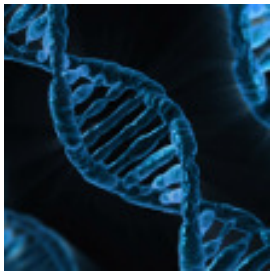

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Combining small-angle X-ray scattering and in-silico modelling in the study of the albumin-detemir complex

Protein drugs are increasingly important in drug development worldwide due their high specificity, potency, and low toxicity. Many protein drugs do, however, suffer from inherent physical instability limiting the manufacturability and formulation development, as well as short plasma half-lives that are incompatible with delivery of an efficacious dose within the appropriate dose regime[1,2]. Human serum albumin (HSA) can be used as an approach to solving both challenges. Firstly, recombinant HSA (rHSA) can be added as an excipient to stabilize drug formulations[1]. Secondly, protein drugs may be designed to bind to HSA *in vivo* and thereby extend their half-lives. An example is the acetylated insulin analogue, insulin detemir (detemir) [2].

In this work, complex formation between rHSA and detemir and how it is influenced by physicochemical properties in different formulations have been investigated using an interdisciplinary approach that combines light scattering, small-angle X-ray scattering (SAXS) measurements and molecular dynamics (MD) simulations.

Based on SAXS data, *ab-initio* and rigid body modelling of the complex between rHSA and a detemir hexamer have been carried out, resulting in four possible detemir binding sites. As rigid body modelling does not take chemical information into account, the binding sites were further investigated by MD simulations and molecular mechanics Poisson-Boltzmann surface area calculations.

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