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The effect of hydrophilic polymers and surface active agents on the solubility of indomethacin

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Summary

This work examines the effect of two surfactants: sodium lauryl sulphate (SLS) and polysorbate 80, and two hydrophilic polymers: polyethylene glycol (PEG 6000) and polyvinylpyrrolidone (PVP) on the aqueous solubility of indomethacin. It is found that all the above solubilizing agents increase the solubility of the drug in the following order: SLS > polysorbate 80 > PEG 6000 > PVP. The work also includes calculation of some thermodynamic functions such as the heat of solution (ΔH) and the free energy change (ΔG). In addition the solvent power of the PEG 400/water system is determined. The number of indomethacin molecules bound to a molecule of PEG is calculated and an equation describing this binding process is proposed.

Introduction

Several techniques have been used to improve the solubility of poorly water-soluble drugs. They, among other things, include the use of surface-active agents and hydrophilic polymers. Several comprehensive reviews on these techniques notably those by Swarbrick (1965), Elworthy et al. (1968) and Florence (1981) have been published. Florence (1981) pointed out that it is difficult to predict the solubility of a drug in a given surfactant due to the molecular shape of the drug which influences its packing into structured micelles.

El-Sabbagh et al. (1978) have reported that indomethacin solubility in various polyoxyethylene derivatives decreased as the polyoxyethylene chain of the surfactant increased. They also noted that increasing the temperature resulted in an increase of

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the efficiency of the surfactants. Increased solubility of indomethacin in PEG was reported by Minkove et al. (1980). Higuchi and Lach (1954) reported the formation of a complex between PEG and phenobarbitone which had a lower solubility than the drug. Miyawaki et al. (1959) and Shihab et al. (1970) on the other hand have reported an increased solubility of *p*-hydroxybenzoic acid esters in the presence of PEG.

It is evident from the above-reported results that one cannot extrapolate data from the literature to his system. Therefore the present work was done in order to examine the solubilizing effect of SLS, polysorbate 80, PVP and PEG on the aqueous solubility of indomethacin. In addition, it includes the determination of ΔH and ΔG of these systems as well as the solvent power of the PEG/water cosolvent system.

Materials and Methods

Materials

Sodium lauryl sulphate (SLS), PVP and PEG were obtained from BDH Chemicals, Poole, U.K. Polysorbate 80 was obtained from Merck, Schuchardt, F.R.G. Indomethacin was obtained from Sigma Chemicals, St. Louis, MO, U.S.A. The water used for this study was triple-distilled having a surface tension of 71–72 $nN \cdot m^{-1}$ at 25°C and obtained from an all-glass still.

Methods

(a) Determination of the effect of solubilizing agent concentration on the equilibrium solubility of indomethacin. An excess of indomethacin was shaken with 10 ml of solubilizing agent solution of different concentrations for 24 h in a constant temperature shaking water bath (Grant, Cambridge U.K.) at 37 ± 0.1°C. A 5-ml sample was then transfered to a syringe and rapidly filtered through a 0.22-μm membrane filter unit (Millipore U.K., London). The concentration of indomethacin was determined spectrophotometrically using a Pye Unicam spectrophotometer model SP6-550 against the appropriate blank at a wavelength of 319 nm. Absorbance values were then converted to the corresponding concentration by reference to a suitable calibration curve.

(b) Effect of temperature on solubility. This was determined by preparing solutions containing 5% PVP, 5% PEG, 1% SLS and 1% polysorbate 80. To each of these solutions an excess of the drug was added. Equilibrium solubility of the drug was then determined in each solution at temperatures ranging from 15 to 50°C as previously described.

(c) Calculation of the solvent power of PEG. The solvent power of PEG 400, was determined by shaking an excess of the drug with solutions containing different volume fractions of PEG 400. The equilibrium solubility was then determined as previously described.

Results and Discussion

The equilibrium solubility of indomethacin in the presence of PVP and PEG is depicted in Fig. 1. An increase in solubility was observed with both polymers. The effect, however, was dependent on the type and concentration of polymer. The change in solubility of indomethacin was greater at lower than at higher concentrations of PEG. The negative deviation exhibited at higher concentrations could be attributed to association among the polymer molecules. This may reduce the effective polymer concentration and hence the number of solubilizing units. In contrast, a linear relationship exists between the solubility of indomethacin and concentration of PVP. This may suggest that PVP molecules did not aggregate at the concentrations used.

The effect of SLS and polysorbate 80 on the solubility of indomethacin is shown in Fig. 2. Increasing the concentration of both surfactants resulted in a linear increase in solubility. This behavior is a typical micelle solubilization (Elworthy et al., 1968; Mulley, 1964). The graph also indicates that SLS is more effective in solubilizing indomethacin than polysorbate 80. This can be attributed to the greater hydrophilic character and to the alkaline pH effect of SLS on indomethacin which is weakly acidic.

Fig. 3 shows that a curvilinear relationship between the number of indomethacin molecules bound per molecule of PEG (X) and the concentration of PEG in solution (C) is obtained. However, when log X was plotted as a function of log C a linear relationship was obtained (Fig. 4). This suggests that X and C are related by the non-linear equation:

$$X = \beta C^{\alpha} \tag{1}$$

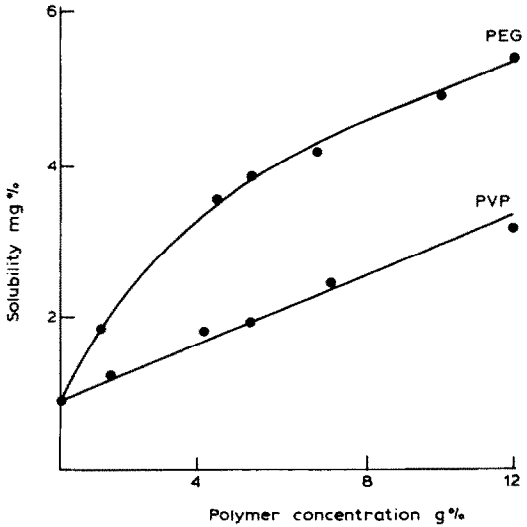

Fig. 1. Effect of PEG and PVP on the equilibrium solubility of indomethacin.

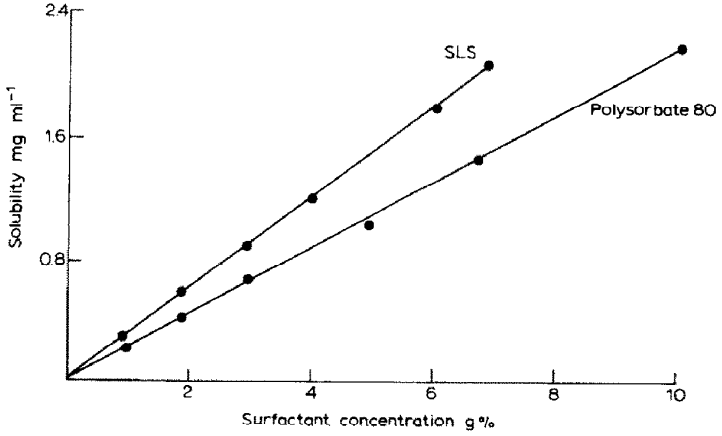

Fig. 2. Effect of SLS and polysorbate 80 on the equilibrium solubility of indomethacin.

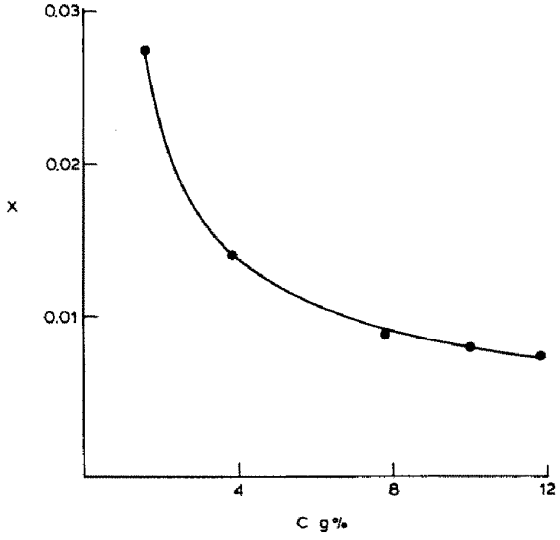

Fig. 3. The relationship between the number of indomethacin molecules bound per molecule of PEG (X) and the concentration of PEG in solution (C).

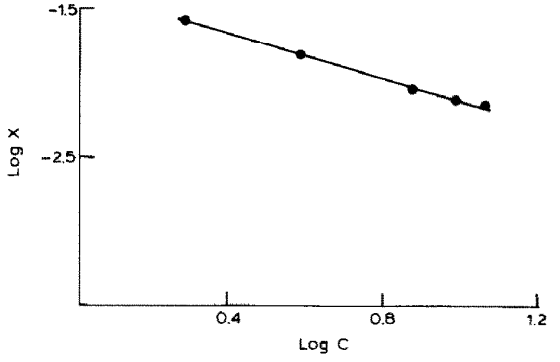

Fig. 4. The relationship between the logarithm of the number of indomethacin molecules bound per molecule of PEG and the logarithm of the polymer concentration.

where α and β are constants for a particular system. The values of β and α as determined from Fig. 4 were 0.0433 and -0.718, respectively; therefore, for this system, i.e. PEG indomethacin

$$X = 0.0433C^{-0.718}$$

The equilibrium solubilities of indomethacin in the various solubilizing agents over the temperature range 15–50°C when plotted according to the van't Hoff equation gave a linear relationship as shown in Fig. 5. The values of the heat of solution for all solubilizing agents was calculated from the slopes of the plots.

The free energy changes at 25°C and atmospheric pressure associated with all systems were determined by Eqn. 2 (Feldman and Gibaldi, 1967)

$$\Delta G = -RT \cdot \ln \frac{S_w}{S_s} \tag{2}$$

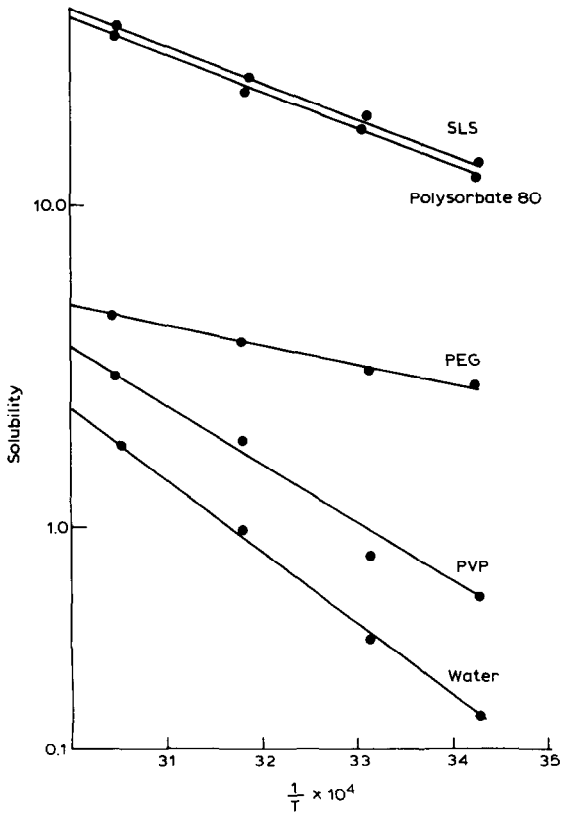

Fig. 5. The relationship between the logarithm of the equilibrium solubility of indomethacin and the reciprocal of the absolute temperature.

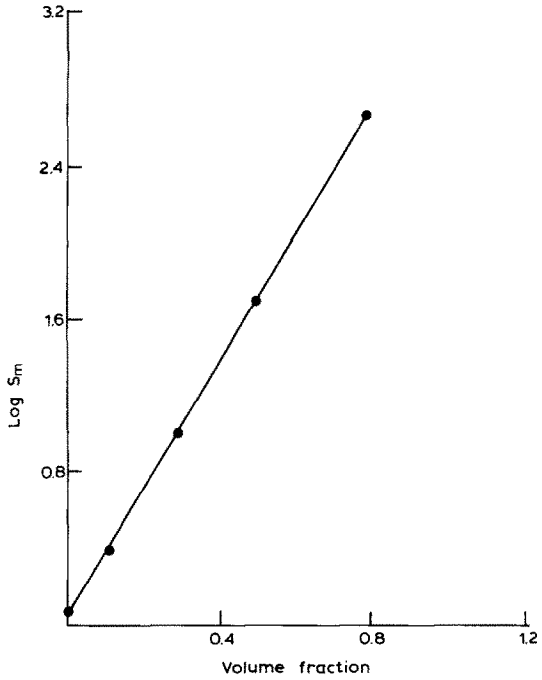

Fig. 6. The relationship between the logarithm of the equilibrium solubility of indomethacin in the PEG 400/water cosolvent system and the volume fraction of PEG.

where S_w and S_s are the solubilities of indomethacin in water and solubilizing agent at a particular temperature, T, and R is the gas constant. The thermodynamic values for all the systems are summarized in Table 1. Based on the ΔH values alone, indomethacin is supposed to be most soluble in 5% PEG ($\Delta H = 2.7$ kcal/mol). However, using the ΔG values at 25°C, the solubility of indomethacin increases in the following order: PVP 5% < PEG 6000 5% < polysorbate 80 1% < SLS 1%. It is believed that the association among the PEG molecules resulted in a more structured system with a low entropy and hence a low negative ΔG value.

The solvent power of PEG 400 for indomethacin was calculated using Eqn. 3

TABLE 1

THE THERMODYNAMIC VALUES FOR THE VARIOUS SOLUBILIZING SYSTEMS

	ΔH (kcal/mol)	ΔG at 25°C (cal/mol)
Tween 1%	4.9	−2198
PEG 5%	2.7	−1142
PVP 5%	8.9	−337
SLS 1%	4.4	−2228
H_2O	12.1	

(Yalkowsky and Roseman, 1981).

$$\log S_m = \log S_w + \sigma f_c \quad (3)$$

where S_w and S_m are the solubilities in water and the solvent system, σ is the solvent power, and f_c is the volume fraction of the solvent. The data obtained when plotted according to Eqn. 3 gave a straight line (Fig. 6) with a slope (σ) equal to 0.30 and an intercept (solubility of indomethacin in water) equal to 0.97 mg%. Yalkowsky et al. (1975) have shown that σ is related to the molecular hydrophobic surface area of the solute and to the interfacial tension of the pure solvent.

The results obtained in this work lead to the conclusion that the aqueous solubility of indomethacin can be increased by the use of hydrophilic polymers and surface-active agents. However, the surface-active agents used, i.e. SLS and polysorbate 80, were more effective than the hydrophilic polymers, namely PVP and PEG. In the determination of the thermodynamic functions of the solubilizing systems, the determination of ΔH alone may not suffice ΔG must also be calculated.

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