Journal of Membrane Science 500 (2016) 86–98

Contents lists available at ScienceDirect

Journal of Membrane Science

journal homepage: www.elsevier.com/locate/memsci

Enablers for QbD implementation: Mechanistic modeling for ion-exchange membrane chromatography

Lalita K. Shekhawat, Apurva P. Manvar, Anurag S. Rathore *

Department of Chemical Engineering, Indian Institute of Technology, Hauz Khas, New Delhi, India

ARTICLE INFO

Article history:
Received 17 August 2015
Received in revised form
26 October 2015
Accepted 27 October 2015
Available online 30 October 2015

Keywords:
Ion-exchange membrane chromatography
Mechanistic modeling
Pseudo-first order and pseudo second order kinetic model
Modified Langmuir kinetic model
Steric mass action kinetic model (SMA)

ABSTRACT

Monoclonal antibody (mAb) based therapeutic products presently dominate the pipelines of most biopharmaceutical companies. Due to the large manufacturing requirements for these products, higher productivity is desirable and membrane chromatography has emerged a possible solution. In this study, a mechanistic model has been proposed for membrane chromatography for predicting product breakthrough at different mAb concentrations. First, Linear, Freundlich, Langmuir, and Temkin isotherms have been evaluated for their suitability with respect to modeling of adsorption of a monoclonal antibody therapeutic on an ion- exchange membrane adsorber. Next, pseudo-first-order, pseudo-second-order, modified Langmuir and steric mass action (SMA) adsorption kinetic models have been evaluated and compared. The results indicate that a combination of Langmuir isotherm and modified Langmuir or the pseudo-first order kinetic model provides the best prediction of mAb adsorption on ion-exchange membrane adsorbers. The final model could be successfully used to understand the adsorption kinetics between complex protein and ligand within the membrane device. The proposed approach would be of significant value to the biotech industry in ensuring the better development of future membrane adsorber devices with optimal sizing.

© 2015 Elsevier B.V. All rights reserved.

1. Introduction

Monoclonal antibody based therapeutic products presently dominate the pipelines of most biopharmaceutical companies. Over the past decade, significant improvements in product titer in the cell culture (over an order of magnitude) combined with the significant production requirements due to the high dosage of these products have resulted in a pressure on downstream processing for creating high-throughput process schemes that can process the required amount of product [1,2].

The major challenge in downstream processing is removal of the various host cell related impurities (such as plasmid deoxyribonucleic acid, host cell proteins), process related impurities (such as leached protein A, viruses), product related impurities (such as aggregates), and modulate product related variants (such as basic and acidic variants) [3]. This is achieved in a typical process by using a combination of chromatography steps with orthogonal separation mechanisms [4–6]. The first step in most purification platform is that of Protein A affinity chromatography [7]. This step is capable of efficiently capturing the product from the myriad of components that are present in the cell culture media as well as clear a significant portion of the host cell related and process related impurities. The following steps could be based on use of cation-exchange, anion-exchange, mixed mode or hydrophobic chromatography interactions as the basis of separation [8,9].

Over the last decade, manufacturers have been gradually substituting some of the conventional packed-bed chromatography with membrane chromatography steps [10–19]. Some key drivers for this trend include: (i) dominant convective mass transfer results in reduced processing time, (ii) faster mass transfer allows users to handle high feed concentrations and thus reduce the total required buffer volume, (iii) improved accessibility to binding sites for large bio-molecules (like viruses, plasmids, large proteins) due to the large pore-sizes (0.45–3 μm) results in higher binding capacities, (iv) higher flow rates allow users to process larger process volumes, (v) macro-porous structure of the membranes results in negligible pore diffusion resistance, and finally (vi) low length to diameter ratio leads to lower pressure drop and allows operations at higher flow rates [18].

The increasing use of membrane chromatography (MC) in downstream processing of therapeutic proteins has also resulted in attempts to model this process. Different configurations of MC capsules are available in market like stacked and pleated membrane adsorbers (MA). Stacked membrane adsorbers are available

* Corresponding author.
E-mail address: asrathore@biotechcmz.com (A.S. Rathore).
URL: http://www.biotechcmz.com (A.S. Rathore).

http://dx.doi.org/10.1016/j.memsci.2015.10.063
0376-7388/© 2015 Elsevier B.V. All rights reserved.

in the form of flat sheet arrangement in which the membranes are stacked in multiple layers in a small capsule whereas in the pleated membrane adsorbers, membranes are either spirally wound or pleated around a core. The flow is axial in stacked membrane adsorber whereas radial in pleated membrane adsorber, respectively. The different configurations of MA generally make them non-uniform in their structure and significantly influence the flow across the membranes. Thus, porosity of the membrane is a critical parameter that impacts the flow across the membranes. Typically, flow homogeneity is assumed due to the homogeneous bulk porosity and systematic distribution of surface porosity across the entire cross-section, as has been demonstrated using Transmission infrared spectroscopy and ATR IR spectroscopy, respectively [20]. Present work concentrates on axial flow configuration i.e. stacked membrane adsorber making it device specific. Two of the most popular models for membrane chromatography are: (i) Roper and Lightfoot model (RLM) that uses different sized continuously stirred tank reactors (CSTRs) on both sides of the membrane to account for deviation from the ideal plug-flow behavior [21], and (ii) Zonal rate model (ZRM) that incorporates the effect of inhomogeneous flow on step performance [14].

In this study, a mechanistic model has been proposed to predict product breakthrough for membrane chromatography. The proposed general rate model (GRM) incorporates the effects of various components involved in an actual chromatography system including convection, external mass transfer through a stagnant film, intra-particle mass transfer and adsorption [22]. The pore diffusion within the pores and film diffusion are neglected. The resulting model has been used to predict the amount of mAb adsorbed (q) *versus* time (t) data. Linear, Langmuir, Freundlich, and Temkin isotherms have been examined at room temperature with the temperature kept constant as is the case during commercial manufacturing. This study helps to identify the conditions which results in high adsorption capacities of the membrane adsorber. Further, modified Langmuir, steric mass action (SMA), pseudo-first order, and pseudo-second order adsorption kinetic models have been evaluated. The first two adsorption kinetic models, namely the modified Langmuir and SMA models, were integrated with transport equations in general rate model and simulated using CADET simulator whereas the latter two adsorption kinetic models, namely the pseudo-first and pseudo-second models, were fitted directly to experimental data using linear regression fit. The results indicate that a combination of Langmuir isotherm and pseudo-first order or modified Langmuir kinetic model provides the best prediction of mAb adsorption on ion-exchange membrane adsorbers.

2. Material and methods

2.1. Materials

Sodium di-hydrogen phosphate monohydrate, di-sodium hydrogen phosphate dehydrate and sodium chloride crystals were purchased from Merck, Germany. The monoclonal antibody (mAb) product was donated to us by a major domestic biopharma producer.

2.2. Method and instruments

Mustang S membranes (pore size: 0.8 μm, bed volume: 0.18 ml) were acquired from Pall Corporation, India. Mustang S is a strong cation exchange membrane with sulfonic acid as functional groups. All breakthrough experiments were performed on ÄKTA Avant chromatography system from GE Healthcare, Uppsala, Sweden, at a flow rate of 2 mL/min and a room temperature of 25 ± 2.5 °C. Tubing connections and other system parameters (e.g. tubing dimensions, ÄKTA Avant chromatography system, and membrane volume) were kept constant. Breakthrough experiments were performed for different loading concentrations of mAb ranging from 0.1 to 0.6 mg/mL. The mAb concentrations were prepared by dissolving mAb in 15 mM phosphate buffer at pH 6.5 for the loading and same buffer is used for equilibration and washing steps. These were then injected into the Mustang S adsorber unit using a sample pump. The output mAb concentrations were measured online using UV absorbance at 280 nm in all breakthrough experiments. The pressure drop across the adsorber was continuously monitored using the built-in pressure transducers in the ÄKTA Avant. After attaining breakthrough at each concentration, elution was performed with 300 mM NaCl in phosphate buffer solution at pH 6.5. Primary analyses and documentation of the chromatograms were performed using Unicorn 6.3 software from GE Healthcare Bio-Sciences, Uppsala, Sweden.

2.3. Software

The modeled equations for membrane and system zones modeled as different combinations of continuously stirred tank (CSTR) and plug flow reactor (PFR) resulted into a large set of differential equations. These differential equations were solved numerically using Chromatography Analysis and Design Toolkit (CADET) [23], a general rate model simulator of chromatography. The GRM model contains a system of non-linear partial differential algebraic equations (PDAEs), discretized in space and time using a mass conserving finite volume method. High order non-linear weighted essentially non-oscillatory (WENO) scheme is used to calculate concentration at cell boundaries. The spatially discretized ordinary differential algebraic equations are integrated using implicit differential-algebraic (IDA) solver from the suite of non-linear and differential-algebraic equation solvers (SUNDIALS) that are available in CADET. It allows the user to simulate the retention profiles of the adsorbed species using the general rate model and to choose from a number of different kinetic adsorption models i.e. modified Langmuir and SMA kinetic models that are present in the CADET library.

3. Mathematical model

3.1. Theory

Modeling of membrane chromatography has been attempted by several researchers [24,25]. Typically, the chromatographic process is considered to be a physical process involving mass transport of the solute molecules through the interstitial bulk volume *via* convection and axial dispersion in the mobile phase (Fig. 1A). The solute concentration in the mobile phase and in the stagnant film around the adsorbent is in equilibrium *via* film diffusion. Further, the solute molecules within the porous adsorbent diffuse into the inner portion of the porous adsorbent through pore diffusion. In the case of membrane chromatography, pore and film diffusion are neglected as mass transfer of solute from mobile phase to binding sites is primarily due to convection. This assumption is valid for membranes with larger pores as this results in an easier access of the binding sites and faster mass transfer rates. Thus, only adsorption–desorption rate kinetics is considered as the rate limiting step in the system as external mass transfer *via* film diffusion and pore diffusion are faster than adsorption as shown in Fig. 1B [26,27].

In the present work, we attempt to model membrane chromatography for predicting product breakthrough at different mAb concentrations using the general rate model. The following are the

Download English Version:

https://daneshyari.com/en/article/632539

Download Persian Version:

https://daneshyari.com/article/632539

Daneshyari.com