Soluble 1:1 complexes and insoluble 3:2 complexes - Understanding the phase-solubility diagram of hydrocortisone and γ-cyclodextrin

The molecular mechanisms underlying the drug-solubilizing properties of γ-cyclodextrin were explored using hydrocortisone as a model drug. The B_S-type phase-solubility diagram of hydrocortisone with Y-cyclodextrin was thoroughly characterized by measuring the concentrations of hydrocortisone and Y-cyclodextrin in solution and the solid phase. The drug-solubilizer interaction was also studied by isothermal titration calorimetry from which a precise value of the 1:1 binding constant (K_{11} = 4.01 \text{mM}^{-1} \text{ at } 20^\circ \text{C}) was obtained. The formation of water-soluble 1:1 complexes is responsible for the initial increase in hydrocortisone solubility while the precipitation of entities with a 3:2 ratio of Y-cyclodextrin:hydrocortisone is responsible for the plateau and the ensuing strong decrease in solubility once all solid hydrocortisone is used up. The complete phase-solubility diagram is well accounted for by a model employing the 1:1 binding constant and the solubility product of the precipitating 3:2 entity (K_{32S} = 5.51 \text{ mM}^5). For such systems, a small surplus of Y-cyclodextrin above the optimum concentration may result in a significant decrease in drug solubility, and the implications for drug formulations are briefly discussed.