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An ultra-scale down method to predict diafiltration performance during formulation of concentrated mAb solutions

Lara Fernandez-Cerezo[1], **Andrea Rayat**[1], **Alex Chatel**[1], **Jennifer Pollard**[2], **Gary J Lye**[1] and **Michael Hoare**[1]
[1]University College London, UK
[2]Merck & Co., Inc., USA

Formulation of monoclonal antibody (mAb) solutions using membrane filtration processing is a critical unit operation in the preparation of antibody therapies. A key constraint in formulation process development, particularly in the early stages of development and when using high protein concentration solutions, is the availability of material for experimental studies. Ultra-scale down (USD) technologies use a combination of critical flow regime analysis, bioprocess modeling and experimentation at the milliliter scale to enable a more effective process development approach significantly reducing process material, cost and time requirements. The ability to predict the performance of large-scale (LS) operations, e.g., flux profile characteristics and changes in protein structure will help maximize the value of eventual high cost pilot-scale runs during process development. In this study a USD membrane device, comprising a sheared cell unit with a rotating disc and with an effective membrane area of 0.00021 m^2 developed at University College London, is used to predict the performance of a LS cross-flow membrane cassette of area 0.11 m^2. The USD set up was designed to mimic the LS in terms of processing volumes, membrane area and process times. Computational Fluid Dynamics (CFD) is implemented to characterize average shear rates as a function of suspension viscosities and disc speed of the USD membrane device. A series of trials at USD scale established the effect of average shear rate on flux and the rate of flux decline during a diafiltration operation reaching 7 diafiltration volumes. A series of LS runs were carried out at different cross flow rates covering a similar range of average shear rates as the USD trials. Good correlation was obtained between USD and LS performance using constant average shear rate over the membrane surface as the basis for scale translation between the two scales of operation. The predicted effect of change in shear rate on flux in USD matched that found in LS. This scale correlation on performance was additionally verified by studying the effect of type and concentration of mAb. The comparable process performance was achieved at USD with 520-fold reduction in effective membrane area, required process material and diafiltration buffer for the trial. Future studies will include membrane concentration operations and evaluating sensitivity to stress-related effects and the impact of operation at higher protein concentrations.

Biography

Lara Fernandez-Cerezo is currently a Doctorate student working towards an Engineering Doctorate degree from University College London sponsored by Merck & Co., Inc., USA. She is working towards establishing an ultra-scale down method to predict large-scale filtration processes of concentrated antibody therapies. During her Doctorate degree, she has developed expertise in computational fluid dynamics modeling, which has been implemented to characterize the ultra-scale down device and different laboratory skills including operation of different membrane filtration systems and analytical techniques for protein quality and quantity measurements.

lara.fernandez-cerezo@ucl.ac.uk

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