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EFFECT OF POLYETHYLENE GLYCOL, SODIUM LAURYL SULFATE AND POLYSORBATE-80 ON THE SOLUBILITY OF FUROSEMIDE

F.A. SHIHAB, A.R. EBIAN and R.M. MUSTAFA

Department of Pharmaceutics, College of Pharmacy, University of Baghdad, Baghdad (Iraq)

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SUMMARY

The effect of polyethylene glycols, sodium lauryl sulfate and polysorbate-80 on the solubility of furosemide was investigated. It was found that all these substances increase the solubility of the drug in water. The increase was in the following order: sodium lauryl sulfate > polysorbate-80 > the polyethylene glycols. The effect of polyethylene glycol was greater, the higher the molecular weight. The influence of temperature on the process was studied in each case, and the thermodynamic parameters in polysorbate-80 and sodium lauryl sulfate solutions were calculated. The effect of electrolytes on the solubility of furosemide in 5% polysorbate-80 solution was also been investigated and it was found that all the electrolytes used increased the solubilizing power of the surfactant at the concentrations employed.

INTRODUCTION

Furosemide is one of the popularly used diuretics. Its solubility in water is very limited. Numerous reports have appeared in the literature concerning the effects of surfactants and hydrophilic polymers on the solubility of slightly soluble drugs. Thakkar and Hall (1967) investigated the solubilization of testosterone by aqueous solutions of polysorbates. Polysorbate-60 showed a greater solubilizing capacity than polysorbate-40 and -20. Thakkar and Hall (1968) have also found that the solubility of the steroid is increased in the presence of ionic surfactants. The relationship between surfactant concentration and solubility of the drug was linear in all cases. A positive temperature effect upon the solubilization of benzoic acid by some non-ionic surfactants was reported by Humphreys and Rhodes (1968).

The polyethylene glycols are extensively used in pharmaceutical preparations. They have been found to interact with some dosage from constituents, forming more or less soluble products. Higuchi and Lach (1954) reported a complex formation between polyethylene glycol and phenobarbitone which results in a decrease in solubility of the drug. Greater solubility of some of the p-hydroxybenzoic acid esters was observed, however, in the presence of polyethylene glycol (Miyawaki et al., 1959; Shibab et al., 1970).

Electrolytes have been reported to affect the solubilizing capacity of certain substances. Klevens (1950) found that the solubility of n-heptane in potassium myristate solution is increased with an increase in the concentration of potassium chloride, while that of n-octanol is decreased. A decrease in the solubilizing power of polysorbate-40 on chlorocresol, in the presence of electrolytes, was observed by Gadalla et al. (1974).

The present report compares the solubility features of furosemide in a non-ionic surfactant, an anionic surfactant and polyethylene glycols of three different molecular weights at different temperatures. It also deals with the effect of electrolytes on the solubility of the drug in polysorbate-80 solution.

MATERIALS AND METHODS

Materials

Furosemide (Hoechst AG)[1]; polysorbate-80 (Riedel De Haen AG); polyethylene glycol 200, 4000, 6000 (Hopkin and Williams); sodium lauryl sulfate (Hopkin and Williams); sodium chloride, sodium sulfate, potassium chloride, potassium sulfate, magnesium chloride (BDH Chemicals Ltd.).

Instruments. Oscillating water bath (Kottermann); spectrophotometer (Pye Unicam SP 6-500).

Method

Excess amounts of furosemide were placed, separately, in flasks containing 20 ml polysorbate-80, sodium lauryl sulfate or polyethylene glycol solutions of different concentrations. The flasks were stoppered and shaken for 24 h in a thermostatically controlled water bath at a specified temperature. At the end of the shaking period, the flasks were allowed to stand for another 2 h at the same temperature. Clear samples were then taken and analyzed spectrophotometrically at 276 nm.

To study the effect of electrolytes, excess amounts of furosemide were transferred to flasks containing different amounts of electrolytes in 5% polysorbate-80 solution and the procedure was completed as above.

RESULTS AND DISCUSSION

The influence of polyethylene glycol 4000 on the solubility of furosemide is illustrated in Fig. 1. The graphs show that polyethylene glycol increases the solubility of furosemide and that this effect is increased as the concentration of the polymer is increased. This was true with the three molecular weights used, as similar graphs were obtained for polyethylene glycols 200 and 6000. The difference was in the extent of

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[1] The authors thank Hoechst AG for the generous supply of this compound.

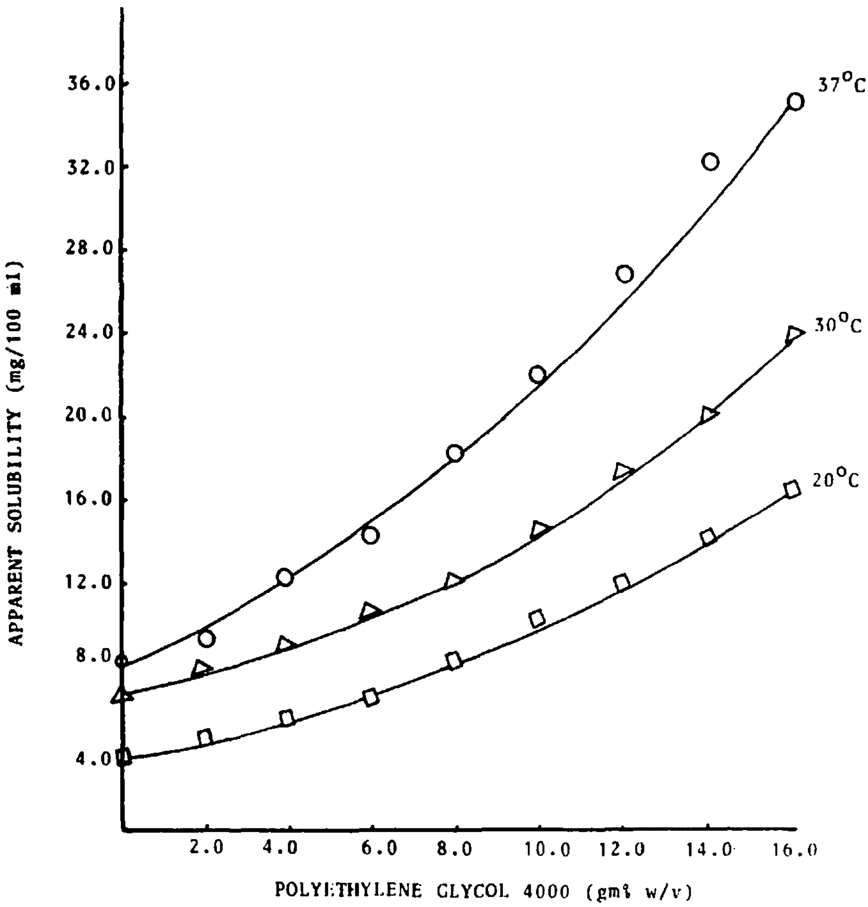

Fig. 1. Solubility of furosemide in aqueous solutions of polyethylene glycol 4000 at different temperatures.

increase in the solubility. It was found that the effect was higher, the higher the molecular weight. The solubility of furosemide in a 10% w/v solution of polyethylene glycol 4000 at 30°C, for example, was 14.6 mg/100 ml (Fig. 1), while that obtained for the drug in the same concentration of polyethylene glycols 200 and 6000 and at the same temperature was 10.2 and 17.3 mg/100 ml, respectively. The increased solubility of the drug may be related to the better cosolvency of the polyethylene glycol–water mixture. Better cosolvency for many drugs has been demonstrated by many workers (Breon and Paruta, 1970; Shihab et al., 1970).

An increase in the solubility of furosemide was also found in the presence of sodium lauryl sulfate and polysorbate-80. The solubility increases linearly with the increase in surfactant concentration in each case. This is typical of micellar solubilization (Elworthy et al., 1968). Fig. 2 depicts the effect of sodium lauryl sulfate on the solubility of furosemide. The solubilizing power of sodium lauryl sulfate was found to be higher than that of polysorbate-80. Considering a surfactant concentration of 3% w/v at 30°C, the

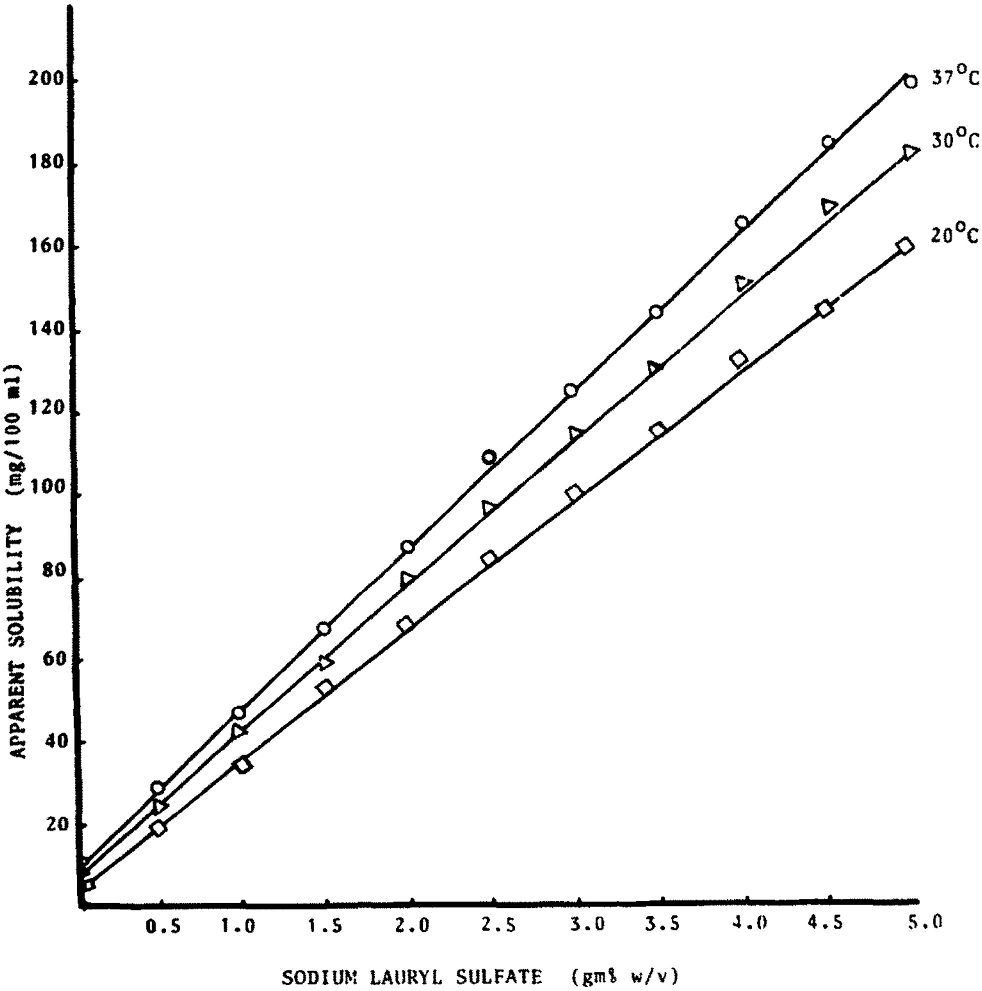

Fig. 2. Solubility of furosemide in aqueous solutions of sodium lauryl sulfate at different temperatures.

solubility of the drug was 114.2 mg/100 ml in the case of sodium lauryl sulfate (Fig. 2) compared to 65.3 mg/100 ml found in the case of polysorbate-80. This is because of the pH effect exerted by the alkaline solutions of sodium lauryl sulfate on furosemide, which is a weak acid.

The effects of temperature on the experimental solubility of furosemide in the presence of polyethylene glycol 4000 and sodium lauryl sulfate are represented in Figs. 1 and 2. The graphs for the different temperatures were similar in shape for each of the systems studied. The increase in temperature was found to increase the solubility of the drug. By plotting the experimental solubility of furosemide in sodium lauryl sulfate and polysorbate-80 solutions against temperature, Fig. 3 was obtained. The graphs indicate a greater temperature effect on the solubilizing power of polysorbate-80 compared to that of sodium lauryl sulfate. The difference in the nature of the two surface active agents and

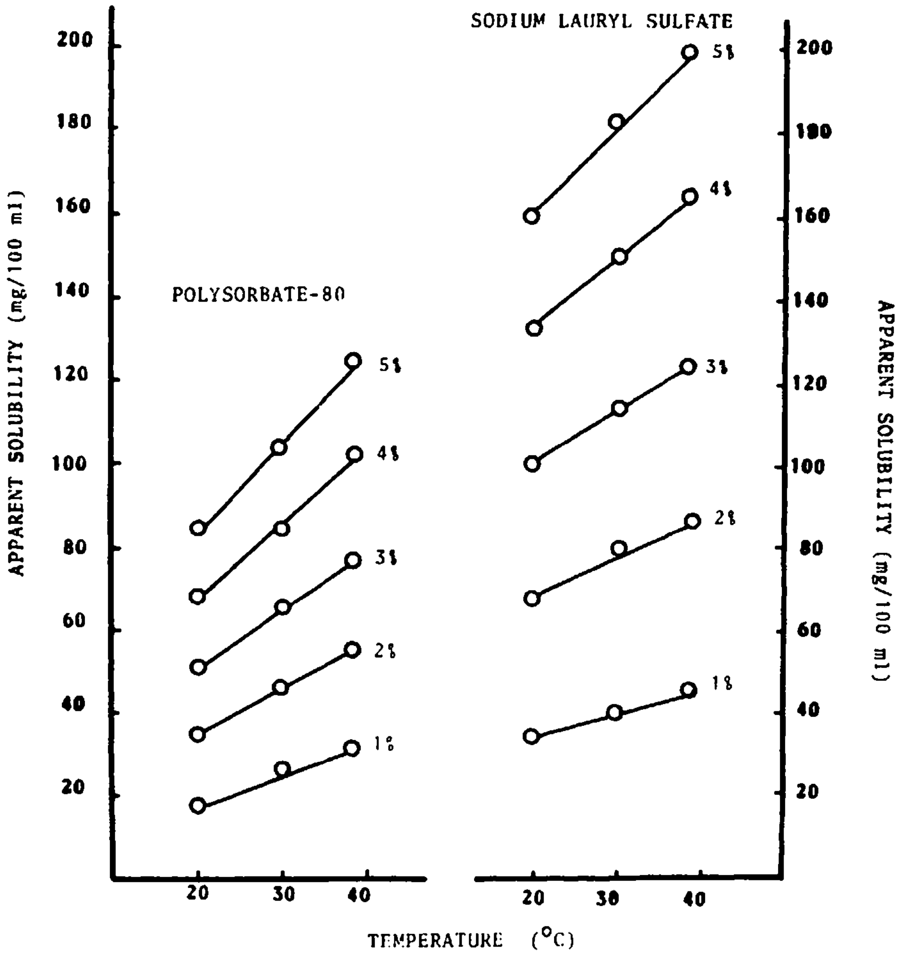

Fig. 3. Influence of temperature on the solubility of furosemide in polysorbate-80 and sodium lauryl sulfate solutions.

in the effect of temperature on the critical micelle concentration, in each case, may explain this observation. The solubility of a solid substance is increased on elevating the temperature, in the presence of an ionic surfactant, while the critical micelle concentration is not changed to an appreciable extent. In the case of non-ionic surfactants, a decrease in the critical micelle concentration was observed when the temperature was raised (Elworthy et al., 1968; Mulley, 1964).

The classical van't Hoff type plots of the equilibrium solubilities of furosemide in polysorbate-80 and sodium lauryl sulfate solutions at different temperatures are represented in Fig. 4, which show reasonably good linear relationships. The heat of solution was calculated from the slopes of these plots (slope = $-\Delta H/2.303\ R$). The free energy change (ΔG) was calculated from the following thermodynamic relationship (Feldman

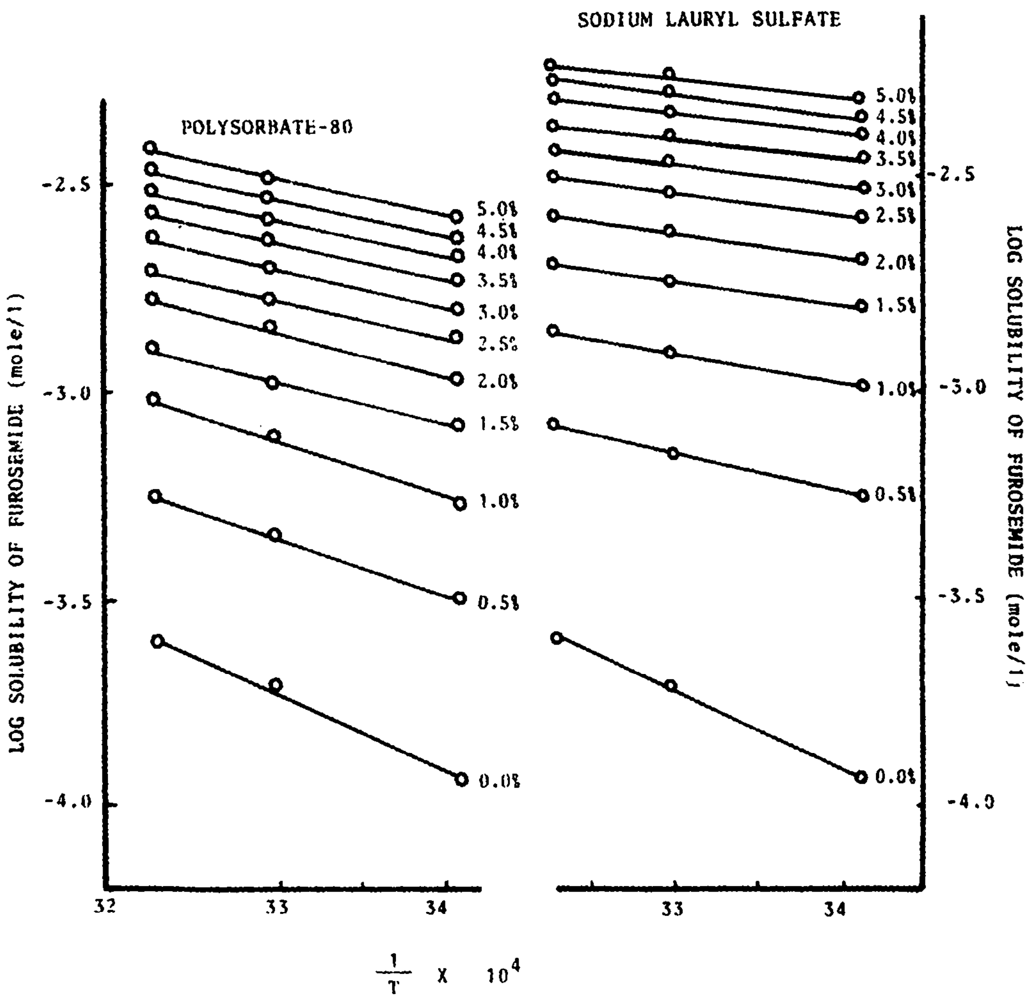

Fig. 4. van't Hoff plots for the solubility of furosemide in polysorbate-80 and sodium lauryl sulfate solutions.

and Gibaldi, 1967):

$$\Delta G = -2.303\ RT \log S_s/S_w$$

S_s/S_w = ratio of the molar solubility of the compound in surfactant solution to that in water. The thermodynamic parameters of furosemide in the surfactant solutions are presented in Table 1. The negative values of the free energy change for the different systems are indicative of the spontaneity of the process in each case. The positive heat of solution explains the increase of solubility of furosemide with temperature.

Table 2 gives the solubility data of furosemide in 5% polysorbate-80 solutions containing different concentrations of electrolytes at 37°C. These data indicate that the electrolytes employed increase the efficiency of the surfactant as a solubilizer. This is because of

TABLE 1

THERMODYNAMIC PARAMETERS FOR FUROSEMIDE IN POLYSORBATE-80 AND SODIUM LAURYL SULFATE SOLUTIONS

Surfactant conc. (% w/v)	Polysorbate-80				Sodium lauryl sulfate			
	ΔH (cal/mol)	ΔG (cal/mol)			ΔH (cal/mol)	ΔG (cal/mol)		
		20°C	30°C	37°C		20°C	30°C	37°C
0.00	8800	–	–	–	8800	–	–	–
0.50	6110	–615	–520	–490	4155	–956	–770	–740
1.00	6110	–914	–840	–815	3180	–1310	–1120	–1050
1.50	4890	–1170	–1020	–1000	2440	–1560	–1340	–1290
2.00	4890	–1320	–1190	–1160	2440	–1710	–1520	–1450
2.50	4400	–1460	–1310	–1270	2440	–1840	–1630	–1590
3.00	4400	–1550	–1400	–1370	2440	–1940	–1740	–1670
3.50	4400	–1630	–1480	–1460	2200	–2020	–1820	–1760
4.00	4400	–1720	–1560	–1530	2200	–2100	–1900	–1840
4.50	4400	–1780	–1620	–1600	2200	–2150	–1980	–1910
5.00	3910	–1840	–1680	–1670	1960	–2200	–2020	–1960

TABLE 2

EFFECT OF ELECTROLYTES ON THE SOLUBILITY OF FUROSEMIDE IN 5% w/v POLYSORBATE-80

Molar conc. of electrolyte	Solubility of furosemide (mg/100 ml) in				
	NaCl	KCl	$MgCl_2$	Na_2SO_4	K_2SO_4
0.00	125.6	125.6	125.6	125.6	125.6
0.01	130.2	127.0	128.2	129.9	131.0
0.02	131.9	129.8	131.4	133.7	134.4
0.05	132.3	131.9	135.5	139.6	144.6
0.10	133.2	132.5	136.4	149.9	147.5
0.20	134.1	134.1	141.4	157.8	160.9

the effect of electrolytes on the critical micelle concentration and micellar volume of nonionic surfactants. It is known that the critical micelle concentration of a surfactant is decreased and the micellar volume is increased in the presence of electrolytes (Elworthy et al. 1968).

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