1)$$

in which D_o is the diffusion coefficient in the aqueous medium in the absence of the polymer, R is the radius of the solute probe, r_f is the polymer chain radius, and ξ is the correlation length, which represents the average mesh size of the network [16].

The development of Eq. (1) was based on a number of assumptions, including: 1) the solute is a hard sphere, 2) there are negligible intermolecular forces of attraction between the solute and the polymer chains, 3) the polymer chains act only as physical obstacles in the diffusive process, 4) the polymer chains are immobile relative to the mobility of the solute over the time scale of the diffusion process, and 5) the distribution of openings between polymer chains can be approximated by a random distribution of straight fibers, described by the Ogston expression [17]. These assumptions restrict the applicability of the model to situations that satisfy these conditions. By the first assumption, the model is not applicable to situations where the solute can reptate. The

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second assumption requires that any potential interaction forces between the solute and the polymer are weak. That the polymer chains are immobile with respect to the movement of the solute molecule has been previously validated for solute diffusion in polymer solutions by considering the relative time scales for solute translation versus polymer chain segment movement over an equivalent distance [18]. Finally, in order to derive the model, a means of calculating the average mesh size necessitated the adoption of an idealized geometry of the polymer chains within the network. The Ogston expression for the distribution of spherical spaces between a random arrangement of straight chains was used as a first approximation, despite the fact that the polymer chains in hydrogels are semi-flexible. The use of this expression yielded very good agreement between the obstruction-scaling model and available data [12], suggesting its potential for representing the spherical spaces between semi-flexible polymer chains. Furthermore, it has been demonstrated recently through simulations of solute partitioning into hydrogels composed of chains of varying chain stiffness, that the Ogston model of the distribution of spherical spaces between polymer chains is applicable to cross-linked polymer networks composed of flexible, semi-flexible, and stiff chains [19].

To use Eq. (1) requires values for the solute radius, the polymer chain radius, and the correlation length. In this study nonionic fluorescein isothiocyanate labeled dextrans were used to ensure that there were negligible forces of interaction between the diffusing solute and the alginate. Dextran is a random coil in solution, and so the appropriate radius to use to assess its restricted mobility within a polymer hydrogel or aqueous solution is its radius of gyration. The chain radius can be calculated from the polymer specific volume by assuming that each monomer can be approximated as a cylinder (vide infra). What remains is a means of calculating the correlation length of the network.

It is assumed that the correlation length of a hydrogel is the same as that of a solution of uncrosslinked linear chains of the same polymer at an equivalent concentration. For polymer solutions, the scaling relationship proposed by De Gennes for concentrations greater than the overlap concentration can be used to estimate the correlation length [16] as,

$$\xi = R_g\left(c^*/c\right)^{\nu}. \tag{2}$$

In Eq. (2), c is the polymer solution concentration, c* is the concentration at which the polymer chains begin to overlap in solution, R_g is the radius of gyration of the polymer, and ν is a scaling coefficient, which has a theoretical value of 0.75 for a good solvent, 1 for a theta solvent, and 0.5 for a marginal solvent [20,21]. Combining Eqs. (1) and (2) yields,

$$D = D_o \exp\left[-\pi\left(\frac{R + r_f}{R_g\left(c^*/c\right)^{\nu} + 2r_f}\right)^2\right]. \tag{3}$$

The polymer solution overlap concentration can be calculated from [22],

$$c^* = \frac{3M}{4\pi N_A R_g^3} \tag{4}$$

in which M is the weight average molecular weight of the polymer, and N_A is Avogadro's constant [16].

Polymer concentration within hydrogels is usually expressed in terms of volume fraction, ϕ, in which case Eq. (2) becomes,

$$\xi = R_g\left(\phi^*/\phi\right)^{\nu}. \tag{5}$$

The solute diffusion coefficient within the hydrogel expression then becomes,

$$D = D_o \exp\left[-\pi\left(\frac{R + r_f}{R_g\left(\phi^*/\phi\right)^{\nu} + 2r_f}\right)^2\right] \tag{6}$$

in which $\phi^* = \nu c^*$ and ν is the specific volume of the polymer.

The objective of this study was to assess the ability of Eq. (6) to provide accurate predictions of the diffusion coefficient of a solute in a hydrogel. In the process, the validity of the assumption that the correlation length of a polymer solution is the same as that of the same polymer in a gel state at an equivalent concentration would also be determined. Sodium alginate was used to prepare hydrogels for this study. Sodium alginate was chosen for a number of reasons. It is widely investigated as a drug delivery and cell bioencapsulation material [23], its physical properties are well characterized, it can be used as an analog for solute diffusion within the extracellular matrix due to its compositional similarity to many extracellular matrix polysaccharides that are also negatively charged [24], and it was used previously for testing the model against diffusion in polymer solutions [18], thereby providing a means of direct comparisons. Alginate hydrogels are typically formed through the ionotropic interaction between the guluronate monomer blocks with divalent cations such as calcium [25]. However, hydrogels formed in this fashion would deviate significantly from the assumed hydrogel structure of an entangled polymer solution. To form hydrogels with only short covalent cross-link points between polymer chains, the sodium alginate was methacrylated and then cross-linked using photoinitated free radical polymerization. The tracer diffusion coefficients of fluorescently labeled dextrans (4, 10, 20 kDa) within alginate hydrogels of varying alginate volume fraction were measured using fluorescence recovery after photobleaching (FRAP) and then compared against the values predicted by Eq. (6).

2. Materials and methods

Unless otherwise stated, all materials were used as received.

2.1. Sodium alginate methacrylation

Methacrylated alginate (MALG) was prepared by reacting sodium alginate with 2-aminoethyl methacrylate, as described by Jeon et al. [26] Sodium alginate, isolated from *Laminaria hyperborea* stipe (Protanal LF 10/60) was obtained from FMC Biopolymer, Drammen, Norway. To prepare MALG, 4.0 g sodium alginate was dissolved in 0.2 L deionized water (Millipore Milli-Q Plus, 18 mΩ cm) over the course of a few hours with periodic stirring by vortex. The resulting solution was diluted with a morpholine buffer to prepare a 0.4 L mixture comprised of 1% sodium alginate (w/v), 0.5 M NaCl (Fisher Scientific), and 50 mM 2-morpholinoethanesulfonic acid (MES, Fisher) at pH 6.5. To activate the carboxyl moieties on the native alginate, 1.06 g N-hydroxysuccinimide (NHS, Acros Organics) and 3.50 g N-(3-dimethylaminopropyl)-N′-ethylcarbodiimide hydrochloride (EDC, Acros Organics) were dissolved in the sodium alginate solution; the activation reaction was conducted under constant agitation for 5 min at pH 6.5. After 5 min, 1.52 g 2-aminoethyl methacrylate hydrochloride (AEMA, Polysciences) and 50 ppm hydroquinone monomethyl ether (MEHQ, Sigma Aldrich) were added and the reaction was maintained at the preceding activation conditions for an additional 24 h in the absence of light. The product (0.4 L) was admixed with a phosphate buffer to prepare a 0.6 L solution of 0.5 M sodium dihydrogen phosphate (Sigma Aldrich) that was left stirring for 24 h at pH 5.0 in the absence of light. The resulting mixture was purified by dialysis (MWCO: 3500, Fisherbrand) against 4.0 L deionized water for 4 days (medium replaced at 2, 4, 8, 24, 48, 72, and 96 h), vacuum filtered (Whatman 42, Nalgene