Solute Partitioning and Diffusion in Hydrogels: Fundamentals of Drug and Comfort-Agent Delivery

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Abstract

Hydrogels are biocompatible and, therefore, extensively applied, for example, in pharmaceutics, biomedicine, tissue engineering, and artificial organ scaffolds. Hydrogels also have application in a wide variety of bioseparation and biosensing processes. We focus specifically on hydroxyethyl-methacrylate (HEMA) /methacrylic acid (MAA) copolymer gels used in soft contact lenses to deliver drugs and comfort/wetting agents to the eye. In all applications, it is important to understand how aqueous solutes of varying size, molecular weight, charge, hydrophobicity, and configuration partition into and out of hydrogels which themselves are of differing water content, crosslink density (i.e., mesh size) and matrix charge density.

Two-photon confocal microscopy and back extraction with UV/Vis-absorption spectrophotometry quantify equilibrium partition coefficients, k, and diffusion coefficients, D, for prototypical drugs, polymers, polyelectrolytes, and proteins transporting in HEMA gels with varying MAA contents.

To express deviation from ideal partitioning, we define an enhancement or exclusion factor, $E \equiv k/\phi_1$, where ϕ_1 is hydrogel water volume fraction. For solute i, E_i is derived as a product of individual enhancement factors for size exclusion (E_i^{ex}), electrostatic interaction (E_i^{el}), and specific adsorption (E_i^{ad}): $E_i \equiv E_i^{ex}\, E_i^{el}\, E_i^{ad}$. To obtain the individual enhancement factors, we employ an extended Ogston mesh-size distribution for E_i^{ex}; Donnan equilibrium for E_i^{el}; and Henry's law characterizing specific adsorption to the polymer chains for E_i^{ad}. Gels mesh sizes are obtained from measured linear oscillatory rheology; solute sizes are determined from measured bulk restricted-cell diffusion coefficients, D_o. Enhancement factors for various solutes vary

between 10^{-3} and 10^{2} depending on gel charge and mesh size, and on solute size, charge, and chemistry. Predicted enhancement factors are in excellent agreement with experiment using no adjustable parameters.

From transient two-photon confocal-microscopy concentration profiles, and back-extraction histories with UV/Vis-absorption spectrophotometry, we measure the corresponding solute diffusivities in the gels. For large molecular-weight dextran polymers, whose molecular size is larger than the average gel mesh size (i.e., they are significantly size excluded with $E_i^{ex} << 1$), the ratio D / D_o is near 10^{-1} indicating transport only through interconnected large mesh domains. We invent large-pore effective medium (LPEM) theory to account for solute size, hydrodynamic drag, and distribution of mesh sizes available for transport in the polymer network. For solutes that interact strongly with the polymer strands (i.e., those solutes with $E_i^{ad} >> 1$), D / D_o is reduced drastically due to specific association with the gel polymer network. Extension of LPEM to this case includes Henry-law constants to account for specific solute adsorption onto the polymer backbone. Again, using no adjustable parameters, diffusivities predicted from the proposed large-pore effective-medium model demonstrate good agreement with experiment. Our effort provides a first step towards a priori design of hydrogels for uptake and delivery of specific water-soluble species by altering gel mesh size, polymer chemistry, and polymer backbone charge.