INTRODUCTION

Virus-like Particles (VLPs) are a promising complex molecular format for the development of vaccines. Their size and shape enable an easy uptake by antigen-presenting cells (APCs) resulting in an effective induction of an adaptive immune response. A very time and labor consuming part in developing a VLP production process is the downstream process development. Conventionally, the operational parameters are optimized by Design-of-Experiments studies (DoE). Dozens of experiments are needed to screen a process design space.

1 MODEL CALIBRATION

Initially only two chromatograms, one gradient and one step-wise elution, were recorded. Using only spectral analysis, 6 different feed components were identified. A radial-flow column model was chosen together with the SMA model for ion-exchange chromatography. Model calibration was accomplished using the built-in peak detection and parameter estimation methods of ChromX. After uncertainty quantification (see Model Quality), a first in silico optimization was done using a combination of a step and a gradient.

2 MODEL QUALITY

While the visual model fits are very good, only the calculated 95% confidence intervals provide information, if the parameters are well identified. The uncertainty of the estimation of components 4 (orange) and 6 (pink), which elute close to the product (green), leads to a possible co-elution. The resulting chromatograms and yield distribution for a 1000-point Latin Hypercube Sampling is shown below.

3 MODEL-BASED PROCESS OPTIMIZATION

Robust elution conditions were developed based on the preliminary model. To improve model quality while aiming for baseline separation, the first step was replaced by a gradient. Most of the host cell proteins could be removed and > 95% of the VLPs could be recovered. Furthermore, the elution conditions achieved the desired base-line separation. Alternately, a flow-through of the first peak could be considered.

IMPROVED PROCESS UNDERSTANDING

Based on the finalized model, understanding of product quality attributes and their relation to process parameters could be shown. This is a requirement of the Quality-by-Design guideline set forth by EMA and FDA. Especially valuable in this case is the mechanistic model’s ability to predict the outcome of a scaled-up process, as the employed annulus shaped monolith is only available in a limited set of sizes. In summary, the combination of a limited set of experiments and a mechanistic model enabled a very efficient process optimization and design space characterization. This novel approach could be used whenever no downstream platform process exists yet.