Predicting Protein-Protein Interactions using the ePC-SAFT Equation Of State

An efficient formulation design based on thermodynamic modeling

Miko Schleinitz, Lea Nolte, Christoph Brandenbusch

Thermodynamic models are increasingly recognized as essential part in pharmaceutical formulation development of "small-molecule" drugs. However, modeling of highly complex (bio-)pharmaceuticals (e.g., monoclonal antibodies) remains a challenging task. Within this work, we developed a modeling approach to access protein-protein and protein-excipient interactions for pharmaceutical proteins in the presence of different excipients using the ePC-SAFT equation of state. This approach gives access to protein phase behavior in these complex solutions and allows to gain a mechanistic understanding on the complex interactions involved enabling an optimized formulation development.

Thermodynamic models are rarely applied in the biopharmaceutical space, due to several challenges of protein formulations compared to small-molecule drugs as e.g., their size/complexity, complex interactions in solution, and the lack of experimental data for fitting pure-component parameters and binary interaction parameters. Heuristic approaches still mark the state-of-the-art for formulation design, including the selection of excipients stabilizing the protein in solution. The insight into molecular interactions gained through this approach is quite unclear. Being able to predict determinants such as B_{22}-(protein-protein interactions) and B_{23}-values (protein-excipient interactions), allows to characterize the nature of intermolecular interactions, and thus the behavior of the protein in solution in the presence of e.g., excipients.

Within this work, we developed an approach to fit ePC-SAFT pure-component parameters of IgG and binary interaction parameters of IgG with excipients to the amino acid sequence of the protein (pure component parameters) as well as static light scattering (SLS) data of varying protein-excipient combinations (binary interaction parameters). Using these parameters, modeling of B_{22}- and B_{23}-values and thus, protein-protein and protein-excipient interactions in the presence of excipients is possible.

Figure 1 shows the modeling results of SLS data (Figure 1A) as well as B_{22}-coefficients of IgG-sucrose systems (Figure 1B) in comparison to experimental data. Even though the absolute values are not matched by the predictions, the increasing trend of B_{22} can be confirmed. Aside B_{22}, the SLS data used to retrieve the cross-virial coefficient B_{23} can also be determined with high accuracy leading to a qualitative as well as quantitative determination of B_{23} between IgG and sucrose (data not shown).

This novel approach proves, that thermodynamic models such as the ePC-SAFT equation of state can be applied successfully to calculate and even predict the complex interactions in aqueous protein solutions. In addition, this method reduces the experimental effort in determining protein-protein and protein-excipient interactions and thus aids to identify optimal formulation conditions for specific proteins.

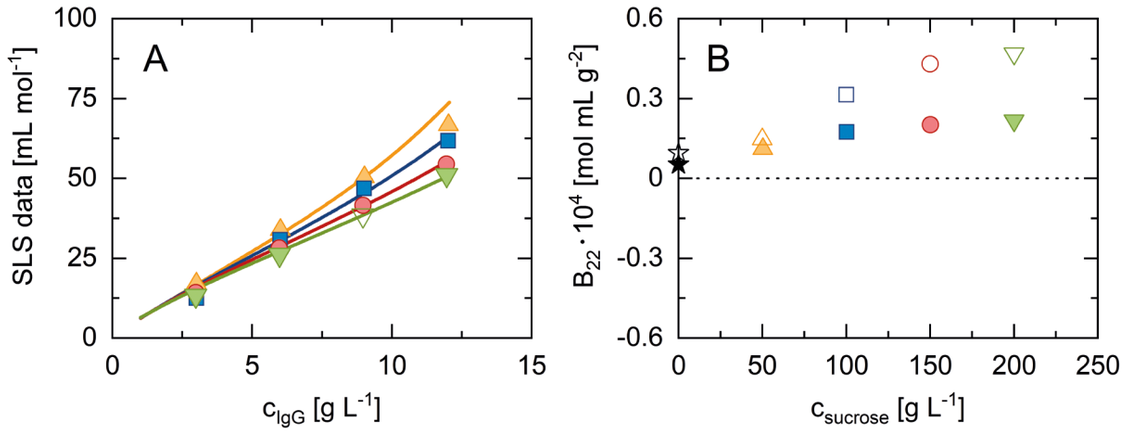

Figure 1: A *SLS data* at pH 7.0, 298.15 K in 50 mM K_2HPO_4-NaH_2PO_4 phosphate buffer and constant sucrose concentration (50 g L^{-1} [triangles], 100 g L^{-1} [squares], 150 g L^{-1} [circles], 200 g L^{-1} [reversed triangles]) as a function of immunoglobulin G concentration. Solid lines correspond to predicted *SLS data* using ePC-SAFT equation of state. B Comparison of experimental B_{22}-values of immunoglobulin G (filled symbols) with predicted B_{22}-values (empty symbols) at pH 7.0 and 298.15 K in 50 mM K_2HPO_4-NaH_2PO_4 phosphate buffer as a function of sucrose concentration.

Publications:
M. Schleinitz, L. Nolte, C. Brandenbusch, J. Mol. Liq. 298, 112011 (2020).

Contact:
lea.nolte@tu-dortmund.de
christoph.brandenbusch@tu-dortmund.de