Mechanistic Modeling as a Tool to Streamline Downstream Process Development, Scale-Up, and Characterization

T. Huuk, T. Hahn, J. Hubbuch

WHEN THE DoE FAILS

In this case study, a high-capacity cation-exchange resin was used to separate an antibody from a low molecular weight (LMW) and two high molecular weight (HMW) species. All simulations, parameter estimation and process optimization were performed with GoSilico's software ChromX.

DoE experiments conducted previously, failed to achieve a process step yield above 70 percent.

IN-SILICO SCALE-UP

This case study shows how simulation can support process scale-up and scale-down. Only the fluid dynamics outside the pore system change while changing the scale. Once inside the pores, the same mechanism applies from small robotic to production columns.

The tested antibody shows a typical Gaussian peak shape under low load conditions, which transforms into a trapezoidal shape with increasing load. This behavior can be described with an extended adsorption isotherm and all model parameters can be determined by peak fitting. Models calibrated from three gradients at 0.6, 1, or 16 mL scale were able to accurately predict the other scales. Further scale-up to pilot and production scale was successfully done for other undisclosed projects.

Therefore, a computer model was calibrated using three gradient elutions measured by means of UV sensor and offline SEC fraction analyses. ChromX automatically generated pseudo chromatograms from the relative fractions content determined by SEC, shown as dashed lines in the plots on the right. All unknown model parameters were determined by curve fitting. The plots show the target protein and all impurities.

The model fits are very good, the median of the difference of the estimated parameters is 12 % in the 0.6 mL scale and 20 % in the 1 mL scale. Most of the small-scale parameters lie within the 95% confidence intervals of the 16 mL scale. Only kp is not well identified.

MODEL QUALITY & PREDICTIVITY

Use the QR Code to sign up for a meeting with us here at BPI West.

Our team is looking forward to give you a short introduction to the technology, further use cases, and ChromX.

LIVE DEMO