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A microfluidic method to measure small molecule diffusion in hydrogels

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ABSTRACT

Drug release from a fluid-contacting biomaterial is simulated using a microfluidic device with a channel defined by solute-loaded hydrogel; as water is pumped through the channel, solute transfers from the hydrogel into the water. Optical analysis of in-situ hydrogels, characterization of the microfluidic device effluent, and NMR methods were used to find diffusion coefficients of several dyes (model drugs) in poly(ethylene glycol) diacrylate (PEG-DA) hydrogels. Diffusion coefficients for methylene blue and sulforhodamine 101 in PEG-DA calculated using the three methods are in good agreement; both dyes are mobile in the hydrogel and elute from the hydrogel at the aqueous channel interface. However, the dye acid blue 22 deviates from typical diffusion behavior and does not release as expected from the hydrogel. Importantly, only the microfluidic method is capable of detecting this behavior.

Characterizing solute diffusion with a combination of NMR, optical and effluent methods offer greater insight into molecular diffusion in hydrogels than employing each technique individually. The NMR method made precise measurements for solute diffusion in all cases. The microfluidic optical method was effective for visualizing diffusion of the optically active solutes. The optical and effluent methods show potential to be used to screen solutes to determine if they elute from a hydrogel in contact with flowing fluid. Our data suggest that when designing a drug delivery device, analyzing the diffusion from the molecular level to the device level is important to establish a complete picture of drug elution, and microfluidic methods to study such diffusion can play a key role.

1. Introduction

Hydrogels are crosslinked, water-swollen, hydrophilic polymers [1]. Entanglements and intra-chain chemical linkages prevent dissolution of polymer chains as the hydrogel swells in water [2,3]. Hydrogels have several favorable properties that make them attractive as biomaterials for in vivo use [4]. Many hydrogels, both physically and chemically crosslinked, have already been established for blood-contacting applications including poly(vinyl alcohol), poly-acrylamides, and poly(ethylene glycol) (PEG). Hydrogels made from PEG are non-toxic, non-immunogenic, prevent protein fouling and have been approved by the Food and Drug Administration (FDA) for human intravenous, oral, and dermal applications [5]. This approval has led to the widespread use of PEG in pharmaceutical and biomaterial applications such as the surface modification of implants and biological grafts [6–9]. Proteins and therapeutic drugs can be immobilized in a PEG hydrogel network; the hydrogel shields the entrapped molecules from enzymes to increase circulation time compared to free injection [10,11]. Currently, there are numerous research programs studying PEG and its hydrogels for tissue scaffolds and controlled drug delivery devices [7,8,11–20]. Part of the reason for this research is to help understand the complex interplay between the structure and property relationships of the hydrogel and optimize hydrogel properties for a particular application and local environment. One property that is critical for device success in both tissue engineering and controlled drug delivery is the diffusion of molecules within a hydrogel.

Diffusion of molecules in a hydrogel depends on the cross-link density of the polymer network, the hydrodynamic radii of the diffusing molecules, and the interactions between the diffusing molecules and the hydrogel [21–31]. Understanding the interplay between these parameters is critical in developing an understanding of diffusive behavior. The simple network model fails to accurately represent the complexity of hydrogel matrices. Once formed, the polymer network is a disordered arrangement of polymer chains consisting of multifunctional junctions, loops, physical entanglements, and unreacted end groups [22,30,31]. The appropriate design of hydrogels for the delivery of therapeutic agents in biological-fluid contacting applications requires an understanding of how the agent will elute from the hydrogel over time in different mass transfer environments. With improved understanding of the diffusive behavior in hydrogels, these materials could be better tailored for specific applications, and devices could be designed to provide a desired release profile for entrapped therapeutic agents.

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The diffusion of molecules in a hydrogel system is typically a transient process, with concentration variations in both position and time. Obtaining data for most diffusive processes is difficult as concentration must be monitored non-invasively for long times and short distances. Many experimental methods aimed at measuring diffusion coefficients for hydrogels involve transferring hydrogel slabs into fresh solutions and monitoring concentration changes in the solution with time. For example, Weber et al. [7] measured diffusion coefficients of various proteins in disk-shaped poly(ethylene glycol) dimethacrylate (PEG-DM) (M_n = 2000 g/mol to 10,000 g/mol) hydrogels by fitting protein-release data to a Fickian diffusion model. Release data was obtained by transferring gels into high concentration glucose solutions at time intervals over the span of 1 h and assaying the protein content of the solution. Diffusion coefficients were found to be on the order of 10^{-6} cm^2/s to 10^{-7} cm^2/s [7]. Khoury et al. [6] injected a protein solution into a hydrogel, allowed the protein–hydrogel system to reach steady state, and used Fluorescence recovery after photobleaching (FRAP) to observe dynamic concentration profiles. Their experiments measured diffusion coefficients ranging from 10^{-6} cm^2/s to 10^{-10} cm^2/s [6].

The estimation of diffusion coefficients can be improved using digital microscopy. Ray et al. used optical methods to quantify diffusion between corn syrup and water by monitoring the interface between the two liquids with a digital camera [32]. Intensity versus position data were extracted from the images and fit to a complementary error function model to determine a diffusion coefficient [32]. Several studies have used optical techniques paired with microfluidic devices to obtain diffusional information for solutes in solution. Culbertson et al. [33] prepared t-junction microfluidic devices and used four different detection methods (static imaging method, stopped flow, varying the applied potential and varying the detection length to determine the diffusion coefficient of rhodamine 6G and several other dyes in aqueous buffer/methanol mixtures along the length of the device. Costin et al. [34] used the refractive index gradient between adjacent laminar flows at two different positions along the flow direction in a microchannel to determine a concentration gradient and calculate diffusion coefficients for PEGs of different molecular weight, sucrose, and lactose solutions. Hatch et al. [35] and Cuchiara et al. [36] measured diffusion of dye into hydrogels (uptake) in a microfluidic device using digital microscopy and fluorescence microscopy images. They used line profiles from the images to extract a diffusion coefficient by fitting the profiles to the one-dimensional, unsteady-state diffusion equation. Cuchiara et al. found diffusion coefficients for different sized solutes diffusing into three different PEG diacrylate hydrogel concentrations and noted the impact of solute diffusivity on seeded cells' viability and metabolic activity when using hydrogels as tissue engineering scaffolds.

The method developed in Cuchiara's paper provides a foundation for this paper. Importantly, their work only considered the uptake diffusional properties of the hydrogels. However, device performance for many applications including drug delivery is impacted by elution from the hydrogel. In this paper, we describe a microfluidic technique that allows the direct, optical measurement of concentration profiles resulting from uptake and elution of a dye molecule to estimate diffusion coefficients of the dye in poly(ethylene glycol) diacrylate (PEG-DA) hydrogels. We also use measurements of eluted dye mass and NMR pulsed field-gradient (PFG) methods to compare and evaluate the diffusion coefficients determined by the optical method. By applying three different methods to measure diffusion coefficients, it is possible to assess both the nature of the diffusion of molecules in a hydrogel and the accuracy of the methods.

1.1. Diffusion theory/background

In this section, we present the basis of expressions needed to extract diffusion coefficients from the various experimental methods that involved the use of microfluidic devices (uptake, elution). The details of the NMR measurements will be summarized in the Methods section.

1.1.1. Uptake measurements

In these experiments, dye from a fluid flowing in the microfluidic channel diffuses into a hydrogel that is initially free of the dye. We assume that transport of material by flow in the channel direction is much greater than that in the gel so that the primary direction of transport in the gel is in the direction perpendicular to the channel flow.

At $t = 0$ the concentration of the dye in the microfluidic channel is increased to C_o. Assuming a constant diffusivity, the transport of dye in the gel can be modeled by the diffusion equation,

$$\frac{\partial C}{\partial t} = D\frac{\partial^2 C}{\partial x^2} \tag{1}$$

with the initial and boundary conditions

$$C(0,x) = 0$$

$$C(t,0) = C_o$$

$$C(t,x\to\infty) = 0$$

The first boundary condition is consistent with the assumption that the rate of mass-transfer external to the gel (by convection) is much greater than the rate of mass-transfer in the gel (by diffusion). The second boundary condition is used because the time-scale for measurements is such that the effects of the far boundary of the gel (a no-flux boundary) are unimportant in the development of the concentration profile (i.e., the sample is assumed to have an infinite extent).

The solution to this model is

$$C(t,x) = C_o\left(1\text{-erf}\left(\frac{x}{\sqrt{4Dt}}\right)\right) = C_o\text{erfc}\left(\frac{x}{\sqrt{4Dt}}\right) \tag{2}$$

which is suitable for comparison to optical imaging measurements of $C(t, x)$.

1.1.2. Elution measurements

The physical set-up for the elution measurements is similar to the uptake measurements except that the hydrogel is initially loaded with the dye and the fluid in the microfluidic channel is free of dye. Hence, the diffusion equation holds once again but with the initial and boundary conditions

$$C(0,x) = C_0$$

$$C(t,0) = 0$$

$$C(t,x\to\infty) = C_0$$

The solution to this model can be obtained by manipulating the expression from Eq. (2)

$$C(t,x) = C_o\text{erf}\left(\frac{x}{\sqrt{4Dt}}\right) \tag{3}$$

As with the uptake measurements, this expression is suitable for comparison to images of dye uptake.

The concentration of dye in the device effluent was also measured. Using the fact that the dye mass flow rate out of the hydrogel along the fluid interface matches the rate of mass flow of dye measured at the device outlet, we have

$$\frac{dM}{dt} = \left(-D\frac{\partial C}{\partial x}\right)\Big|_{x=0} A \tag{4}$$