THE HYDRODYNAMICS OF MICRO-PARTICLE SLURRIES IN HOLLOW FIBER MEMBRANES

A Thesis in
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by

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ABSTRACT

Downstream processing is a significant bottleneck in the production of protein-based pharmaceuticals and accounts for a large fraction of manufacturing costs. Countercurrent tangential flow chromatography (CTC) has been proposed as an alternative to traditional column chromatography with increased throughput and lower cost. In the CTC system, a concentrated slurry of resin particles flow through a series of static mixers and hollow fiber membrane modules in a countercurrent arrangement, with binding, washing, and elution performed sequentially. Initial studies have demonstrated the feasibility of this process, with the individual modules operated below the critical flux to insure stable filtration without fouling.

The overall objective of this thesis was to develop a more comprehensive and fundamental understanding of the hydrodynamic behavior of concentrated resin slurry particles in hollow fiber membranes. The critical flux was evaluated for a variety of resin particles, ranging in size from 10 to 45 µm, over a range of cross flow velocities, particle concentrations, and in different buffer solutions.

Experimental data indicate that the critical flux ($J_{\text{CRIT}}$) varies linearly with the wall shear stress ($\tau_w$) over a wide range of conditions. The ratio of $J_{\text{CRIT}}/\tau_w$ was thus used as a fundamental parameter to describe the critical flux for a given particle and feed concentration. $J_{\text{CRIT}}$ decreased with increasing feed particle volume fraction and was essentially independent of the buffer condition and particle size.

The critical flux data were analyzed using the Brownian diffusion, shear-induced diffusion, and inertial lift models. The linear dependence on the wall shear stress is in agreement with the form predicted by the shear-induced diffusion model, but this model was unable to
explain the observed dependence on particle size and concentration. Instead, it appears that the critical flux is determined by a critical (maximum) value of outlet particle concentration, which was equal to about 40% of the dense packed concentration. These results provide important insights into the hydrodynamic conditions needed for stable operation of the hollow fiber membrane modules employed in countercurrent tangential chromatography systems.
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LIST OF ABBREVIATIONS

\( a \)  \hspace{1cm} \text{Particle Radius}

CTC  \hspace{1cm} \text{Countercurrent Tangential Flow Chromatography}

\( C_0 \)  \hspace{1cm} \text{Initial Ethanol Concentration}

\( C_f \)  \hspace{1cm} \text{Final Ethanol Concentration}

\( C_{\text{feed}} \)  \hspace{1cm} \text{Feed Impurity Concentration}

\( C_1 \)  \hspace{1cm} \text{Two Stage CTC Inter-Stage Impurity Concentration}

\( C_{\text{out}} \)  \hspace{1cm} \text{Two Stage CTC Outlet Impurity Concentration}

\( D_P \)  \hspace{1cm} \text{Particle Diameter}

\( J \)  \hspace{1cm} \text{Filtrate Flux}

\( J_{\text{crit}} \)  \hspace{1cm} \text{Critical Membrane Flux}

\( K \)  \hspace{1cm} \text{Mass Transfer Coefficient}

\( L \)  \hspace{1cm} \text{Channel (Membrane Fiber) Length}

\( n \)  \hspace{1cm} \text{Number of Filtration Cycles}

\( N \)  \hspace{1cm} \text{Number of Fibers}

\( Q_{\text{feed}} \)  \hspace{1cm} \text{Volumetric Flow Rate of the Feed}

\( Q_{\text{permeate}} \)  \hspace{1cm} \text{Volumetric Flow Rate of the Permeate}

\( Q_{\text{retentate}} \)  \hspace{1cm} \text{Volumetric Flow Rate of the Retentate}

\( \text{PBS} \)  \hspace{1cm} \text{Phosphate Buffered Saline}

\( P_{\text{in}} \)  \hspace{1cm} \text{Pressure at the Membrane Inlet}

\( P_{\text{out}} \)  \hspace{1cm} \text{Pressure at the Membrane Outlet (Retentate)}

\( P_{\text{permeate}} \)  \hspace{1cm} \text{Pressure of the Permeate Stream}

\( r_0 \)  \hspace{1cm} \text{Fiber Radius (Inner)}
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<td>TMP</td>
<td>Trans-Membrane Pressure</td>
</tr>
<tr>
<td>U</td>
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<td>$V_f$</td>
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<td>Bulk Solution Particle Volume Fraction</td>
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<tr>
<td>$\rho_0$</td>
<td>Fluid Density</td>
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CHAPTER 1

Introduction

1.1 Background

The advent of recombinant DNA technology has led to the production of a wide range of protein-based pharmaceuticals. This includes a range of hormones, clotting factors, and more recently monoclonal antibodies, with the latter used in the treatment of a variety of autoimmune disorders and cancers. Much of the manufacturing cost encountered in the production of recombinant protein products lies in the downstream purification process needed to remove the host cell proteins, DNA, endotoxins, and other impurities generated in the bioreactor [1]. Recent advances in cell culture technology and bioreactor design have led to significant increases in the titer of these biological products; current antibody processes routinely deliver antibody concentrations in excess of 3 g/L. This has led to a significant bottleneck in downstream processing, with Low et al. concluding that the “bottleneck in recovery processes is the first adsorptive column [2].” Currently available separation technologies like column chromatography and membrane ultrafiltration have shown only small to moderate improvements in capacity over the past 20 years, which are insufficient to meet the needs of these high titer antibody processes [3].

In order to overcome the current bottleneck in downstream processing, a number of investigators have explored alternatives to traditional column chromatography. Examples include membrane adsorbers, charged ultrafiltration membranes, and protein precipitation [4, 5]. More recently, Oleg Shinkazh developed and patented a countercurrent tangential flow
chromatography (CTC) system that has the potential to significantly increase the productivity and reduce the cost of chromatography for the purification of high value biological products [6, 7]. In contrast to column chromatography, the separation in CTC is effected with the resin particles flowing in a concentrated slurry through a series of hollow fiber membrane modules (described in more detail in the next section). Initial studies demonstrated the feasibility of this approach for the purification of a model two-component protein mixture by ion exchange chromatography. These results also showed the importance of the hydrodynamic behavior of the chromatography resin particles in the hollow-fiber membrane modules. This early work on CTC provides the overall motivation for the current study.

1.2 Countercurrent Tangential Chromatography (CTC)

The CTC system operates by passing a slurry of resin particles (with attached chromatographic ligands) through a series of static mixers and hollow fiber membrane modules. For example, in the binding step for a monoclonal antibody, the feed material (containing the antibody as well as a variety of impurities) is mixed with a concentrated slurry of protein A affinity beads that are highly selective for binding the antibody. The resulting suspension is thoroughly mixed in a static mixer that provides sufficient residence time for the product to bind to the resin. The resin is then passed through a semipermeable hollow fiber membrane module that is designed to retain the resin particles while removing fluid and unbound proteins. The resin and feed flow countercurrently through a series of mixers / hollow fiber modules, enhancing product binding while minimizing buffer requirements. The resin particles are then washed in a second set of static mixers / hollow fiber modules to remove any unbound proteins and impurities, with the countercurrent flow reducing the amount of wash buffer required to
achieve very high degrees of impurity removal. The product is eluted from the resin by contacting the particles with an appropriate elution buffer, with the elution steps again conducted in a series of static mixers / hollow fiber modules. The design of a two-stage CTC batch system is shown in Figure 1.1. This setup can be used for binding, washing, and elution with the individual steps performed one after another. It is also possible to perform the binding, washing, elution, and re-equilibration steps in series, with the resin flowing directly from one step to another to form a continuous system (with the resin recycled directly to Slurry Tank 1 after completion of the re-equilibration step) [6].

![Diagram of a two-stage CTC system](image)

**Figure 1.1:** Diagram of a two-stage CTC system where SM1 and SM2 are static mixtures and HF1 and HF2 are hollow fiber modules. P1, P2, P3, and P4 are pressure transducers connected directly to a computer for data logging. The individual stages in the system are shown by the dotted rectangles (adapted from [6]).

One of the critical factors in the design and operation of the CTC system is the need to ensure stable filtrations rates in the individual hollow fiber membrane modules, which requires
that one avoid, or at least minimize, membrane fouling. This can be done by ensuring operation at a filtrate flux (volumetric filtrate flow rate divided by the membrane area) that is below the “critical filtrate flux” for the particular resin slurry in the given hollow fiber membrane module. The critical flux is defined as the value of the filtrate flux at which membrane fouling begins to occur, usually seen by the onset of a non-linear relationship between the transmembrane pressure and the filtrate flux. The critical flux is often evaluated by running experiments at a series of constant values of the filtrate flux, tracking the transmembrane pressure as a function of time during the constant flux filtration; the critical flux is defined as the flux at which the transmembrane pressure increases throughout the filtration period. Operation below the critical flux allows the modules to be used for extended filtration times without any significant increase in transmembrane pressure, i.e., in the absence of any membrane fouling that would cause a reduction in the permeability of the membrane. The physical basis for the critical filtrate flux and its experimental determination are discussed in more detail in Chapter 2 of this thesis.

The CTC system operates most efficiently at high values of the conversion (X) in the individual hollow fiber modules, where the conversion is defined as:

\[ X = \frac{Q_{\text{permeate}}}{Q_{\text{feed}}} \]  

(2.1)

where \( Q_{\text{permeate}} \) and \( Q_{\text{feed}} \) are the volumetric flow rates of the permeate and feed streams, respectively. For a two-stage CTC washing stage where impurities are assumed to pass freely through the membrane, the concentrations of the impurities in the liquid phase in the permeate and retentate are equal. The material balance for the impurities in the two stages can be written as:

**Stage 1:** \( C_{\text{feed}}Q_{\text{feed}} + C_{\text{out}}Q_{\text{permeate}} = C_1Q_{\text{permeate}} + C_1Q_{\text{feed}} \)

**Stage 2:** \( C_1Q_{\text{feed}} = C_{\text{out}}Q_{\text{permeate}} + C_{\text{out}}Q_{\text{feed}} \)
where $C_{\text{feed}}$, $C_1$, and $C_{\text{out}}$ are the impurity concentrations in the feed, between the two stages, and in the outlet, respectively. Combining these equations provides an expression for $C_{\text{out}}/C_{\text{in}}$ as a function of $X$. Typical results for one-stage and two-stage systems are shown in Figure 1.2 along with the calculated values for a CTC system in which the buffer is sent directly from stage 2 to stage 1. At low conversions, the CTC system shows similar impurity removal to a one-stage system; however, at high conversions the CTC system provides much greater impurity removal, with the final concentration approaching that for a two-stage system (but with half the required volume of buffer). Note that more than two stages can be used for each step to achieve even greater degrees of impurity removal.

Figure 1.2: Final contaminant fraction for a two-stage CTC washing step (solid curve). Also shown are results for a one-stage system (dashed blue) and a two-stage system with no permeate recycle (dashed gray).
Initial feasibility studies of the CTC system were performed with a feed containing 10% by volume of the MacroPrep 25Q ion-exchange resin at a flow rate of 51 mL/min. The critical flux was found to occur at 77% conversion, where the conversion is defined as the cumulative permeate flow rate divided by the feed flow rate. Operation of a two-stage CTC system with the conversion fixed at 75% gave very stable hydrodynamics, with no change in the transmembrane pressure over a 60 min experiment. A batch process involving binding, washing, and elution steps gave a bovine serum albumin (BSA) product at a yield of 94±2% with greater than 99% purity (no detectable levels of myoglobin used as a model impurity [6]).

1.3 Thesis Scope

Although the initial feasibility studies for the CTC system demonstrated that it was possible to operate the hollow fiber modules below the critical flux, there was no fundamental understanding of the factors that led to the critical flux nor was there any information on how the critical flux depends on the properties of the slurry particles or the device operating conditions. The overall objective of this thesis was to evaluate the critical flux for a wide range of resin particles of interest in countercurrent tangential chromatography and to use these data to develop a more fundamental understanding of the effects of particle size, particle concentration, feed flow rate, and particle surface chemistry on the critical flux.
2.1 Membrane Fouling

A membrane is, at the simplest level, a semipermeable barrier that selectively allows transport of one or more species while retaining (or at least hindering the transport) of other species. The retention of one or more species during filtration will lead to an accumulation of that species at the upstream surface of the membrane, a phenomenon that is typically referred to as concentration polarization and is shown schematically in Figure 2.1 [8]. The particles that are retained by the membrane form a layer whose concentration is higher than that in the bulk suspension, generating a diffusive transport down the concentration gradient and back into the bulk solution. At steady state, this concentration-driven transport exactly balances the convective particle transport associated with the pressure-driven filtration, with the concentration profile above the membrane remaining constant with time. If the pressure-driven particle flux is greater than the rate of back diffusion, the particles will accumulate on the membrane surface, leading to the formation of a particle cake or deposit that provides an additional resistance to fluid flow.

Membrane fouling refers to the alteration (typically degradation) in membrane properties during the course of the filtration process. Fouling can occur via a number of different mechanisms, including adsorption, pore blockage, pore constriction, deposit (or cake) formation, and gel formation [9].
**Figure 2.1:** A schematic showing concentration polarization in the solution immediately above a membrane due to the filtration flux (shown by red arrows).

Adsorptive fouling typically occurs because of attractive forces between the membrane surface and the particles within the suspension. This will cause the particles to adhere to the surface of the membrane pores, reducing the effective pore diameter and blocking access to the pores (Figure 2.2a). Adsorptive fouling is often important for proteins and surfactants (surface-active) molecules, particularly with hydrophobic membrane materials. Adsorptive fouling is generally unimportant for large particles—the shear forces in the hollow fiber module should be sufficient to overcome any adsorptive forces in this system.

Pore blockage occurs by the physical entrapment of particles at the pore entrance or within the depth of the membrane (Figure 2.2b). Pore blockage is usually most important for particles that are smaller than, or similar in size to, the membrane pores. Very large particles are typically unable to effectively block the small pores on the membrane surface.

Deposit formation, also referred to as cake filtration, occurs when a layer of particles is captured on the external surface of the membrane (Figure 2.2c). This particle deposit provides a significant additional resistance to flow in series with that provided by the membrane. In addition, the presence of a thick particle cake will decrease the effective size of the lumens of the hollow fiber membranes, increasing the pressure gradient needed to pump the feed solution through the membrane module.
Gel formation refers to the development of an actual gel layer, typically thought of as a thermodynamic phase transition, on the membrane surface due to the high concentration of retained species. Gel formation is most common with macromolecules like proteins that can accumulate to very high concentrations, and thus exceed their solubility limit, due to concentration polarization effects in the membrane device [9].

In tangential flow filtration, such as that used in the CTC system, the feed solution flows tangentially across the membrane surface and thus perpendicular to the direction of filtration. This tangential flow creates a significant wall shear stress at the surface of the membrane, which can re-entrain many of the solutes / particles that are deposited on the membrane surface. This leads to much higher permeate flux in tangential flow systems compared to normal flow (or dead-end) filtration. Tangential flow filtration is used in almost all large-scale pressure-driven filtration processes employing even moderately concentrated feed solutions [10]. Normal flow filtration is used for virus removal and sterile filtration (bacteria removal) in which the retained species are present at very low concentrations.
2.2 Critical Flux

2.2.1 Theory

The critical flux is generally defined as the maximum value of the filtrate flux at which fouling does not occur. This definition was originally proposed in 1995 by Bacchin et al [9]. However, the concept of a critical flux dates back at least to the work of Cohen et al. in 1986 [11]. Cohen et al. found that operation at a high filtrate flux caused particles to deposit on the membrane surface, leading to coagulation and fouling. In contrast, when the membrane device was operated at low filtrate flux, the particles remained in suspension and were thus unable to foul the membrane.

Figure 2.3 shows images of a membrane surface operated both below and above the critical flux. When operated below the critical flux, there was no significant change in the number of particles present on the membrane surface even after prolonged filtration. In contrast, when the same membrane was operated at a flux that was greater than the critical flux, a layer of particles formed rapidly on the membrane surface and continued to increase in density and thickness over time – the entire membrane was covered with a dense particle layer after only 45 s of filtration.
In addition to irreversible fouling, it is also possible for fouling to be “reversible” in response to small changes in operating conditions. For example, Figure 2.4 shows the results of an experiment in which the system was initially operated at a filtrate flux above the critical flux ($J_{\text{crit}}$), but then the flux was reduced to below $J_{\text{crit}}$ while the feed was continually circulated through the module. In this case, the reduction in flux allowed the shear flow and back diffusion to transport particles away from the membrane surface, effectively reversing the membrane fouling. However, in many situations the only way to reverse fouling is to stop the filtration process and clean the membrane using appropriate physical (e.g., backflushing) and / or chemical (e.g., NaOH or surfactants) methods.
Figure 2.4: Images of the membrane after filtration of 6.4 μm latex particles at: (a), (b), (c) and (d) various times during filtration at a flux above the critical flux; (e) and (f) at later times when the flux had been decreased below the critical flux (adapted from [12]).

2.2.2 Measuring the Critical Flux

There are a number of different approaches used to experimentally measure the critical flux. The most common approach is to operate the membrane device at a series of filtrate flux set-points, with the trans-membrane pressure (TMP) monitored as a function of time:

\[ TMP = \frac{P_{in} + P_{out}}{2} - P_{permeate} \]  

(2.1)
where $p_{in}$ is the inlet (feed) pressure, $p_{out}$ is the exit (retentate) pressure, and $p_{permeate}$ is the pressure on the permeate size of the membrane. In the absence of any fouling, the filtrate flux should vary linearly with the TMP with the slope equal to the permeability of the clean membrane. Thus, fouling can be considered to occur whenever the transmembrane pressure required to maintain a given filtrate flux exceeds the TMP measured during filtration of pure water [9]. This definition of fouling is known as the “strong form” of the critical flux and is shown schematically in Figure 2.5. However, this definition ignores the effects of concentration polarization and reversible fouling, both of which may lead to an increase in TMP even in the absence of any irreversible loss in membrane permeability.

The weak form of the critical flux is often defined as the value of the filtrate flux at which the relationship between flux and TMP first deviates from linearity [9]. This method can account for concentration polarization and reversible fouling, both of which typically lead to a linear relationship between the TMP and flux. A comparison of the strong and weak form of the critical flux is shown in figure 2.5.
Figure 2.5: A comparison of the strong and weak definitions for critical flux. The arrows indicate the critical flux.

The critical flux experiment used in this thesis evaluated the TMP as a function of time at several values of the flux set point (determined by a pump on the filtrate exit line). The flux set points were periodically increased until the critical flux had been surpassed and some type of fouling was observed, typically seen by a continuous increase in TMP during operation at a constant value of the flux. Figure 2.6 shows two example data sets (flux and TMP versus time) along with the procedures used for determining the critical flux: (1) a non-constant TMP at a fixed flux and (2) a non-linear increase in a plot of TMP as a function of the filtrate flux. Note that in some experiments, the TMP – flux plot became non-linear even though the TMP attained a stable value at higher values of the flux.
2.3 Theory and Modeling

2.3.1 Overall Model

A wide variety of models have been proposed to predict the critical flux for particle suspensions in membrane filtration processes. Most of these models have been based on one of the following four concepts: Brownian diffusion, shear-induced diffusion, surface interaction, and lateral migration (inertial lift). A comparison of the predicted values of the critical flux given by these models are shown in Figure 2.7, along with experimental results for different latex and ferric oxide particles, with the data plotted as a function of the particle radius. The
critical flux initially decreases with increasing particle size, attaining a minimum around a particle radius of 0.02 µm, before increasing at larger particle size.

Figure 2.7: A comparison of the predicted values of the critical flux given by the different theoretical models. Also shown for comparison are experimental data with different latex and ferric oxide particles. Results shown at a Reynolds number of 1500 and feed volume fractions on the order of 10^{-3} (adapted from [9]).

There have been relatively few studies of the critical flux for larger particles. Figure 2.8 summarizes results for particles between 3 and 11.9 µm in size. The critical flux seems to vary linearly with the crossflow velocity (or shear rate). However, it is important to note that these data were obtained at much lower particle concentrations than those used in countercurrent tangential chromatography systems (less than 0.1% by volume instead of 5-40% in CTC) and none of the experiments reported in Figure 2.8 used hollow fiber membrane modules.
Figure 2.8: A comparison of the critical flux for several particles varying from 3 to 11.9 µm. Yeast has a diameter of 5µm. Particle concentrations were 0.05-0.057% by volume. A flat tangential flow filtration module was used with an anodized aluminum membrane with a pore size of 0.2 µm (adapted from [12]).

2.3.2 Brownian Diffusion Model

The Brownian diffusion model assumes that the filtrate flux is limited by the formation of a thin concentration boundary layer consisting of a high concentration of retained particles that accumulates on the surface of the membrane. The thickness of this boundary layer is determined by the balance between convection towards the membrane due to the filtrate flux and back-diffusion away from the membrane and into the bulk solution. If the membrane device is operated at a filtrate flux in excess of this balanced condition, the particles will continue to accumulate on the membrane surface leading to fouling and a rapid increase in transmembrane pressure [10].
2.3.3 Shear-induced Diffusion Model

The shear-induced diffusion model is developed using the same underlying principles as the diffusion model; however, the back diffusion flux is assumed to be controlled by shear-induced hydrodynamic diffusion instead of Brownian diffusion. Shear-induced diffusion arises from the random displacements of particles in the shear flow of a concentrated suspension [10]. The shear-induced diffusion coefficient is proportional to the shear rate and to the square of the particle radius. It is thus negligible for very small particles (<10 nm), but becomes much larger than the Brownian diffusion coefficient for larger particles (>100 nm). As shown in figure 2.7, Bacchin et al. [9] found that the shear-induced diffusion model provided the best description of the critical flux for particles between about 5 and 10 µm in size, although these data were for very dilute suspensions compared to those encountered in continuous tangential chromatography.

The critical flux in the shear-induced diffusion model is developed as follows. The one-dimensional convective-diffusion equation in the concentration polarization boundary layer is integrated over the boundary layer thickness (from $z = 0$ to $z = \delta$), with the ratio of the diffusion coefficient to the boundary layer thickness set equal to the bulk mass transfer coefficient yielding [10]:

$$
\langle J \rangle = \langle K \rangle \ln\left[\frac{\phi_w}{\phi_b}\right]
$$

(2.2)

where $\phi_w$ is the volume fraction at the wall and $\phi_b$ is the particle volume fraction in the bulk suspension. The average value of the mass transfer coefficient, $\langle K \rangle$, is then evaluated using the Leveque solution for the corresponding heat transfer problem under conditions where the boundary layer is much thinner than the channel dimension [10]:

$$
\langle K \rangle = 0.81 \left(\frac{Y_0 D_s}{L}\right)^{1/3}
$$

(2.3)
where $\gamma_0$ is the wall shear rate and $L$ is the channel length. The effective particle diffusion coefficient ($D_s$) in Equation (2.3) is set equal to the shear-induced diffusion coefficient:

$$D_s = 0.3 \gamma_0 a^2$$

(2.4)

where $a$ is the particle radius. Equation (2.4) is valid for particle volume fractions in the bulk suspension, $\phi_b$, between around 0.2 and 0.45. The shear rate for flow in a tube (such as a hollow fiber membrane) is given as [13]:

$$\dot{\gamma}_0 = \frac{4v}{r_o}$$

(2.5)

where $v$ is the average suspension velocity and $r_o$ is the radius of the tube. Substitution of Equations (2.3) – (2.5) into Equation (2.2) gives the following expression for the critical flux:

$$\langle j \rangle = 0.312 \frac{v}{r_o} \left( \frac{a}{L} \right)^{1/3} ln\left[ \frac{\phi_w}{\phi_b} \right]$$

(2.6)

Equation (2.6) predicts the average pressure-independent flux varies linearly with the feed velocity and with the particle radius to the 4/3 power. The linear dependence on feed velocity is consistent with the experimental results previously shown in Figure 2.8. Note that the particle volume fraction at the membrane surface, $\phi_w$ is typically set equal to the maximum packing concentration for the particle suspension. $\phi_w$ is thus around 70% volume fraction for hard spheres [10, 14] but can approach 95% for very deformable particles like red blood cells [10].

Expanding upon the linear relationship between $J_{CRIT}$ and $v$ as observed in Figure 2.8, it was proposed by Gésan-Guiziou et al. [15] that the critical flux be correlated with the wall shear stress ($\tau_w$). The best fit value of the slope for the linear regression fit of data for $J_{CRIT}$ as a function of $\tau_w$ can then be used as the critical descriptive parameter for any given particle size and concentration [16] as well as flow geometry [17]. Figure 2.9 shows typical results for this correlation and the regimes in which the permeate flux will remain stable (steady) or unstable (divergent).
Figure 2.9: The critical operating ratio $J/\tau_w$ during microfiltration of skimmed milk (adapted from [15]).

The wall shear stress, $\tau_w$, and shear rate are directly related to each other via the suspension viscosity [13]:

$$\tau_w = \gamma_0 \mu$$  \hspace{1cm} (2.7)

where $\mu$ is the viscosity. Dividing Equation (2.7) into Equation (2.6) provides the values of $J_{CRIT}/\tau_w$ predicted by the shear-induced diffusion model:

$$\frac{J_{CRIT}}{\tau_w} = \frac{0.078}{\mu} \left( \frac{a^4}{L} \right)^{1/3} \ln\left[ \frac{\phi_w}{\phi_B} \right]$$  \hspace{1cm} (2.8)

2.3.4 Inertial Lift Model

The inertial lift (or lateral migration) model assumes that back transport of particles is due to hydrodynamic interactions with the flow boundary giving rise to a lateral migration of particles away from the membrane surface. Inertial lift is the result of the “non-linear interaction of a particle with the surrounding flow field under conditions where the Reynolds number based on the particle size is not negligible…so the nonlinear inertia terms in the Navier-Stokes
equation play a role [10].” The inertial lift force varies with the square of the shear rate and with the particle radius to the 4th power – these inertial forces thus become significant only for very large particles (greater than 10 µm or even 100 µm in size depending on the value of the wall shear rate).

The critical flux given by the inertial lift phenomena is typically expressed as [10]:

\[ J = 0.036 \frac{\rho_0 a^3}{\eta_0} \left( \frac{4 \nu}{\tau_0} \right)^2 \]

where \( \rho_0 \) is the fluid density, \( \eta_0 \) is the permeate viscosity, and \( U \) is the average velocity. The flux predicted by Equation (2.9) tends to dominate for very large particles or for systems with very high shear rates due to the dependence on \( a^3 \) and \( \gamma^2 \). The inertial lift model can also be rewritten to explicitly evaluate \( J_{\text{CRIT}}/\tau_W \):

\[ \frac{J_{\text{CRIT}}}{\tau_W} = 0.036 \frac{\rho_0 a^3}{\eta_0 \mu} \left( \frac{4 \nu}{\tau_0} \right) \]

(2.10)

2.3.5 Surface Interaction Model

The surface interaction model was proposed by Cohen et al. [11] and is a semi-empirical model based on a description of particle-particle interactions in the membrane system. Cohen et al. developed the model to describe their results with ferric hydroxide particles as shown in figure 2.7. This model assumes that fouling originates by means of a first-order physicochemical reaction within a concentration / reaction boundary layer at the membrane-solution interface. After this initial stage, a slower flux-controlled deposition stage occurs which causes the foulant layer to grow linearly with time [11].
CHAPTER 3
Materials and Methods

3.1 Buffer Preparation

Phosphate buffered saline (PBS) solutions were prepared by dissolving 0.018 M of NaCl, 0.00036 M KCl, 0.0013 M Na$_2$HPO$_4$ * 2 H$_2$O, and 0.000026 KH$_2$PO$_4$ (analytical grade) in deionized water obtained from a NANOpure Diamond water purification system (Branstead Thermolyne Corporation, Dubuque, IA). The solution pH was measured using a Thermo Orion pH meter Model 402 (Beverly, MA) and was adjusted to pH 7.4 using 0.1 M NaOH or HCl as needed.

3.2 Slurry Preparation

3.2.1 Slurry Types

Table 3.1 provides the resin names, manufacturers, and particle diameters for all resins used in this thesis. All resins were obtained from the manufacturer in 20% ethanol as a storage solution.

<table>
<thead>
<tr>
<th>Name</th>
<th>$d_p$ (μm)</th>
<th>Manufacturer</th>
<th>City</th>
</tr>
</thead>
<tbody>
<tr>
<td>Poros 10A</td>
<td>10</td>
<td>Applied Biosystems</td>
<td>Foster City, CA</td>
</tr>
<tr>
<td>Poros 20 OH</td>
<td>20</td>
<td>Applied Biosystems</td>
<td>Foster City, CA</td>
</tr>
<tr>
<td>MacroPrep 25Q</td>
<td>25</td>
<td>Bio-Rad</td>
<td>Hercules, CA</td>
</tr>
<tr>
<td>Poros 45A</td>
<td>45</td>
<td>Applied Biosystems</td>
<td>Foster City, CA</td>
</tr>
</tbody>
</table>

3.2.2 Buffer Exchange
The slurry was prepared for the experiments as follows. The concentrated slurry (typically in 20% ethanol) was added to an Amicon 8200 stirred cell (Millipore Corp., Bedford, MA) fitted with a 0.5 μm pore size polyethersulfone membrane (Millipore Corp., Bedford, MA). Approximately three times the slurry volume of 15 mM PBS was added. The stirred cell was placed on a magnetic stir plate and the device was air pressurized to approximately 35 kPa (5 psi). Filtration was continued until the suspension volume was reduced to the initial slurry volume. This process was repeated 5 times, which should reduce the ethanol concentration to less than 0.1% by volume based on the appropriate mass balances for this type of discontinuous diafiltration process:

\[ C_f = C_0 (1 - X_r)^n \]  
(3.1)

where \( C_f \) is the final ethanol concentration, \( C_0 \) is the initial ethanol concentration, \( X_r \) is the volume reduction fraction (\( X_r = 0.75 \) for these experiments), and \( n \) is the number of filtration cycles used in the diafiltration process.

### 3.2.3 Slurry Concentration Measurement

The particle concentration in the resin slurry was measured using a Beckman Coulter Allegra X-12R Centrifuge with an SX4750 Swinging-Bucket Rotor (Beckman Coulter, Inc., Brea, CA). Samples were spun at 3000 rpm for 5 min. If the packed particles at the bottom of the centrifuge tube were still able to flow after the centrifugation, the sample was re-centrifuged but for a longer period of time. The relative volume fraction of particles was calculated from the ratio of the height of the packed particles in the centrifuge tube to the total height of the centrifuge tube.
3.3 Critical Flux Measurement

3.3.1 Experimental Setup

Critical flux experiments were performed with Spectrum X35E-901-02N polyethersulfone hollow fiber membranes with a pore size of 0.5 μm (Spectrum Laboratories Inc., Rancho Dominguez, CA). Each module contained 9 fibers approximately 65 cm in length and 1 mm in inner diameter giving a membrane area of 200 cm². The module was mounted vertically and the feed port was connected to a Masterflex 7550-60 peristaltic pump (Cole-Parmer, Vernon Hills, IL) that provided slurry from a pressurized reservoir that was mixed using a magnetic stirrer. A second identical pump was connected to the permeate outlet at the top of the module with the bottom permeate port capped shut. The retentate and permeate outlets were both returned to the pressurized slurry tank. The experimental setup is shown schematically in Figure 3.1.
3.3.2 Startup Procedure

The feed pump was initially connected to a tank containing 15 mM PBS that was used to flush the system and fully wet out the membrane. The PBS was initially pumped through the hollow fiber module with the permeate pump shut off, i.e., with all of the flow directed through the fiber lumen. After a minimum of 2 min of operation, the permeate pump was turned on and set to a volumetric flow rate that was equal to one-half the feed rate. The permeate side of the module was then flushed for a minimum of 2 min, the permeate pump was stopped, and the feed line was connected to the slurry tank. As soon as the slurry was visible in the retentate tubing,
the retentate and permeate exit lines were connected to the slurry tank which was then pressurized to 5 to 20 psig.

3.3.3 Critical Flux Experiment

The inlet (feed), outlet (retentate), and permeate pressures were continuously monitored throughout the filtration process using Vernier GBS-BTA gas pressure transducers connected to a Samsung computer using a LabQuest computer interface (Vernier Software and Technology, Beavertown, OR). The system was allowed to equilibrate at the initial (low) permeate flow rate as shown by a stabilization of all pressure readings. The permeate flow rate was then increased making sure that the outlet particle concentration would increase by no more than 5%. The pressures were then monitored at this new permeate flow rate for a minimum of 2 min. The entire procedure was repeated, with the permeate flow rate increased approximately every 2 min, until the measured TMP became “unstable” as indicated by a rise in TMP during the course of the filtration. Once the critical flux was passed, the permeate pump was slowly ramped down to zero.

After the permeate flow had stopped, the system was de-pressurized and 15 mM PBS was pumped through the system to displace the slurry. After all visible resin had been removed, the retentate stream was switched to waste and the buffer flow rate was increased to 500 mL/min for 2 min to remove any remaining particles. The module was then washed with 0.1 M NaOH at a feed flow rate of 500 mL/min for 2 min. The module was then removed and back-washed with water for an additional 1 min by hand.
3.3.4 Data Analysis

The pressure data were exported as a comma-separated variable file and then imported into Wolfram Mathematica software (Wolfram Research, Champaign, IL) for subsequent analysis. Due to the pulsatile nature of the pumps, TMP values were time-averaged over approximately 8 s. To calculate the critical flux, the center third of the TMP data for each permeate flow rate were averaged to eliminate any transitional pressures between fluxes. A linear fit was applied to the first two average TMP values. The next two average TMP values were compared to the linear fit. If the next point deviated from the line by more than 7.5% and deviated less than the following point, the critical flux was assumed to have been passed. If not, the linear fit was extended to include the next data point and the following two points were analyzed. The comparison of two data points ensures that any one-time variability in the system (i.e. movement of the pressure sensors) does not impact the critical flux. An example of the critical flux analysis was shown previously in figure 2.6.

3.3.5 Slurry Concentration Analysis

Due to resin-hold up in the concentrated slurry in both the membrane and the retentate line, the entrance slurry concentration tends to change slightly throughout the entire experiment. The actual slurry concentration at any given time was calculated using a simple mass balance based on the system block flow diagram shown in Figure 3.2.
Figure 3.2: A block flow diagram of the critical flux experimental setup.

The mass balance for the resin leads to the following expression for the outlet volume fraction ($\phi_2$) in terms of the inlet volume fraction ($\phi_1$)

$$\phi_2 = \frac{\phi_1}{1-x}$$

(3.1)

assuming that there is no particle accumulation in the membrane. The total volume of resin in the system was evaluated using equation 3.2:

$$\phi_{initial} V_{total} = \phi_2 (0.5 V_m + V_r) + \phi_1 (0.5 V_m + V_f + V_t)$$

(3.2)

The concentration of resin particles in the lumens of the hollow fiber membranes was estimated as the mean value between $\phi_1$ and $\phi_2$, which is consistent with a linear particle concentration
profile within the module. Equations 3.1 with 3.2 are combined to evaluate the particle concentration in the slurry over the course of the experiment.

\[
\frac{\phi_1}{\phi_{initial}} = \frac{V_f + V_r + V_m + V_l}{1 - \chi (0.5 V_m + V_r) + (0.5 V_m + V_f + V_l)}
\] (3.3)

All calculations of \(\phi_1\) and \(\phi_2\) used in this thesis were based on equation 3.3.
CHAPTER 4

Results and Discussion

4.1. System Behavior

Typical experimental data for the TMP from a critical flux experiment performed with a 10% slurry of Macro-Prep 25Q resin at a feed flow rate of 250 mL/min are shown in Figure 4.1a. The pressure monitoring system recorded TMP values once per second, with the rapid oscillations in TMP reflecting the pulsatile nature of the peristaltic pumps. For t < 150 s, the permeate pump was closed, with the feed simply recirculated through the module. The permeate flow rate was increased every 150 s, with the TMP recorded as a function of time over each interval. The mean TMP remained constant during each period prior to t = 1650 s. At longer times, the TMP showed a small rise after the flux was increased, with the TMP then stabilizing at a constant value.

Figure 4.1b shows a plot of the mean TMP as a function of the permeate flux. The data are highly linear for permeate fluxes below $180 \times 10^{-6}$ m/s (corresponding to a permeate flow rate of 210 mL/min). In contrast, the plot of mean TMP became non-linear at higher flux, with the TMP increasing quite dramatically at permeate flux above about $200 \times 10^{-6}$ m/s. The data in Figure 4.1b were used to evaluate the critical flux as $J_{crit} = 180 – 190 \times 10^{-6}$ m/s, corresponding to a conversion of 80-82% and an outlet particle concentration of 43-47% by volume.

Figure 4.1c shows the feed and permeate pressures as a function of time during the flux excursion experiment shown in Figure 4.1a. At low permeate flux, both the feed and the permeate pressures decrease with time. The reduction in the feed pressure is due to the increase
in conversion and the corresponding reduction in the axial pressure drop through the module $(P_{\text{feed}} - P_{\text{retentate}})$ as the permeate flow rate was increased; the retentate (exit) pressure in this system remained constant due to the pressure imposed on the recycle line back to the feed tank. The behavior is very different at high permeate flow rates, with the increase in feed pressure arising from the increase in axial pressure drop caused by the increase in suspension viscosity at the high particle concentrations that exist near the fiber exit under these conditions. Note that a similar increase in feed pressure would occur if a particle cake formed on the membrane surface, decreasing the effective fiber radius. The change in pressure behavior occurs at $t \approx 1050$ s, which is the time at which the system first exceeded the critical filtrate flux based on the results in Figure 4.1b.
Figure 4.1: Experimental data during a flux excursion experiment for the 10% Macro-Prep 25Q at a feed flow rate of 250 mL/min: (a) TMP and permeate flux as a function of time, (b) mean TMP as a function of permeate flux, and (c) feed side pressure (black) and the permeate pressure (red) with time.
In some experiments, the TMP actually became unstable at a certain value of the permeate flux. This behavior was most commonly seen with the smaller particles at lower feed flow rates (below 250 mL/min). A typical set of results is shown in Figure 4.2a for a flux excursion experiment using a 10% slurry of MacroPrep 25Q resin at a feed flow rate of 50 mL/min. The behavior at short times was similar to that seen in Figure 4.1, although the TMP values were quite low due to the low flow rates in this experiment. In contrast, the TMP began to increase slightly before stabilizing for $t > 1000$ s, corresponding to a permeate flux of $39 \times 10^{-6}$ m/s (yielding a permeate flow rate of 46 mL/min). This behavior is likely due to the formation of a cake layer on the membrane surface, with the increase in TMP reflecting the increase in resistance with time as the cake grows in thickness (and possibly density) before reaching a steady state resistance to permeate flux. After 1600 s, the permeate flux was further increased to $40 \times 10^{-6}$ m/s (corresponding to a permeate flow rate of 48 mL/min). In this regime, the TMP begins to increase and does not stabilize. This type of increase in TMP with time was often observed for low cross flow velocity experiments, particularly with smaller particles. The critical flux for this experiment corresponds to a conversion of 85-90% with an outlet slurry concentration of 43-52% by volume.
Figure 4.2: Flux excursion data for the 10% MacroPrep 25Q at a feed flow rate of 50 mL/min. (a) TMP and flux as a function of time, (b) mean TMP as a function of filtrate flux.
4.2 Reproducibility of Data

Although the evaluation of the critical flux based on the TMP data in Figures 4.1 and 4.2 might appear to be somewhat arbitrary, the critical flux values were highly reproducible for repeat experiments performed under comparable experimental conditions. For example, Figure 4.3a shows TMP data for 2 flux excursion experiments for a 10% slurry of Macro-Prep 25Q resin at a feed flow rate of 250 mL/min, while Figures 4.3b and c show data for repeat experiments with a 10% slurry of Poros 10A resin at feed flow rates of 250 and 100 mL/min, respectively. In order to account for the variability in the pressure gauges, the data for each experiment have been shifted so that the initial TMP was equal to 0 psi (at J = 0). Note that the individual experiments were performed on different days using a separate batch of resin particles.

The TMP values for the repeat experiments were essentially identical, with the small variations lying within the expected experimental variability for the pressure gauges. Table 4.1 shows the calculated values of the critical flux for each trial and the percent difference in calculated critical flux between trials. The largest difference occurred for the trials where the feed flow rate was lowest. This is likely the result of the larger size of the permeate flux step relative to feed flow rate associated with the limited precision of the permeate pumps.
Figure 4.3: Repeat flux excursion experiments for (a) 10% Macro-Prep 25Q at a feed flow rate of 250 mL/min and for a 10% Poros 10A resin at feed flow rates of (b) 250 mL/min and (c) 100 mL/min
Table 4.1: Experimental average values of the critical flux, $J_{CRIT}$, for repeated trials.

<table>
<thead>
<tr>
<th>Experiment</th>
<th>Average Critical Flux, $J_{CRIT} \times 10^6$ m/s</th>
<th>Percent Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>10% MacroPrep 25Q with 250mL/min feed flow rate</td>
<td>174</td>
<td>158</td>
</tr>
<tr>
<td>10% Poros 10A with 250mL/min feed flow rate</td>
<td>156</td>
<td>142</td>
</tr>
<tr>
<td>10% Poros 10A with 100mL/min feed flow rate</td>
<td>52</td>
<td>60</td>
</tr>
</tbody>
</table>

4.3 Effect of Cross Flow Velocity on the Critical Flux

Figure 4.4 shows the calculated values of the critical flux for 4 different resins, all with a feed concentration of 10%, as a function of the wall shear stress, $\tau_w$, which was evaluated using Equation (2.7). The critical flux for each resin varies linearly with $\tau_w$, with $r^2$ values of greater than 0.998 and an intercept that goes directly through the origin.

The linear relationship between the critical flux and the wall shear stress is in good agreement with the form given by the modified shear-induced diffusion model given by Equation (2.8). In contrast, the modified inertial lift model, Equation (2.10), predicts a non-linear relationship between the critical flux and the wall shear stress. The data in Figure 4.4 thus indicate that the inertial lift model cannot accurately represent the shear stress dependence of the critical flux data obtained with the chromatographic particles examined in this study.
Figure 4.4: Critical flux for (a) Poros 10A, (b) Poros 20OH, (c) MacroPrep 25Q, and (d) Poros 45A as a function of $\tau_w$ with a feed concentration of 10%. A linear fit, consistent with the shear-induced model, is shown in gray and the inertial lift model is shown in red.

4.4 Effect of Particle Volume Fraction on the Critical Flux

Figure 4.6 shows results for $J_{\text{CRIT}} / \tau_w$ for the Poros 20 and MacroPrep 25Q resins as a function of the particle volume fraction in the feed suspension, $\phi_1$. Note that the particle volume fraction was evaluated from the height of the packed particle layer obtained during centrifugation. Thus, the values of $\phi_1$ reported in Figure 4.5 are not true volume fractions but are instead equal to the ratio of the actual particle volume fraction to that of the densely packed particle layer. The blue and red curves in Figure 4.5 are the calculated values of the shear-induced diffusion model using $\phi_w = 1.0$, corresponding to a wall concentration equal to the
particle volume fraction in the packed bed, and also with $\phi_w = 0.42$. This latter value is consistent with the calculated particle volume fraction at the exit of the module based on the measured values of the critical flux over a range of feed concentrations.

The calculated values of $J_{CRIT}/\tau_w$ decrease with increasing particle volume fraction for both resins, although the dependence on the volume fraction appears to be much weaker than that predicted by the shear-induced diffusion model, particularly for the Poros 20OH resin. The agreement between the data and the shear-induced diffusion model (using $\phi_w = 0.42$) is much better for the MacroPrep 25Q, although the experimental results lie below the model at very small particle volume fractions and above the model at high volume fractions.
Figure 4.5: Critical flux data for (a) the Poros 20OH and (b) the MacroPrep 25Q resin as a function of particle volume fraction in the feed. The blue and red curves are the calculated values of the critical flux for the shear-induced diffusion model assuming $\phi_w=1$ and 0.42, respectively.
4.5 Effect of Buffer Conditions on the Critical Flux

Table 4.2 shows data for the critical flux at different buffer salt concentrations pH. The experiments were performed with a the MacroPrep 25Q ion exchange resin at a particle volume fraction of 0.1. The calculated values of the critical flux were essentially independent of both pH and salt concentration, suggesting that electrostatic interactions associated with the surface charge of the particles has no effect on the critical flux.

Table 4.2: Critical flux range for MacroPrep 25Q resin with $\phi_1 = 0.10$ for varying buffer salt concentration and pH.

<table>
<thead>
<tr>
<th>Buffer Salt Concentration (mmol/L)</th>
<th>Buffer pH</th>
<th>J_{\text{CRIT}} (10^{-6} \text{ m/s})</th>
</tr>
</thead>
<tbody>
<tr>
<td>15</td>
<td>5.4</td>
<td>154.0 - 163.0</td>
</tr>
<tr>
<td></td>
<td>7.4</td>
<td>158.0 - 163.0</td>
</tr>
<tr>
<td></td>
<td>8.4</td>
<td>163.0 - 167.0</td>
</tr>
<tr>
<td>150</td>
<td>5.4</td>
<td>154 - 163</td>
</tr>
<tr>
<td></td>
<td>7.4</td>
<td>163 - 167</td>
</tr>
<tr>
<td>500.0</td>
<td>5.4</td>
<td>167.0 - 171.0</td>
</tr>
</tbody>
</table>

4.6 Effect of Particle Size on the Critical Flux

Figure 4.6 shows data for the critical flux as a function of particle radius at a constant particle volume fraction of 0.1. The data are plotted as the ratio of the critical flux to the wall shear stress based on the linear relationship discussed in the previous section. Normalizing the data in this manner allows results from multiple experiments at slightly different wall shear stress to be analyzed in a single plot. The predicted dependence of the critical flux given by the shear-induced diffusion model (equation 4.1) is shown as the dashed gray curve.
Figure 4.6: $J_{\text{CRIT}}/\tau_w$ as a function of resin particle diameter where $\phi_1 = 0.10$. The red circles indicate the average value fit in section 4.3 and the gray curve is the shear-induced diffusion model.

The experimental data for the critical flux are essentially independent of the particle diameter; a linear regression fit to the data in Figure 4.6 gave a slope that was not statistically different than zero. This is in sharp contrast to predictions of the shear-induced diffusion model which gives a critical flux (or $J_{\text{CRIT}}/\tau_w$) that increases with particle diameter to the $\frac{4}{3}$ power.

4.7 Hydrodynamic Analysis

The experimental data from the flux excursion experiments for the different resins are summarized in Table 4.3, with results shown for the calculated values of the particle volume fraction at the exit of the module when $J = J_{\text{crit}}$. A range of $\phi_{\text{CRIT}}$ values are shown at each feed
velocity, corresponding to the flux values just before and after the TMP data became non-linear. Although there is some scatter in the data, the calculated values of $\phi_{\text{CRIT}}$ are essentially independent of the feed velocity, which is consistent with the linear dependence of the critical flux on the wall shear stress discussed previously in Section 4.3. The final column shows the mean value of the exit particle volume fraction for each resin, calculated as the average of the upper and lower limits on $\phi_{\text{CRIT}}$ for all of the feed velocities. The mean values of the exit particle volume fraction, $\bar{\phi}_{\text{CRIT}}$, appear to be essentially the same for all of the chromatographic resins, even though the resins vary in particle diameter from 10 to 45 µm.

**Table 4.3:** The calculated values of the exit particle volume fraction at $J = J_{\text{crit}}$ for the different chromatographic resins as a function of the feed velocity. The final column shows the mean value of the exit particle volume fraction.

<table>
<thead>
<tr>
<th>$D_p$ (µm)</th>
<th>$v$ (m/s)</th>
<th>$\phi_{\text{CRIT}}$ (%V)</th>
<th>$\bar{\phi}_{\text{CRIT}}$ (%V)</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>0.12</td>
<td>32.5 - 37.8</td>
<td>38</td>
</tr>
<tr>
<td></td>
<td>0.24</td>
<td>32.5 - 45.1</td>
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<tr>
<td></td>
<td>0.59</td>
<td>37.8 - 45.1</td>
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<td></td>
<td>1.18</td>
<td>38</td>
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<tr>
<td>20</td>
<td>44.3 - 48.5</td>
<td>35.5 - 45.7</td>
<td>42</td>
</tr>
<tr>
<td></td>
<td>35.0 - 40.5</td>
<td>35.3 - 40.7</td>
<td></td>
</tr>
<tr>
<td></td>
<td>43.0 - 46.9</td>
<td>36.2 - 38.8</td>
<td></td>
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<tr>
<td>25</td>
<td>43.3 - 47.3</td>
<td>34.7 - 47.9</td>
<td>42</td>
</tr>
<tr>
<td>45</td>
<td>43.3 - 47.3</td>
<td>34.7 - 47.9</td>
<td>40</td>
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</table>

The similarity in the calculated values of $\bar{\phi}_{\text{CRIT}}$ suggest that the critical flux may be determined more by the fluid flow characteristics of the hollow fiber module and the packing characteristics of the particle suspensions than by the boundary layer effects described in the shear-induced diffusion model. In order to explore this further, we used a very simple model accounting for the change in pressure gradient associated with the reduction in retentate flow rate, $q$, and the increase in suspension viscosity, $\mu$, with increasing conversion:
where \( N \) and \( R \) are the number and radius of the hollow fibers respectively. There are a variety of correlations available for the viscosity of concentrated suspensions, most of which are based on a power-law type function [18]:

\[
d = f_{\text{max}} - f \times f_{\text{pack}}
\]

\[
\mu = \left( \frac{8}{N \pi R^4} \right) Q \mu
\]

where \( \phi_{\text{max}} \) is the maximum particle volume fraction at which the suspension remains fluid and \( \phi_{\text{pack}} \) is the particle volume fraction in the packed particle layer obtained in the centrifuge. The particle volume fraction increases along the length of the module due to the filtration:

\[
\phi_2 = \frac{\phi_1 Q_{\text{feed}}}{Q_{\text{retentate}}}
\]

where \( Q_{\text{feed}} \) and \( \phi_1 \) are the inlet volumetric flow rate and volume fraction and we have assumed that the particles are fully retained by the membrane.

Figure 4.7 shows a plot of the pressure gradient normalized by the pressure gradient at the inlet conditions as a function of the conversion for an inlet particle concentrations of 5 and 10% assuming that \( \phi_{\text{max}} = \phi_{\text{pack}} = 0.64 \). The pressure gradient initially decreases with increasing conversion going through a minimum at 86% conversion for the 5% feed and at 72% conversion for the 10% feed. These conversions correspond to outlet particle concentrations of \( \phi = 0.36 \) for both feeds. Although this is slightly below the maximum outlet particle concentrations seen in Table 4.3, the discrepancy is relatively small given the uncertainties in the values for \( \phi_{\text{max}} \) and \( \phi_{\text{pack}} \). Operation at higher conversions would lead to a large increase in the axial pressure gradient, potentially causing rapid growth of a particle deposit at the inlet of the hollow fiber modules (i.e., in the region where the local transmembrane pressure drop is greatest). Note that
the formation of this type of particle deposit would tend to constrict the fiber diameter, further increasing the local pressure gradient as given by Equation (4.1).

Figure 4.7: Ratio of outlet pressure gradient to feed pressure gradient as a function of conversion (X). The red and gray curves correspond to feed volume fractions of 0.1 and 0.05 respectively.
CHAPTER 5

Conclusions

5.1 Conclusions

This thesis examined the hydrodynamic behavior of concentrated slurries of chromatographic particles in hollow fiber membrane modules, with the experimental conditions representative of those encountered in countercurrent tangential flow chromatography (CTC) systems. The particle suspensions all exhibited a critical filtrate flux, with data for the flux versus transmembrane pressure remaining linearly and stable (independent of time) when the system was operated at a filtrate flux that was below the critical flux for that suspension. These results provide the first extensive data set describing the critical flux behavior for chromatographic particles with diameters between about 10 and 50 µm.

All of the chromatographic resins showed a linear relationship between $J_{\text{crit}}$ and the wall shear stress ($\tau_w$), with $r^2$ values greater than 0.998. The best fit value of the slope for the linear regression fit provided an appropriate measure of the critical flux characteristics for each resin at any given feed concentration. This allowed data for experiments with slightly different cross-flow velocities to be analyzed simultaneously. The linear relationship between $J_{\text{crit}}$ and $\tau_w$ was consistent with the form given by the shear-induced diffusion model, although the observed dependence of the critical flux on both particle size and concentration showed significant discrepancies with the model.

Data obtained over a range of buffer conditions showed no effect on the critical flux, suggesting that interparticle (electrostatic) interactions were unimportant in this system due to the very small ratio of the Debye length to the particle diameter ($< 10^{-4}$). There was also no
obvious dependence of the critical flux on the particle size for diameters between 10 and 45 µm. Interestingly, the outlet particle volume fraction ($\bar{\phi}_{CRIT}$), equal to the outlet fraction when the filtrate flux is equal to $J_{crit}$, was essentially constant for all resins and operating conditions, suggesting that the critical filtrate flux may be determined primarily by the flow characteristics of the concentrated suspension in the hollow fiber membrane modules. A simple mathematical model was developed for the variation of the local pressure gradient arising from the change in retentate flow rate and particle concentration with increasing conversion that was in at least qualitative agreement with the experimental observations.

Additional research will be required to quantify the relationship between $J_{CRIT}/\tau_w$ and the properties of the resin, the membrane, and the fluid flow characteristics. In particular, it would be very important to perform experiments using modules with different length and different permeability to independently control the filtrate flux and the outlet particle concentration. For example, shorter modules would have to be operated at much higher filtrate flux to obtain the same outlet particle concentration. These data would hopefully provide a much more rigorous test of the simple hydrodynamic model developed in this thesis.
REFERENCES


