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Notes

Some parameters for the solubilization of nitrofurazone and ultraviolet light absorbers by nonionic surfactants

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Summary

The solubility method was used to study the solubilization of nitrofurazone, Uvinul D-50 and Uvinul N-35 in aqueous nonionic surfactant solutions. Enhancement of solubilization with increase in temperature was observed. The solubility of each solubilizate in buffered surfactant solutions maintained a linear relationship with the molar surfactant concentration. The standard free energy change, ΔG_s^o, was negative for all systems, indicating spontaneous solubilization, and increased slightly with increasing hydrophilic chain length. However, ΔG_s^o was essentially independent of temperature. Measurements of the molecular extinction coefficient in nonionic surfactant solution suggest that the value of the molecular extinction coefficient of nitrofurazone at both 260 and 375 nm was always greater than that of UV absorbers.

Solubilization enhances the solubility of sparingly soluble compounds and indications that surfactants may modify the stability of drugs (Riegelman, 1960) have increased the need for further knowledge. Although solubilization has been extensively investigated (e.g., Mulley, 1964; Swarbrick, 1965; Elworthy et al., 1968a), there are few reports on the thermodynamics of the process (Simons and Rhodes, 1971; Barry and El Eini, 1976).

In this work, the solubilization of nitrofurazone and ultraviolet light absorbers, e.g., Uvinul D-50 and Uvinul N-35, in aqueous solutions of nonionic surfactants at different temperatures and pH values, was studied and a number of thermodynamic parameters were derived. In addition, the molecular extinction coefficient of these compounds was studied in nonionic surfactant solution. The aim was to evaluate the use of ultraviolet light absorbers in protecting the drug, as-

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sessed on the basis of their uptake into micelles formed by surfactants with various hydrophilic and hydrophobic chain lengths, expressed by changes in free energy, molecular extinction coefficient and pH.

The materials and solubilization method used were the same as those reported earlier (Shahjahan and Enever, 1991). The partition coefficient (k) between n-hexane and water was determined by dissolving the compound in either phase according to its solubility and spectrophotometric analysis of solute in both phases after equilibration at 25°C. The partition coefficient (k_m) for the distribution of the solute between the micellar and aqueous phase of a surfactant at a given temperature was calculated in a manner similar to that devised by Smith et al. (1974). For every compound, the partition coefficients were calculated at each of the different concentrations of a given surfactant, and the mean value was considered to be the partition coefficient for that surfactant/solubilizate system.

The solubilities of Uvinul D-50, Uvinul N-35 and nitrofurazone in water (Table 1) and in surfactant solutions increased with temperature. Two separate factors need to be considered when evaluating the effect of temperature on solubilization: firstly, the changes in temperature may alter the aqueous solubility of the solubilizate and, secondly, a temperature change may bring about modifications of the properties of the micelles themselves. Data concerning the former phenomenon are listed in Table 1 indicating the increase in aqueous solubility with temperature. The efficiency of micellar solubilization (taken to be the slopes of plots of micellar solubility in mol l^{-1} vs surfactant concentration) increased with temperature for each solubilizate. Solubilization by polyoxyethylene nonionic surfactants at different temperatures is complicated by the effect of temperature on the solubility of the surfactant itself. The CMC values decreased with increasing temperature in line with an inverse temperature-solubility relationship for nonionic surfactants. The aqueous solubility of polyoxyethylene surfactants is attributed to hydrogen bonding between the ether oxygen of the ethylene oxide chain and water molecules. When the temperature increases these bonds break and the hydrophilicity of the polyoxyethylene chain is reduced, rendering the surfactant less soluble so that micellization occurs at a lower concentration. Micelles of nonionic surfactants rapidly grow in size with increasing temperature which may be due in part to both greater hydrophobicity of the monomer and geometric considerations based on different configurations of the polyoxyethylene chains at different temperatures affecting the mode of packing of the monomers in the micelle (Elworthy et al., 1968b). Micellar size increases slightly with temperature until a threshold, about 20°C below the cloud point, is reached. Above this temperature, the size increases exponentially and micelles may become asymmetric. Since it is expected that the cloud points of the surfactants used are well above the highest temperature studied (35°C), any drastic change in micellar structure is unlikely to occur (Barry and El Eini, 1976). The enhancement of solubilization with increasing temperature in the present study may result from the increase in micellar size referred to previously and the fact that micelles are formed at lower concentrations at higher temperatures.

TABLE 1

Aqueous solubilities of ultraviolet light absorbers and nitrofurazone at various temperatures

Solubilizate	Solubility (mol l^{-1})		
	15°C	25°C	35°C
Uvinul D-50	0.000724	0.000772	0.001801
Uvinul N-35	0.000004	0.000010	0.000013
Nitrofurazone	0.000702	0.001086	0.001677

Figs 1 and 2 show plots of the solubility of Uvinul D-50 and nitrofurazone in McIlvaine's buffer at the various pH values (2.2–8). Due to the low solubility of Uvinul N-35 in aqueous medium, it was difficult to obtain meaningful results regarding the effect of pH on its solubility. Fig. 1 clearly demonstrates that, at pH 4, Uvinul D-50 exhibits minimum solubility, while much greater solubility occurs at pH 8. Since the pH of distilled water containing these compounds is usually between pH 5 and 6, by comparing the solubility in distilled water and buffer solution at

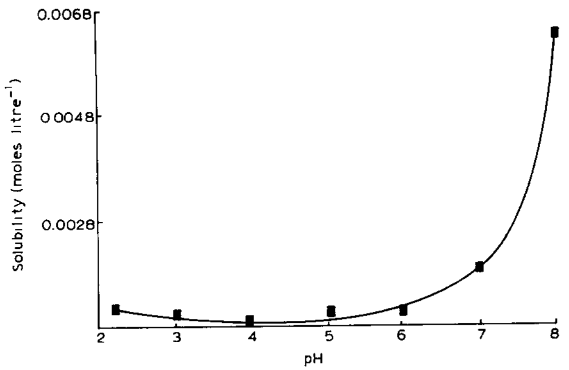

Fig. 1. Effect of pH on the solubility of Uvinul D-50 at 25°C.

TABLE 2

Partition coefficients of solubilizates between micellar and aqueous phases from solubility data (k_m) and between n-hexane and water (k) at 25°C

Solubilizate	k_m				k
	Texofor A14	Texofor A1P	Texofor A30	Brij 35	
Uvinul D-50	758	996	1 238	901	0.001
Uvinul N-35	2 494	3 490	3 824	2 142	68.076
Nitrofurazone	19	26	27	19	0.007

pH 5 or 6 it was observed that the buffer components increase the solubility of Uvinul D-50. However, as shown in Fig. 2, with nitrofurazone the solubility decreased as the pH of the buffer solution was increased. In addition, it was found that buffer components led to a slight decrease in the solubility of nitrofurazone. Since the solubilizates in the surfactant solutions were observed to have pH values of approx. 6, with the exception of the Brij 35 solution, the solubility of these solubilizates was determined in Brij 35 solution buffered at pH 6 and compared with those in unbuffered solution at 25°C. It was found that the solubility of each solubilizate in buffered solution still followed a linear relationship with the molar concentration of surfactant. However, the solubility appeared to increase slightly for ultraviolet light absorbers while that of nitrofurazone remained roughly the same.

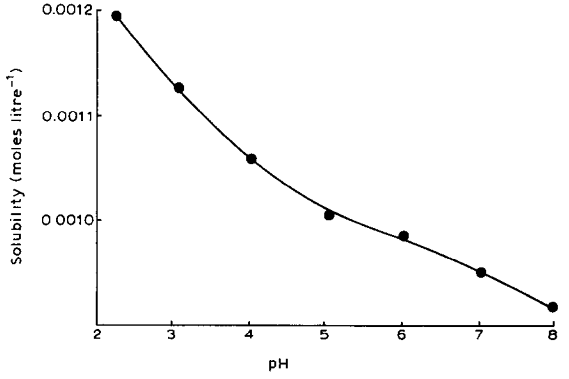

Fig. 2. Effect of pH on the solubility of nitrofurazone at 25°C.

The linear relationship determined between the amount solubilized and surfactant concentration for a given solubilizate indicated that solubilization could be interpreted on the basis of the distribution law, according to which solubilizate molecules partition between the micellar and aqueous phases. The results shown in Table 2 reveal that the partition coefficient (k_m) between micellar and aqueous phases as estimated from the solubility data at 25°C is highest for Uvinul N-35 and lowest for nitrofurazone. For each solubilizate, the k_m value increased with increase in polyoxyethylene chain length in the Texofor series. By comparing the k_m values for Texofor A1P and Brij 35 for each solubilizate it can be seen that the k_m value for Uvinul N-35 decreases markedly with decreasing hydrocarbon chain length, while Uvinul D-50 and nitrofurazone show no change of comparable magnitude. This is in accordance with their solubility trends, since the solubility of Uvinul N-35 was affected by the hydrocarbon chain length to a greater extent than nitrofurazone or Uvinul D-50 (Shahjahan and Enever, 1991).

Partition coefficients (k) between *n*-hexane and water show a similar pattern to that of the k_m values with the exception of Uvinul D-50. Uvinul D-50 shows the lowest k values whilst its k_m value is intermediate between that of nitrofurazone and Uvinul N-35. This is due to the greater extent of interaction with the polyoxyethylene mantle than with the pure hydrocarbon portion of the micelle, as the cross-section of a polyoxyethylene surfactant micelle offers the complete range of polarity from the hydrocarbon core, via the semipolar polyoxyethylene, to pure water on the micellar surface.

The standard free energy change, ΔG_s^o (kJ mol^{-1}), for the transfer of 1 mol of solute from the solution to the micelle is given by

$$\Delta G_s^o = -RT \ln k_m \quad (1)$$

The free energy changes for solubilization are listed in Table 3. For all systems ΔG_s^o was found to be negative, indicating spontaneous solubilization, and, at constant temperature, ΔG_s^o increased slightly with increasing hydrophilic chain length. The effect of temperature on changes in free energy was slight and probably within the limit of experimental error, so that ΔG_s^o for a given surfactant/solubilizate system has been assumed to remain constant between 15 and 35°C.

From the spectral curves of a particular compound in a given medium, the absorbance at 260 and 375 nm was measured. The average of three determinations was taken and the molecular extinction coefficients were calculated. The molecular extinction coefficient of nitrofurazone and Uvinul N-35 at 260 and 375 nm decreased with increasing ethylene oxide content of the surfactants while that of Uvinul D-50 remained virtually unchanged. On the other hand, the molecular extinction coefficients of nitrofurazone and Uvinul D-50 were found to increase with greater hydrocarbon chain length while that of Uvinul N-35 did not change appreciably. The molecular extinction coefficient of nitrofurazone at both 260 and 375 nm in every case was found to be higher than that of the ultraviolet light absorbers. Examination of the data for the two ultraviolet light absorbers shows that although the molecular extinction coefficient of Uvinul D-50 was much greater than that of Uvinul N-35 at 375 nm, at 260 nm both were virtually the same.

It can be seen from the above data that the molecular extinction coefficient of the drug in surfactant solution decreased with increasing polyoxyethylene chain length whilst it increased with greater hydrocarbon chain length. Therefore, it would appear to be logical to expect that a nonionic surfactant with an ethylene oxide chain length even longer than that of Texofor A30 would be a suitable vehicle for the drug with respect to its photostability. When the protective effects of the two ultraviolet light absorbers are compared for a given molar concentration of absorber, Uvinul D-50 appears to be more effective due to its higher molecular extinction coefficient. Further studies on the photostability of the drug in nonionic surfactant solutions in the presence

TABLE 3

Free energy changes (ΔG_s^o) for solubilization in nonionic surfactants at different temperatures

Nonionic surfactant	Temperature (°C)	Uvinul D-50	Uvinul N-35	Nitrofurazone
Texofor A14	15	−3.71	−4.80	−1.77
	25	−3.93	−4.63	−1.74
	35	−3.73	−4.87	−1.70
Texofor A1P	15	−3.92	−5.00	−1.98
	25	−4.09	−4.83	−1.93
	35	−3.94	−5.06	−1.89
Texofor A30	15	−3.96	−5.04	−2.05
	25	−4.22	−4.88	−1.95
	35	−4.03	−5.09	−1.95
Brij 35	15	−3.82	−4.76	−1.86
	25	−4.03	−4.54	−1.74
	35	−3.79	−4.85	−1.74

of absorbers are being conducted and will be reported in a forthcoming article.

References

Barry, B.W. and El Eini, D.I.D, Solubilization of hydrocortisone, dexamethasone, testosterone and progesterone by long-chain polyoxyethylene surfactants. *J. Pharm. Pharmacol.*, 28 (1976) 210–218.

Elworthy, P.H., Florence, A.T. and Macfarlane, C.B., *Solubilization by Surface Active Agent*, 1st Edn, Chapman and Hall, London, 1968a, p. 61.

Elworthy, P.H., Florence, A.T. and Macfarlane, C.B., *Solubilization by Surface Active Agent*, 1st Edn, Chapman and Hall, London, 1968b, p. 45.

Mulley, B.A., In Bean, H.S., Beckett, A.H. and Carless, J.E. (Eds), *Advances in Pharmaceutical Sciences*, Vol. 1, Academic Press, London, 1964, p. 86.

Riegelman, S., The effect of surfactants on drug stability. I. *J. Am. Pharm. Assoc., Sci. Ed.*, 49 (1960) 339–343.

Shahjahan, M. and Enever, R.P., Solubilities of nitrofurazone and ultraviolet light absorbers in polyethylene glycols and nonionic surfactants. *Int. J. Pharm.*, 70 (1991) 9–18.

Simons, K.J. and Rhodes, C.T., Solubilization of testosterone by *n*-alkyl poly(oxyethylene). *Pharmazie*, 26 (1971) 623–626.

Smith, C.G., Kennedy, D.R. and Nairn, J.G., Hydrolysis kinetics of benzocaine and homologs in the presence of a nonionic surfactant. *J. Pharm. Sci.*, 63 (1974) 712–716.

Swarbrick, J., Solubilized systems used in pharmacy. *J. Pharm. Sci.*, 54 (1965) 1229–1237.