SELF-ASSEMBLY OF AMPHIPHILIC DRUG BETA BLOCKERS IN AQUEOUS SOLUTION

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Background:

Some amphiphilic drugs behave like surfactants and self-assemble in aqueous solution and form 'micelle-like' structures when their concentration exceeds a given – critical micelle – concentration[1]. Such micelles can significantly affect the solubility, membrane permeability and ultimately the therapeutic activity of the drugs from which they are formed[2,3]. In the study presented here, we sought to understand, at the molecular level, the structure-function relationship of the β-blocker, propranolol hydrochloride, in relation to its aggregation behaviour in aqueous solution, and thereby to gain insight into the impact of these phenomena on its therapeutic activity.

Methods:

Small angle neutron scattering (SANS) studies of propranolol hydrochloride (propHCl) dispersed have been performed to determine the behaviour of propHCl in aqueous solution. Complementary ^{1}H-NMR dilution studies and full-atom molecular dynamics (MD) studies, with the simulations run over 6000 ns, of the drug self-assembly process have been performed.

Results:

The SANS data clearly show that the propHCl forms aggregates in aqueous solution. The aggregates grow with concentration, and become smaller with increased temperature. The SANS data obtained for propHCl shows the aggregates are well fitted as prolate ellipsoids with a 'dry' core consisting primarily of the naphthyl moieties. MD simulations of the corresponding systems show that the drug forms polydisperse aggregates in aqueous solution, with the shape, size, and internal core-shell structure of the aggregates consistent with those of the aggregates obtained from model-fitting the SANS data. The NMR studies also confirms the existence of aggregates of the propHCl in aqueous solution. NMR in combination to the other two techniques, indicates the dominant interacting moiety of propHCl in the self-assembly process is the naphthyl rings.

Conclusions:

PropHCl forms aggregates which grow larger at higher concentrations, and become smaller with increased temperature. The aggregates are prolate ellipsoids with a 'dry' core consisting of naphthyl rings. The driving force for self-aggregation of propHCl is likely to be π-π stacking.

References:

1. Attwood and Florence (1984) Surfactant systems, Chapman & Hall.
2. Vauquelin and Packeu (2009) Molecular and Cellular Endocrinology, 311, 1.
3. Mizogami et al. (2010) European Journal of Anaesthesiology, 27, 829.