Ruprecht-Karls-Universität Heidelberg
Medizinische Fakultät Mannheim
Dissertations-Kurzfassung

Mechanistic modeling and scale-up investigation of a preparative two-column purification step for a biopharmaceutical polypeptide

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Biopharmaceuticals represent some of the best accomplishments of modern medicine. Over the last decades, more and more new biopharmaceutics have been developed to treat a wide range of diseases. Nevertheless, the purification process of a biopharmaceutical is still a challenging task. Currently, the method of choice for high-resolution product purification mainly focuses on chromatographic techniques. In this work, a preparative multicomponent chromatographic two-column purification process was modeled using mini-columns for model calibration. A polypeptide showed an uncommon anti-Langmuirian to Langmuirian elution behavior on the cation-exchange chromatography resin at low and high loading conditions. On the reversed-phase resin, however, the polypeptide exhibits a Langmuirian elution behavior. The elution behavior of the polypeptide on the cation-exchange resin could be successfully described using an extended version of the self-association isotherm under consideration of the activity coefficients for the solute salt and the protein species. The elution behavior on the reversed-phase resin was successfully modeled using a mechanistic model describing multiple effects between the organic modifier, salt modulator, and protein species. Multicomponent experiments showed that the mechanistic model can describe the competitive behavior between the polypeptide, two product-, and one process-related impurity variant with high accuracy on both chromatographic steps.
Since model calibration was done with pre-packed mini-columns, the scalability of these columns and the developed mechanistic model to larger column volumes was investigated and showed a strong dependency on each column's specific parameters and their unique packing quality. Under consideration of column-specific parameters, the pre-packed mini-column is scalable to larger column dimensions. Furthermore, under consideration of the packing inhomogeneities of each column, successful scale-up simulations with the developed mechanistic model could be done.
With a coupled multicomponent two-column simulation sampling study, the influence of product purity and load was investigated for each chromatographic step and evaluated in a multivariate analysis. This work showed the full potential of the developed model for the two-column purification process, which could be used in further process development and optimization studies.