Design of ion exchange membrane chromatography for downstream bioprocessing

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The separation and purification of valuable biomolecules, such as antibodies and proteins, play an increasingly important role in biopharmaceutical applications supporting the development and production of therapeutics, immunodiagnostics and vaccines [1]. The drastic increase in market demands, such as recent surge in vaccine productions related to the Covid-19 pandemic, has induced great challenges on biopharmaceutical manufacturing, particularly in downstream processing [2]. Although protein purification is typically achieved with column chromatography, it presents major challenges due to the high material cost, ultra-high pressure and mass transfer resistance due to diffusion-dominant transport, and difficulty to scale up for a larger production capacity. Membrane chromatography is recognized as a potential solution to streamline downstream processing due to its enhanced process throughput, scalability and production continuousness [1]. In particular, the success of ion exchange membrane chromatography (IEMC) as a polishing step to remove impurities in protein purification has been demonstrated in laboratory and preparative scales [3]. Although there is limited commercial adoption for large-scale production, the concept of IEMC has attracted many interests and tremendous research progress has been made in the last decade [4]. Nevertheless, the guidelines for designing high throughput IEMC systems for bioprocessing are still unclear.

In this study, based on the review of recent development in the literature and our research, we aim to identify the key performance-determining factors in the design of high throughput IEMC systems. Although some of the modern laboratory-made membranes with polymeric chains of surface charge exhibited much higher binding capacity that is equivalent or beyond that of traditional resins, a trade-off was identified considering the significant loss of process throughput (i.e., permeability) due to the grafted layer on the surface, e.g., up to 40%. We thus highlight the recent advancements in nanofibrous membranes with 3D structure and high throughput as compared to conventional type. The roles of membrane characteristics and flow dynamics in affecting the protein binding performance of the membrane, selectivity and process throughput are critically analyzed**. Figure 1** gives a comparison of several reported membranes of different types in terms of the effects of the structural parameters and surface properties on the protein binding performance, highlighting the importance roles of specific surface area and charge properties. The typical surface morphology of different types of membranes is also presented in **Figure 1** (from left to right), i.e., nanofibrous, microfibrous and conventional type with foam-like structure. Although it was identified to have equally important contribution to the membrane performance, the role of flow dynamics in IEMC applications was not sufficiently understood. The importance of rationally-designed membrane modules in downstream purification of proteins is hence analyzed.

Overall, a comprehensive analysis was provided on the recent academic advancements, highlighting the research gaps in this research domain towards the design of next generation high throughput IEMC systems.

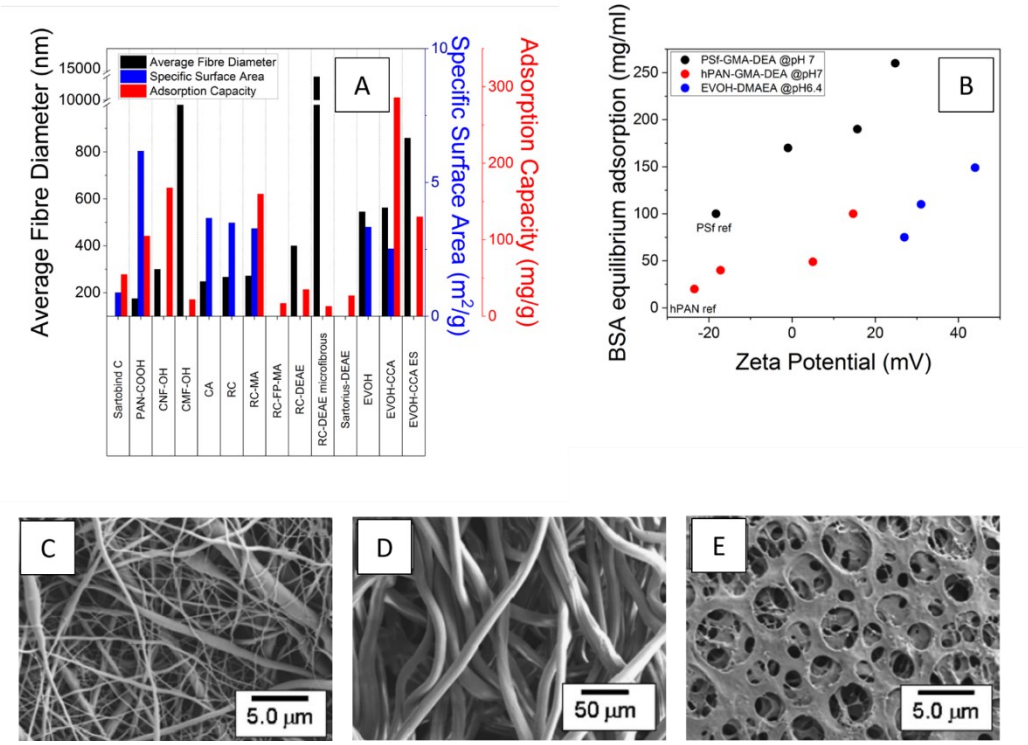

Figure 1. (A): evaluation of average fibre diameter (black), BET specific surface area (blue) and corresponding protein adsorption capacity (red) across a series of membrane adsorbers with lysozyme as model protein in most cases. (B): variation of BSA adsorption equilibrium as a function of the zeta potential. (C), (D) and (E): left to right: typical surface morphology of membrane adsorbers applied in IEMC with nanofibrous and microfibrous structure, compared to commercial membrane with foam-like morphology [4-5].

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