Oligomerization of a Glucagon-like Peptide 1 Analog: Bridging Experiment and Simulations

The glucagon-like peptide 1 (GLP-1) analog, liraglutide, is a GLP-1 agonist and is used in the treatment of type-2 diabetes mellitus and obesity. From a pharmaceutical perspective, it is important to know the oligomerization state of liraglutide with respect to stability. Compared to GLP-1, liraglutide has an added fatty acid (FA) moiety that causes oligomerization of liraglutide as suggested by small-angle x-ray scattering (SAXS) and multiangle static light scattering (MALS) results. SAXS data suggested a global shape of a hollow elliptical cylinder of size hexa-, hepta-, or octamer, whereas MALS data indicate a hexamer. To elaborate further on the stability of these oligomers and the role of the FA chains, a series of molecular-dynamics simulations were carried out on 11 different hexa-, hepta-, and octameric systems. Our results indicate that interactions of the fatty acid chains contribute noticeably to the stabilization. The simulation results indicate that the heptamer with paired FA chains is the most stable oligomer when compared to the 10 other investigated structures. Theoretical SAXS curves extracted from the simulations qualitatively agree with the experimentally determined SAXS curves supporting the view that liraglutide forms heptamers in solution. In agreement with the SAXS data, the heptamer forms a water-filled oligomer of elliptical cylindrical shape.

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