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Predicting performance of constant flow depth filtration using constant pressure filtration data

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ABSTRACT

This paper describes a method of predicting constant flow filtration capacities using constant pressure datasets collected during the purification of several monoclonal antibodies through depth filtration. The method required characterisation of the fouling mechanism occurring in constant pressure filtration processes by evaluating the best fit of each of the classic and combined theoretical fouling models. The optimised coefficients of the various models were correlated with the corresponding capacities achieved during constant flow operation at the specific pressures performed during constant pressure operation for each centrate. Of the classic and combined fouling models investigated, the Cake-Adsorption fouling model was found to best describe the fouling mechanisms observed for each centrate at the various different pressures investigated. A linear regression model was generated with these coefficients and was shown to predict accurately the capacities at constant flow operation at each pressure. This model was subsequently validated using an additional centrate and accurately predicted the constant flow capacities at three different pressures (0.69, 1.03 and 1.38 bar). The model used the optimised Cake-Adsorption model coefficients that best described the flux decline during constant pressure operation. The proposed method of predicting depth filtration performance proved to be faster than the traditional approach whilst requiring significantly less material, making it particularly attractive for early process development activities.

1. Introduction

The market for therapeutic monoclonal antibodies (mAb) has seen unprecedented growth in recent years and this expansion is predicted to continue over the next decade [1]. To meet product supply for this increasing market and to ensure potential new drug candidates are manufactured effectively, pharmaceutical and biotechnology companies are required to operate across a wide range of scales, including large-scale manufacturing performed in vessels up to 20,000 L in addition to research development activities carried out using small or micro-scale systems. One of the challenges of operating at multiple scales is the need for flexible and scalable downstream processing unit operations. Depth filtration is an adaptable and scalable unit operation that has gained wide acceptance as the technique of choice for the clarification of mammalian cell culture broth post-centrifugation [2]. Accurate estimations of the optimum filter sizing of this key unit operation are critical. Over-sizing of the filter is uneconomic and under-sizing of the filter can result in process-related issues such as increased fouling in subsequent chromatographic stages thus shortening column lifetime and efficiency [3,4] or filter blockage resulting in loss of material. For constant flow operation the optimum filter area or capacity is defined as the cumulative volume of material filtered until a maximum pressure is reached [5] whereas the capacity for constant pressure is determined as the volume of material processed before a minimum flow rate is reached [6]. The optimum capacity of this unit operation is difficult to predict and can be influenced by a large number of parameters, including mode of operation, type of cell line, level of aggregates, cell culture conditions and centrifuge operating conditions [2]. Typically in an industrial environment, depth filtration trials are performed in constant flow mode on a scale-down mimic that predicts

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Nomenclature

a	cake model coefficient (L m^{-2})
b	cake model exponential coefficient (m)
A	available membrane frontal area (m^2)
$CF_{Cap,i}$	filter capacity at constant flow for a given pressure (L m^{-2})
J	flux (L m^2 h^{-1})
$J_v(0)$	initial flux (L m^2 h^{-1})
$J_v(t)$	flux relative to available membrane area (L m^2 h^{-1})
K_A	complete blocking constant (m^2 L^{-1})
K_C	cake filtration constant (m^2 L^{-1})
K_{Com}	complete blocking constant (m^2 L^{-1})
K_I	intermediate blocking constant (m^2 L^{-1})
K_S	standard blocking constant (m^2 L^{-1})
LMH	liters per meter per hour (L m^{-2} h^{-1})
P	pressure (bar)
R_{filter}	specific resistance to filtration (m^{-1})
R^2	coefficient of determination
t	time (h)
V	volume filtered (m^3)

Greek letters

α_O	Cake-Adsorption model coefficient (L m^{-2} h^{-1})
$\alpha_{1,2,}$	Cake-Adsorption model coefficients (L^2 m^{-4} h^{-1})
$\alpha_{3,4}$	Cake-Adsorption model coefficients (L^4 m^{-6} h)
μ	solution viscosity (Pa s)

the capacity at large-scale for each material tested. One of the problems of this approach is that it is time-consuming and material-intensive, particularly in comparison to capacity predictions performed in constant pressure mode. Fundamentally constant pressure and constant flow are operated differently. In constant flow operation a positive displacement pump is required to ensure the constant flow is maintained throughput the run. The pressure drop across the filter increases to maintain this constant flow due to foulant build up with time. In contrast, during constant pressure operation the initial flux through the filter is relatively high and decreases gradually as the filter fouls resulting in the hydrodynamic conditions at the filter surface changing over time [7]. This initial high flux can result in severe fouling [8] and therefore subsequently reduce the overall capacity of the filter. Hence the majority of biopharmaceutical processes operate in constant flow mode to maximize the available filter area. Miller et al. [7] demonstrated comparable fouling behavior between constant flow and constant pressure operation during dead-end ultrafiltration of an emulsified oil for low constant flow operation (< 62 LMH) with deviations between the modes of operation found for flows about this value. Furthermore, Bolton et al. [9] and Chellam and Xu [10] demonstrated comparable fouling characteristics between the two modes of operation during the dead-end ultrafiltration of various materials ranging from antibody preparations to bacteria. Little research has investigated the conversion of constant pressure to constant flow operation for depth filtration.

Understanding membrane fouling remains a major challenge due to the multiple factors influencing this highly complex mechanism. Upstream processing conditions including cell viability and centrifuge operation can greatly influence the feed material onto a primary recovery depth filter resulting in significantly varied filtration properties [11]. Furthermore, the filters typically have an anisotropic pore structure resulting in various fouling mechanisms from deposition to adsorption of solutes to the membrane surface, cake layer formation, concentration polarisation and build-up of osmotic pressure [7]. In an attempt to simplify these highly complicated mechanisms various mathematical models have been applied to quantify the observed fouling. A limitation of these blocking models is that they are semi-empirical and assume the fouling mechanism is solely related to the physical blockage of the pores or inner pore walls as a result of the particles depositing onto the surface [12]. However, his generalisation has been widely implemented and successfully approximated the observed fouling during dead-end microfiltration [8,13–15], ultrafiltration [16,17] and depth-filtration [18,19]. The four classic models outlined in the literature are referenced as Complete blocking, Standard blocking, Cake filtration and Intermediate blocking [15]. Combination models have also been investigated which incorporate two or more of the classic models in conjunction. These have been shown to describe better the observed fouling in filters where classic models fail [17]. Most research has focused on the application of these mathematical models to define the fouling properties of proteins in dead-end microfiltration systems during constant pressure operation [9,13,15] or ultra-filtration [17,18]. Depth filtration operates slightly differently than these absolute filters and mainly retains the particles in the filter media, however these fouling models have been successfully demonstrated to model the observed fouling [19]. Sampath et al. [15] showed that these mathematical models can characterise the fouling of depth filters during the loading of a *Pichia pastoris* fermentation during constant pressure operation. Hlavacek and Bouchet [16] implemented the models to explore the fouling behaviours at constant flow and demonstrated the ability of the intermediate model to fit the pressure increase of bovine serum albumin (BSA) solutions filtered through various different membrane types. Similarly, Ho and Zydney [13] modelled constant flow microfiltration of protein, while Chellam and Xu [10] used these blocking laws to analyse the constant flow microfiltration of colloids. As depth filtration post centrifugation is the primary clarification method for large-scale mammalian cell manufacturing there is a need to investigate the various fouling modes that occur during both constant flow and constant pressure operation.

The ability to translate across constant flow and constant pressure models in filtration studies would be a major step forward and result in significant savings of time and valuable test materials for filter sizing studies. Bolton et al. [9] investigated the transition between these two modes of operation on dead-end microfiltration through characterisation of a bovine serum albumin foulant on a membrane filter. They found that the parameter coefficients of various theoretical models used to fit the flux decline during constant pressure operation could be used within the constant flow model to predict the observed pressure increase. However, with this method some models require calculation of the initial pressure drop for constant flow operation or the initial flux decline for constant pressure operation to generate predictions in the different mode.

Our study provides a methodology to accurately predict the capacity of depth filtration operated under constant flow utilising only constant pressure flux decline data. The flux decline of a wide range of industrially relevant centrates was characterised under constant pressure operation by evaluating the fit of various theoretical fouling models. Subsequently, constant flow experiments were conducted to determine the capacity of each of the centrates investigated. The model was found to be highly robust based on a low root mean square error for cross-validation. Additional experiments were performed to validate further the model and demonstrate its ability to predict accurately capacity at constant flow using data performed at constant pressure while also using significantly less material. This method may be highly beneficial at an early stage in the development of new molecules or proteins where material and time resources for process studies are often in short supply.