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Theoretical analysis of the ultrafiltration behavior of highly concentrated protein solutions

Elaheh Binabaji [a], Junfen Ma [b], Suma Rao [b], Andrew L. Zydney [a,*]

[a] Department of Chemical Engineering, The Pennsylvania State University, University Park, PA 16802, United States
[b] Amgen Inc., One Amgen Center Drive, Thousand Oaks, CA 91320, United States

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ABSTRACT

Ultrafiltration is currently used for the concentration and formulation of monoclonal antibody solutions with target protein concentrations of up to 200 g/L or higher. The filtrate flux and maximum achievable antibody concentration in these systems is strongly influenced by the intermolecular interactions and non-ideal behavior in these highly concentrated protein solutions. The objective of this work was to develop a theoretical framework for analyzing the ultrafiltration of highly concentrated protein solutions accounting for the complex thermodynamic and hydrodynamic behavior in these systems. A modified polarization model was developed to describe the bulk mass transfer characteristics. In addition, the model accounts for the back-filtration phenomenon that occurs at very high protein concentrations due to the large pressure drop through the module associated with the high viscosity of the antibody solutions. Model parameters were evaluated from independent data for the protein osmotic pressure, osmotic virial coefficients, and viscosity. Model calculations demonstrate the importance of back-filtration, with numerical results in good agreement with experimental data for both the filtrate flux and maximum achievable antibody concentration obtained in a Pellicon 3 tangential flow filtration module. These results provide important insights into the key factors controlling the ultrafiltration behavior of highly concentrated protein solutions as well as a framework for the design and optimization of these ultrafiltration processes.

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1. Introduction

Ultrafiltration is the most commonly used method for concentration and final formulation of recombinant therapeutic proteins, most of which are delivered by injection [1–3]. Ultrafiltration of highly active hormones (e.g., insulin), cytokines (e.g., interferon), and clotting factors (e.g., Factor VIII) is relatively straightforward since these proteins are delivered at low to moderate concentrations [2]. In contrast, monoclonal antibodies need to be formulated in highly concentrated solutions (up to and exceeding 200 g/L) to achieve the desired dosage in the limited volumes that can be delivered by subcutaneous injection, creating significant challenges for ultrafiltration [1].

Most theoretical descriptions of the filtrate flux in ultrafiltration systems are developed using a “stagnant film” model based on solution of the steady-state one-dimensional diffusion equation:

$$N_s = J_v C - D\left(\frac{dC}{dy}\right) \tag{1}$$

where N_s is the protein flux, J_v is the filtrate flux (volumetric filtrate flow rate per unit membrane area), and C is the local protein concentration at position y measured from the membrane surface into the bulk solution. Eq. (1) can be integrated across the concentration boundary layer (with thickness δ) assuming that the protein diffusion coefficient (D) is constant to give the classical concentration polarization model for a fully retentive membrane (i.e., $N_s=0$) [4]:

$$J_v = k_m \ln\left[\frac{C_w}{C_b}\right] \tag{2}$$

where $k_m=D/\delta$ is the protein mass transfer coefficient, and C_w and C_b are the protein concentrations at the membrane surface and in the bulk solution, respectively. A variety of expressions are available for the mass transfer coefficient in different modules [5], with these correlations developed from experimental data (obtained from both mass and heat transfer experiments) and from solution of the appropriate convection–diffusion equation in a particular

* Corresponding author. Fax: +1 814 865 7846.
E-mail address: zydney@engr.psu.edu (A.L. Zydney).

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flow system (e.g., laminar flow over a flat plate).

Although, Eq. (2) often provides an accurate description of the filtrate flux, this simple polarization model cannot be used with highly concentrated solutions due to the assumptions of a constant diffusion coefficient and constant viscosity, both of which neglect the significant protein–protein interactions that occur within the concentration polarization boundary layer. A number of different approaches have been proposed to address the limitations of the classical stagnant film model. For example, Aimar and Field [6] accounted for the effects of the high viscosity of the concentrated solution near the membrane surface by multiplying the mass transfer coefficient in Eq. (2) by the correction factor $(n_b/n_w)^{0.27}$ where η_b and η_w are the viscosities evaluated using the bulk and wall concentrations, respectively. Gekas and Hallstrom [7] used a similar approach but with a correction factor based on the Schmidt number, $(Sc_b/Sc_w)^{0.11}$ where $Sc=\frac{\eta}{\rho D}$, to account for the dependence of both the solution viscosity (η) and diffusion coefficient (D) on the protein concentration (with ρ the solution density). Kozinski and Lightfoot [8] argued that the product of the diffusion coefficient and viscosity was constant based on the Stokes–Einstein equation, and that this was the key parameter governing mass transfer in a rotating disk ultrafiltration module. Zydney [9] took a different approach by incorporating the concentration dependence of the diffusion coefficient directly in Eq. (1), both through the protein mobility and the use of the gradient in the chemical potential (instead of the gradient in the protein concentration) for the driving force for diffusion, although no attempt was made to account for the concentration dependence of the viscosity.

The objective of this work was to develop a more accurate model for the filtrate flux in the ultrafiltration of highly concentrated protein solutions that properly accounts for: (1) the effects of intermolecular interactions on the thermodynamic driving force for diffusion, (2) the concentration dependence of the solution viscosity, and (3) the large parasitic pressure losses due to flow through the tangential flow filtration (TFF) module which can, under some circumstances, lead to back-filtration near the device exit. The key thermodynamic (virial coefficients) and hydrodynamic (viscosity) properties were evaluated from independent experimental measurements using a highly purified monoclonal antibody. The model predictions are compared with experimental data for the ultrafiltration of the same antibody in a linearly scalable screened TFF cassette used extensively in bioprocessing applications for final product formulation [2]. The model is in good agreement with the experimental results, providing important additional insights into the key factors controlling the filtrate flux during ultrafiltration of highly concentrated protein solutions.

2. Theoretical development

2.1. Modified polarization model

As discussed by Zydney [9], the diffusive solute flux in highly concentrated solutions is proportional to the gradient in the chemical potential (μ) instead of the gradient in the solute concentration, so that Eq. (1) becomes:

$$N_s = J_v C - \frac{DC}{RT}\left(\frac{d\mu}{dy}\right) \tag{3}$$

where R is the ideal gas constant and T is the absolute temperature. The gradient in the chemical potential can be rewritten in terms of the protein osmotic pressure (Π) as:

$$\left(\frac{d\mu}{dy}\right) = \frac{M_p}{C}\left(\frac{d\Pi}{dC}\right)\left(\frac{dC}{dy}\right) \tag{4}$$

where M_p is the protein molecular weight. The osmotic pressure (Π) is conveniently expressed using a virial expansion as [5]:

$$\Pi = RT\left\{2\left[\left(\frac{ZC}{2M_p}\right)^2 + m_s{}^2\right]^{\frac{1}{2}} - 2m_s\right\} + RT\left(B_1C + B_2C^2 + B_3C^3\right) \tag{5}$$

where the first term is the Donnan contribution with Z the net protein charge, m_s is the molar salt concentration, and B_1, B_2, and B_3 are the osmotic virial coefficients. Eq. (5) has been truncated after the third osmotic virial coefficient (B_3), which is sufficient to describe the behavior of concentrated monoclonal antibody solutions up to concentrations of at least 250 g/L [10]. Note that the analysis presented by Zydney [9] only considered the term involving the second virial coefficient without the Donnan contribution. The diffusion coefficient in Eq. (3) is also a function of the protein concentration due to the dependence of the protein mobility on the local solution viscosity:

$$D = D_0\left(\frac{\eta_0}{n}\right) \tag{6}$$

where D_0 and η_0 are the diffusivity and viscosity in the limit of an infinitely dilute solution. Note that Eq. (6) has been used previously by Kozinski and Lightfoot [7] (among others) for describing diffusion in concentrated protein solutions; this form is also consistent with Einstein's analysis of Brownian diffusion in terms of the particle mobility. Eqs. (4) to (6) can be substituted into Eq. (3), with the resulting equation integrated over the concentration boundary layer thickness (δ) to give the following expression for the filtrate flux:

$$J_v = \frac{D_0}{\delta}\int_{C_b}^{C_w}\left(\frac{\eta_0}{\eta}\right)\left(\frac{M_p}{RT}\right)\left(\frac{d\Pi}{dC}\right)\frac{dC}{C} \tag{7}$$

where D_0/δ is related to the mass transfer coefficient and the derivative of the osmotic pressure is evaluated from Eq. (5). Eq. (7) reduces to the classical stagnant film model (Eq. (2)) when the solution viscosity is constant ($\eta=\eta_0$) and the osmotic pressure is a linear function of concentration, i.e., under conditions where there are no intermolecular interactions. Eq. (7) can be integrated using an appropriate relationship for the viscosity as a function of the protein concentration; this is discussed in more detail in the results.

The boundary layer thickness in Eq. (7) is determined by the module geometry (e.g., channel height, spacer, module length, etc.) as well as the device hydrodynamics (e.g., feed flow rate). In addition, the variation in solution viscosity alters the growth of the concentration polarization boundary layer thickness as discussed by Aimar and Field [6]. Previous experimental and theoretical studies have shown that the boundary layer thickness typically depends on $Sc^{1/3}$ where Sc is the Schmidt number [5]. Eq. (7) was thus rewritten as:

$$J_v = k_0\left(\frac{\eta_b}{\eta_0}\right)^{1/3}\int_{C_b}^{C_w}\left(\frac{\eta_0}{\eta}\right)\left(\frac{M_p}{RT}\right)\left(\frac{d\Pi}{dC}\right)\frac{dC}{C} \tag{8}$$

where $k_0=D_0/\delta$ is the mass transfer coefficient that would exist in the absence of any non-idealities, i.e., with constant viscosity and with $d\Pi/dC$=constant.

There is considerable debate in the literature over the factors that determine the wall concentration in the stagnant film model. Some investigators have evaluated the wall concentration based on the solubility (or “gel”) concentration for the particular protein, while others have assumed that the wall concentration is

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