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A scale-down cross-flow filtration technology for biopharmaceuticals and the associated theory

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ABSTRACT

Use of microfiltration (MF) and ultrafiltration (UF) in cross-flow mode has been intensifying in downstream processing for expensive biopharmaceuticals. A scale-down cross-flow module with ring channel was constructed for reducing costs and increasing throughput. Commensurate with its validation, a new scale down (or scale up) theoretical framework has been further developed to 3 operational parities: (1) ratio of initial sample volume to membrane area, (2) shear force adjacent to membrane surface, and (3) initial permeate flux. By keeping identical initial physicochemical properties, we show that these 3 operational parities are equivalent to 2 further time-dependent theoretical parities for flux and transmission respectively. Importantly, transmission sensitively reflects membrane conditions for partially transmissible molecules or particles. Computational fluid dynamics simulation was conducted to confirm nearly identical shear forces for the mini and its reference filters. Permeate fluxes in suspension containing *Escherichia coli* phage T7, a monoclonal antibody (MAb) or other proteins, and transmission (with phage T7) were measured. For application demonstration, diafiltration and concentration modes were applied to the MAb, and separation mode to a mixture of bovine serum albumin and lysozyme. In conclusion, the developed scale-down filter has been shown to behave identically or similarly to its reference filter.

1. Introduction

Cross-flow filtration (CFF) is a matured industrial technology widely used in pharmaceutical, biopharmaceutical and other industries (Baruah et al., 2005). Compared with dead-end filtration, CFF can effectively minimize concentration polarization, reduce membrane fouling and thus prolong membrane life cycle (Charcosset, 2012).

Ultrafiltration (UF) and microfiltration (MF) have been increasingly adopted in downstream processing of expensive biopharmaceutical manufacturing, notably monoclonal antibodies (MAb) production. With more and more MAbs turning to biosimilars, their future commercial success will largely depend on bioprocessing innovations where UF and MF have been playing pivotal roles in effectively reducing manufacturing costs. In addition, development of emerging gene therapy products pressingly requires competent filtration technologies (Wan et al., 2005).

To develop or select suitable filtration unit operations, it is essential to fully understand all the relevant filtration mechanisms and optimization strategies (Reis and Saksena, 1997). To develop such customized filtration operations, conventionally numerous lab-scale experiments are required and consequently the resultant costs for expensive products like MAb can be unacceptably high.

To reduce such R&D costs, it is usually acceptable to either use appropriate mathematical models or conduct scale-down experiments (Brown et al., 2011). By in large, it is notorious difficult

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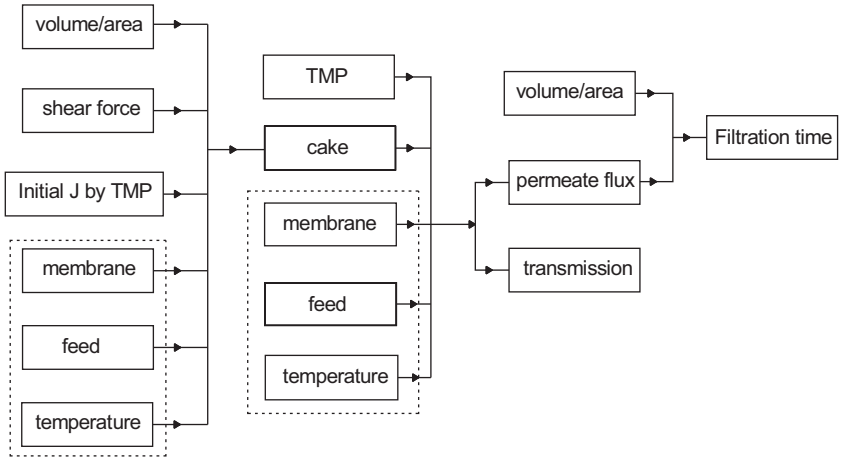

Fig. 1. Schematic on interactional hierarchy of relevant physiochemical and operational parameters. An arrow refers to a cause-outcome relationship. Note that physiochemical properties, feed, temperature and membrane, are the same between the lab and mini filters.

to have a mathematical model that fits all process aspects. Using only a small amount of samples, a scale-down technology offers opportunities for accurate predictions on laboratory scale and large production scales (Ma et al., 2010). Indeed, over the past decade a portfolio of downstream processing unit operations has been successfully scaled down (Hutchinson et al., 2009; Lopes and Keshavarz-Moore, 2012; Titchener-Hooker et al., 2008; Tustian et al., 2007).

To scale down a filtration process for studying membrane fouling, a pulsed sample injection technique was design for a stirred cell UF module (15.73 ml working volume) (Ghosh, 2002). A similar module was scaled down to accommodate merely 6 ml working volume for MAb separation (Wan et al., 2005). A stirred cell module was further scaled down to accommodate only 1.5 ml working volume (Ma et al., 2010). Each of these scaled-down modules contains only a single filtration unit and has no potential for multi-unit expansion. To demonstrate high-throughput potential, multi-well MF filters were tested for *Escherichia coli* fermentation broth (Jackson et al., 2006). Industry invariably relies on CFF to downstream process biopharmaceuticals, but all the above scale-down projects have been based on dead-end filtration. For CFF module, the Pellicon XL series filtration cartridges from Millipore (with 50 cm^2 membrane area) has been validated to be accurate in 1:10,000 fold scale-up, but a minimum of 15 ml feed volume is needed and is suitable for only a single unit usage.

The objective of this work is thus to fabricate a novel scale-down CFF module (mini filter), capable of high-throughput and inexpensive installation. A ring channel scale-down filter (for a minimum of 3 ml feed volume) was designed for using the popular 25 mm diameter round membrane and its filtration performance was compared with the validated 50 cm^2 Pellicon XL lab-scale TFF system. Success in scale-down depends on having the same or similar permeate flux and transmission between the 2 scales at identical shear force. Transmission is defined as the ratio of particle densities (protein concentrations) between permeate and retentate. Before filtration experiment, CFD simulation was used to compare the 2 filters and then to adjust inlet flow rate of the mini filter until their shear forces become identical. To accurately test and validate filtration performance of this novel scale-sown filter, we have taken the opportunity to develop the following theoretical framework.

2. Theoretical framework

Filtration performance is inevitably of non-steady state nature: both permeate flux (J) and transmission (T) decline with time owing to increasing concentration polarization and membrane fouling. To scale down such a process, it is imperative to keep both J and T identical at any time between different filter scales under the same physiochemical condition (feed, membrane, and temperature). The 2 theoretical parities can be elaborated to the following 3 operational parities (Fig. 1). Note that subscripts *lab* and *SD* refer to laboratory and scale-down filters respectively.

2.1. Operational parity (1): identical feed volume per unit membrane area

The feed volume per unit membrane area affects filter cake and filtration time (see Fig. 1 for the other influencing factors), and so the ratio between initial processing volume (V) and effective membrane area (A) for the 2 scales should be kept identical, that is

$$\frac{V_{lab}}{A_{lab}} = \frac{V_{SD}}{A_{SD}} \quad (1)$$

2.2. Operational parity (2): identical shear force

The shear force, resulted from the liquid flowing above the membrane, continuously washes away filter cake and may also affect feed bioactivities (see Fig. 1 for the other influencing factors). It is important to keep shear force identical between the 2 scales for scaling down. Cross flow shear force may be described by:

$$\gamma = \frac{6\mu Q}{h^2 w} \quad (2)$$

where γ is shear force (Pa), μ viscosity (Pa s), Q inlet flow rate ($m^3\ s^{-1}$), h flow channel height (m), and w flow channel width (m).

To reach the same shear force for the 2 scales, Eq. (2) requires,

$$\frac{Q_{lab}}{h_{lab}^2 w_{lab}} = \frac{Q_{SD}}{h_{SD}^2 w_{SD}} \quad (3)$$

2.3. Operational parity (3): identical initial permeate flux made by TMP adjustment

Cross-flow filtration flux at any time may be expressed by Darcy's law:

$$J = \frac{TMP}{R \times \mu} \quad (4)$$

where R is filtration resistance (m^{-1}), TMP *trans*-membrane pressure drop (Pa), μ retentate viscosity (Pa s), and J permeate flux (LMH or $m\ s^{-1}$). Though the same membrane is used, the overall