DESIGN AND OPTIMIZATION OF MEMBRANE CHROMATOGRAPHY PROCESS FOR MONOCLONAL ANTIBODY CHARGE VARIANT SEPARATION

Sathish Nadar, The University of Queensland,
s.nadar@uq.edu.au
Balaji Somasundaram, The University of Queensland
Marcela Charry, The University of Queensland
Jagan Billakanti, Global Life Sciences Solutions Australia Pty Ltd
Evan Shave, Patheon Biologics, Pharma Services Group, Thermo Fisher Scientific
Kym Baker, Patheon Biologics, Pharma Services Group, Thermo Fisher Scientific
Linda H.L. Lua, The University of Queensland

Key Words: Membrane chromatography, high throughput process development, charge variants, disposable technologies, flexible manufacturing

The manufacturing scale implementation of membrane chromatography to purify monoclonal antibodies has gradually increased with the shift in industry focus towards flexible manufacturing and disposable technologies. Membrane chromatography is used to remove process-related impurities such as host cell proteins and DNA, leachates and endotoxins, with improved productivity and process flexibility. However, application of membrane chromatography to separate product-related variants such as charge variants has not gained major traction due to low binding capacity. The work reported here demonstrates that a holistic process development strategy (Figure 1) to optimize static binding (pH and salt concentration) and dynamic process (loading density, flowrate, and gradient length) parameters can alleviate the capacity limitations. The study employed high throughput screening tools and scale-down membranes for intermediate and polishing purification of the model monoclonal antibody. An optimized process consisting of anion exchange and cation exchange membrane chromatography reduced the acidic variants present in Protein A eluate from 89.5 % to 19.2 % with target protein recovery of 71 %. The membrane chromatography process also cleared host cell protein to below limit of detection with 6 to 30-fold higher loading density, compared to earlier reported values. The results confirm that membrane chromatography is effective in separating closely related product variants when supported by a well-defined process development strategy.

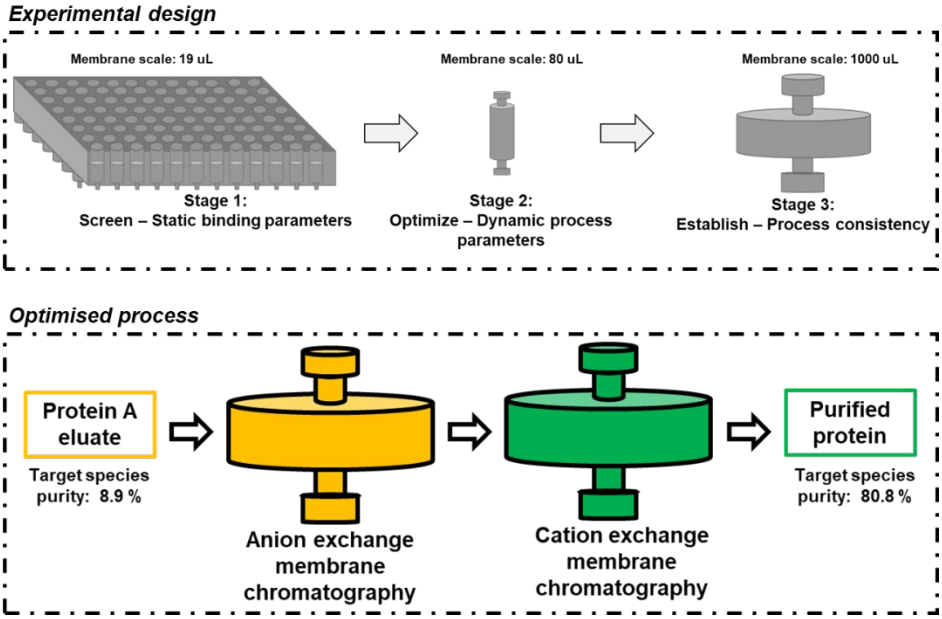

Figure 1: A 3-stage process development approach for implementing membrane chromatography for intermediate and polishing purification of a mAb that achieved target charge variant clearance at industrially relevant loading densities.