Equilibrium Partitioning and Covalent Binding of Flexible Polymers in Gelss

by

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Submitted to the Department of Chemical Engineering
on February 9, 2001 in Partial Fulfillment of
the Requirements for the Degree of
Doctor of Philosophy

Abstract

The ultrafiltration of blood across the walls of renal glomerular capillaries is the first step in urine formation. Progressive damage to those capillaries is a feature common to all major forms of chronic kidney disease. The glomerular basement membrane (GMB), consisting primarily of collagen IV, laminin, and heparan sulfate proteoglycan, is one of the structures which affect the permeability properties of these walls. The long-term goal of this research is to explore the connection between GMB structure and function by discovering which components primarily determine GMB permeability properties. Previous studies suggested that the GMB behaves as a composite gel containing a mixture of coarse and fine polymer fibers, the coarse fibers corresponding to collagen IV and laminin and the fine fibers being glycosaminoglycans such as heparan sulfate. The objective of the research described here was to explore the hypothesis by synthesizing composites that might mimic the physical properties of GBM; particularly the water (Darcy) permeability. Composite gels were synthesized using agarose (similar to collagen IV in size, network properties, and charge) and dextran (similar in heparan sulfate in radius). The agarose and dextran are covalently linked together by irradiation with an electron beam. Darcy permeabilities of composite gels were measured as functions of pressure and gel composition. Statistically significant decreases in Darcy permeability were obtained with the addition of minimal amounts of dextran while the addition of modest amounts of dextran reduced the Darcy permeabilities an order of magnitude. A portion of the hydrogels in this study were found to mimic GBM Darcy permeability. In addition each of these gels possessed a total solid volume fraction comparable to current estimates of GBM solid fraction. Available Darcy permeability theories had fair to excellent agreement with measured data.

In this research the partition coefficient was an especially important parameter in characterizing hydrogel composition. That is it was needed to predict how much dextran could be incorporated into a given agarose gel. A theory was developed to describe the equilibrium partitioning of a flexible polymeric solute between a dilute solution and a medium consisting of a randomly oriented array of fibers (e.g., a fibrous membrane or gel). The fibers were regarded as long, rigid cylinders and the solute was modeled as a chain consisting of n mass points joined by n-1 rectilinear segments. Results were obtained for freely jointed chains with fixed bond angles, using a combination of analytical and computational (e.g., Monte Carlo) techniques. The predicted partition coefficient (Φ, the solute concentration in the fibrous material divided by that in the bulk solution) proved to be sensitive to the number of fibers included; typically 50 or more nearest neighboring fibers were needed to obtain a convergent result. The values of Φ decreased as fiber volume fraction, molecular size, or number of mass points was increased selectively. As the bond angle was increased from 0° (a chain folding back on itself) to 180° (a rod-like chain), Φ first decreased and then increased. The model predictions agreed reasonably well with literature partitioining data for various polymeric solutes in hydrogels, especially when the radius of gyration was no more than a few times the fiber radius. With the radius of gyration specified, the model predictions were fairly insensitive to whether the bond angle was fixed or random.

The theory was subsequently extended to describe the equilibrium partitioning of flexible linear polymers between a concentrated polymer solution and a medium consisting of a randomly oriented array of fibers. The fibers were represented as long, rigid cylindrical segments joined at specified bond angles. A Monte Carlo technique combined with excluded volume concepts was used to describe steric interactions among chains and between chains and fibers. The partition coefficient was predicted to increase markedly when the bulk solution concentration of the polymer was elevated. This sensitivity of Φ to bulk concentration was observed even at concentrations that were well below critical overlap values. The partition coefficient decreased significantly as fiber volume fraction or molecular size were increased, but tended to be less sensitive to the structural details of the chain (segment number, segment radius, and bond angle). To test the theory, partition coeffieients for dextran in agarose gels were measured as a function of agarose volume fractions, dextran size, and dextran concentration. The trends in the data were in good qualitative agreement with the theory. Over the range of dextran concentrations studied, as much as a five-fold increase in Φ was observed. Quantitative agreement between the predictions and data was reasonably good at the higher dextran concentrations, although the theory consistently underestimated the dextran partition coeffieients in the more dilute solutions.

Certain agarose-dextran hydrogels synthesized in this study mimicked GBM water permeability and provided experimental evidence that, at least with respect to water flow, GBM microstructure can be adequately approximated as a matrix containing two distinct fiber types. Because these hydrogels matched the GBM in water permeability, elements of microstructure and total solid content, it is reasonable to believe that macromolecular transport through these gels may be similar to that in GBM tissue. Indeed continued evaluation of these hydrogels as potential GBM analogs will require measurements of macromolecular permeabilities.

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