Solution structures of long-acting insulin analogues and their complexes with albumin - DTU Orbit (14/11/2019)

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The lipidation of peptide drugs is one strategy to obtain extended half-lives, enabling once-daily or even less frequent injections for patients. The half-life extension results from a combination of self-association and association with human serum albumin (albumin). The self-association and association with albumin of two insulin analogues, insulin detemir and insulin degludec, were investigated by small-angle X-ray scattering (SAXS) and dynamic light scattering (DLS) in phenolic buffers. Detemir shows concentration-dependent self-association, with an equilibrium between hexamer, dihexamer, trihexamer and larger species, while degludec appears as a dihexamer independent of concentration. The solution structure of the detemir trihexamer has a bent shape. The stoichiometry of the association with albumin was studied using DLS. For albumin-detemir the molar stoichiometry was determined to be 1:6 (albumin:detemir ratio) and for albumin-degludec it was between 1:6 and 1:12 (albumin:degludec ratio). Batch SAXS measurements of a 1:6 albumin:detemir concentration series revealed a concentration dependence of complex formation. The data allowed the modelling of a complex between albumin and a detemir hexamer and a complex consisting of two albums binding to opposite ends of a detemir dihexamer. Measurements of size-exclusion chromatography coupled to SAXS revealed a complex between a degludec dihexamer and albumin. Based on the results, equilibria for the albumin-detemir and albumin-degludec mixtures are proposed.

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