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Rapid Communication

Molar solubility of felodipine in different aqueous systems

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Summary

The molar solubility of felodipine in water was calculated and experimentally determined. A polyoxyethylene-polyoxypropylene block copolymer (Synperonic T304) and sodium lauryl sulfate as surfactants and ethanol as cosolvent were used as solubilizing agents. Significantly different molar solubilities were determined for felodipine according to the approach used to achieve solubilization. Such differences are the result of the different mechanisms of solubilization of the additives.

The efficacy of a drug can be severely limited for drugs having a low aqueous solubility. It is known that the side effects of some drugs are the result of their poor solubility. The ability to increase aqueous solubility can thus be a valuable aid to increasing the efficacy and/or reducing the side effects of certain drugs for the parenteral, topical and oral administration of drug solutions (Yalkowsky and Valvani, 1977; Yalkowsky, 1981).

Surfactant solubilization is extremely important in pharmaceutical systems and is by far the most extensively studied technique for solubilization. There are also several additional techniques which can be employed to solubilize drugs. Solubilization by cosolvents, complexing agents, crystal modification, and prodrug formation, either individually or in combination, can provide an extremely valuable means of solubilizing drugs. Although such methods tend to be used less frequently, they can be potentially more powerful than surfactant solubilization for increasing aqueous solubility.

In this study, the ideal mole fractional solubility, X_i, and aqueous solubility, X_w, of crystalline felodipine, a very slightly soluble calcium antagonist (solubility about 0.5 mg/l), were evaluated and the solubility of felodipine in water and in different aqueous systems was determined experimentally. The ideal mole fractional solubility of a solute is given by (Hildebrand and Scott, 1962):

$$\log X_i = \frac{-\Delta Hf(T_f - T)}{T_f\ 3.303RT} - \frac{\Delta C_p}{R}\left[\frac{\Delta H_f(T_f - T)}{2.303T} + \log\frac{T_f}{T}\right] \quad (1)$$

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TABLE 1

Molar solubility of felodipine in water

		Log X	Log S	S (mol/l)
Ideal molar solubility				
Eqn 1	25°C	−1.664	0.076	1.191
	37°C	−1.600	0.140	1.382
Eqn 2	25°C	−1.665	0.075	1.188
Molar solubility (25°C)				
Eqn 3		−8.140	−6.400	0.398×10^{-6}
Eqn 4		−9.007	−7.267	0.054×10^{-6}
Experimental molar solubility				
	25°C	−7.625	−5.885	1.303×10^{-6}
	37°C	−7.245	−5.505	3.125×10^{-6}

where T and T_f denote temperature and fusion point, respectively, in K. ΔH_f represents the molar heat of fusion, and ΔC_p is the heat capacity difference between the crystalline and molten forms of the drug. Eqn 1 can be simplified by replacing $(\Delta H_f/T_f)$ with ΔS_f, the entropy of fusion, by assuming that ΔC_p is small compared to ΔS_f, by conversion to °C, and by assuming that $T = 298$ K (25°C), to give (Yalkowsky and Valvani, 1980):

$$\log X_i = \frac{-\Delta S_f}{1364}(\text{m.p.} - 25) \quad (2)$$

where m.p. denotes the melting point (in °C). The estimation of ideal solubility now requires only knowledge of the solute's melting point and entropy of fusion.

The aqueous solubility of a crystalline solute (X_w^c) can be expressed according to (Yalkowsky, 1981a):

$$\log X_w^c = -\log \text{PC} - 0.01\ \text{m.p.} - 0.69 \quad (3)$$

The overall effect of the partition coefficient (PC) and melting point (m.p.) on aqueous solubility has been examined (Yalkowsky and Valvani, 1980) for a large number of organic non-electrolytes. The above authors found, by regression analysis, that:

$$\log X_w = -1.05 \log \text{PC} - 0.012\ \text{m.p.} - 0.97 \quad (4)$$

which is in excellent agreement with Eqn 3.

The solubility of felodipine in different aqueous systems was determined spectrophotometrically at 240 nm after 5 h shaking at 25°C to achieve saturated concentration. The surface tension of aqueous systems was determined using the drop-volume method (Weser, 1980) at 25°C as the mean value of three measurements.

The ideal mole fractional solubility of felodipine, calculated on the basis of Eqns 1 and 2, is far beyond the aqueous solubility evaluated from Eqns 3 and 4 (Table 1). The experimental aqueous solubility of felodipine is of the same order of magnitude as that calculated.

Different approaches to the solubilization of felodipine were used. Surfactants (Synperonic T304, ICI, U.S.A.; and sodium lauryl sulfate, Henkel, Germany) and cosolvent (ethanol, Kemika, Yugoslavia) in concentrations of the same solution surface tension were prepared (Table 2).

The soluble surface-active block copolymer poloxamine Synperonic T304, like other polyoxyethylene and polyoxypropylene copolymers, has been used widely in pharmaceuticals. In the case of solubilization of felodipine, Synperonic T304 did not affect the solubility of felodipine significantly. At the low concentrations used to solubilize felodipine, the copolymer monomers are believed to form monomolecular micelles

TABLE 2

Concentration and surface tension of the solubilizing systems investigated (25°C)

	Surface tension, $(\times10^{-3})$ (N/m)					
	72	59	55	52	45	37
Conc. EtOH (v/v%)	0.00	3.26		14.20	25.14	36.08
Conc. SLS (w/w%)	0.00	0.10		0.20	0.30	0.40
Conc. Synperonic T304 (w/w%)	0.00		0.20	0.36	0.74	1.15

through a change in configuration in solution. At higher concentrations, the monomolecular micelles associate to form aggregates of varying size which have the ability to solubilize drugs (Collett and Tobin, 1979), however, the solution changes from the molecular to the colloidal form.

From the group of ionic surfactants sodium lauryl sulfate (SLS) was used. At surfactant concentrations of 0.1–0.4 w/w%, the solubility of felodipine increased significantly with increasing surfactant concentration and decreasing surface tension of the surfactant solution (Fig. 1).

Cosolvents such as ethanol, propylene glycol, polyethylene glycol and glycerine are routinely employed to aid the solubilization of drugs in aqueous vehicles. In some cases, the use of an appropriate cosolvent can increase the aqueous solubility of a drug by several orders of magnitude.

Ethanol as a cosolvent in aqueous solutions of felodipine led to a considerable extent of solubilization. On increasing the ethanol concentration to 36 v/v%, the molar solubility of felodipine was found to increase to 3.24×10^{-3} mol/l, corresponding to a 2500-fold greater value as compared to that in water.

The molar solubility of felodipine in surfactant or cosolvent systems demonstrates a logarithmic relationship with the surface tension, γ, of the solvent used (Fig. 1): i.e., ethanol aqueous system, $\log S = 2.696 - 0.141\ \gamma$; SLS aqueous system, $\log S = 0.786 - 0.106\ \gamma$; Synperonic T304 aqueous system, $\log S = -5.174 - 0.007\ \gamma$. On comparison of the molar solubilities of felodipine at the same value of the solution surface tension between the different solubilization approaches (surfactants or cosolvent), markedly different molar solubilities were found. Such differences re-

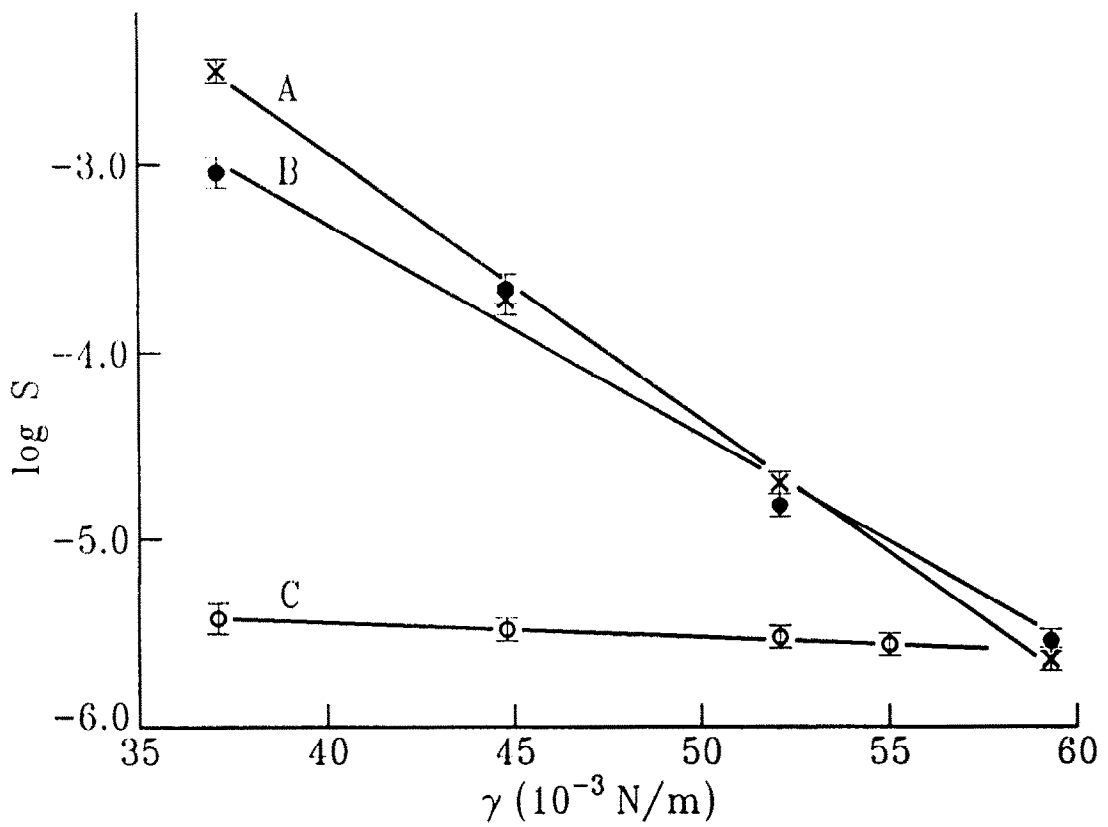

Fig. 1. Experimental values of the molar solubility of felodipine vs surface tension of the solubilizing system: A, ethanol aqueous system; B, SLS aqueous system; C, Synperonic T304 aqueous system.

sult from differing mechanisms of solubilization of these excipients.

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