THERMODYNAMIC ANALYSIS OF THE DISSOLUTION OF TRIMETHOPRIM INTO AQUEOUS PEG 4000

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The dissolution rates of poorly soluble drugs may be enhanced by formulation as dispersions in solid polyethylene glycols (Chiou and Riegelman 1971). However, the mechanisms by which these increases occur are as yet poorly understood. One proposed mechanism has involved solubilisation of the drug by the carrier at the dissolving surface (Hargreaves 1986). It is therefore useful to understand the nature of the aqueous interactions between the drugs and polyethylene glycols. The present study involves the use of solution calorimetry, differential scanning calorimetry and solubility studies in order to characterise the thermodynamic parameters associated with the dissolution of the drug in both water and aqueous PEG 4000.
Trimethoprim (Wellcome) was chosen as the model drug, studies being conducted at 310K in both distilled water and in 20% w/v aqueous PEG 4000 (Hoechst). The drug solubility was measured in the two liquids using the method described by Molyneaux (1984). Heats of solution were obtained using a Tronac 450 Adiabatic Calorimeter (Tronac Inc.) for a range of sample sizes. Each sample was dissolved in 50mls of solvent and the resultant heat change measured. A linear relationship was found between the heat of solution and sample weight up to saturation solubility, after which no increase was observed. This linear response allowed the molar heat of solution to be calculated. The heat of fusion of trimethoprim was taken from the literature value of 46.55kJ/mol (Chatham 1985). The data was analyzed using an expanded version of the model proposed by Craig and Newton (1988), whereby the heat of solution (ΔH_S) was considered to be the sum of the enthalpies of solid bond breakage (ΔH_F), which may be obtained indirectly from the heat of fusion (Craig and Newton 1988), and solvent-solute mixing (ΔH_M). In the present study, the enthalpy and the free energy of the three processes were also calculated as follows. The free energy of the dissolution process (ΔG_S) was calculated from the solubility data using standard equations. Similarly, as the breakage of the solid bonds was considered to be a melting, and hence equilibrium process, the free energy of solid bond breakage (ΔG_F) was taken as 0. From this information it was possible to calculate all three thermodynamic parameters for each process using the Gibbs equation.
The results for the aqueous and 20% w/v PEG 4000 systems are given in Table 1. The changes in the enthalpy and molar entropy of mixing show the presence of PEG 4000 to increase the exothermic enthalpy of interaction but to decrease the entropy of the process compared to pure water. The method therefore provides a means of quantifying the interactions between drugs and the solvents in which they are dissolved.

Table 1: Thermodynamic parameters associated with the dissolution of trimethoprim (kJ/mol, ΔS in J/Kmol)

	Dissolution			Solid Bond Breakage			Solvent-Solute Mixing		
	ΔG_S	ΔH_S	ΔS_S	ΔG_F	ΔH_F	ΔS_F	ΔG_M	ΔH_M	ΔS_M
Water	-25.76	27.05	170.33	0	30.38	97.99	-25.76	-3.33	72.34
20% PEG 4000	-20.73	24.29	145.20	0	30.38	97.99	-20.73	-6.09	47.21

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