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Hydrophobic ion-pairing of low molecular weight heparin with cationic amphiphiles

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Purpose: Conventional therapeutic administration of low molecular weight heparin (LMWH) is limited to parenteral administration due to unfavorable physicochemical properties restricting effective permeation across biological membranes. To augment LMWH flux across biological membranes using contributions of transcellular transport mechanisms, this study explored formation of electrostatically stabilized association complexes via ion-pairing with the lipophilic cationic amphiphiles (Stearylamine, tallo wamine acetate and dicocoamine).

Methods: LMWH/cationic amphiphiles interactions were assessed using molar ratios ranging from 1:0 to 1:40. Unbound LMWH was quantified spectrophotometrically at λ=630 nm using the Azure A assay. Dynamic laser light scattering technology was applied to estimate hydrodynamic diameter and zeta potential of LMWH/cationic surfactants association complexes. Thermodynamic properties of the interaction between LMWH and cationic surfactants were quantified in the presence of different formulation variables using isothermal titration calorimetry (ITC) technique.

Results: Addition of cationic amphiphiles solutions to LMWH solution lead to gradual increase in complexation efficiency suggesting molecular association of the oppositely charged ion species. At molar ratios of LMWH: Cationic amphiphiles [1:30 mol/mol], complexation efficiency was 97.629%±0.5, 95.643%±7.5 and 90.385%±5.2 upon using Stearylamine, tallow amine acetate and dicocoamine, respectively. In parallel, formation of colloidal association complexes was detected exhibiting mean hydrodynamic diameters between 300-500 nm and zeta potential values of -1.79±0.9 to -32.8±1.4 mV. Binding of LMWH to cationic surfactants was exothermic except for LMWH/dicocoamine complex where endothermic reaction was observed. The enthalpy change (ΔH) was -2.984, -3.854 and +2.395 kcal/mol, at a defined stoichiometry of 0.655, 0.559, and 0.243 for complexes with stearylamine, tallow amine acetate and dicocoamine, respectively. Greater ionic strength, temperatures and pH significantly increased dissociation constant (*Kd*) of the formed complexes.

Conclusion: Thermodynamic analysis revealed that LMWH/cationic amphiphiles interactions are predominantly driven by electrostatic forces. As a consequence, association complexes may enhance overall permeation properties of LMWH across biological membranes. Thus, may offer the opportunity for oral administration of this anticoagulant in the future.

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