International Journal of Pharmaceutics, 70 (1991) 9–18
Elsevier Science Publishers B.V.
ADONIS 037851739100153C

IJP 02290

Solubilities of nitrofurazone and ultraviolet light absorbers in polyethylene glycols and nonionic surfactants

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(Received 18 July 1990)
(Accepted 20 August 1990)

Key words: Nitrofurazone; Ultraviolet light absorber; Uvinul D-50; Uvinul N-35; Solubility; Nonionic surfactant; Polyethylene glycol; *Z* value

Summary

Nonionic surfactants or polyethylene glycols were used to enhance the solubilities of nitrofurazone and ultraviolet light absorbers in aqueous solution. The ultraviolet light absorbers were representative of two structural classes, the substituted benzophenone (Uvinul D-50) and the substituted acrylonitriles (Uvinul N-35). The site of solubilization of drug and ultraviolet light absorbers in the surfactant micelles was investigated. The solubility results suggest that all three solubilizates are distributed between both the hydrophilic and hydrophobic regions of the micelles. Determination of the relative regions of solubilization in the micelle by comparing the changing *Z* values fits well with the data obtained from the solubility measurements for Uvinul D-50 and nitrofurazone but not for Uvinul N-35. The reason for the apparent anomalous *Z* value results with Uvinul-35 in surfactant solutions is not clear. The relatively low solubilities of the solubilizates in polyethylene glycol solutions, in particular Uvinul N-35, as compared to those in the surfactants emphasises the advantage of using the phenomenon of micelle formation to increase the solubility of these slightly water-soluble compounds.

Introduction

Nitrofurazone is a member of the nitrofuran class of chemotherapeutic agents. It has an antibacterial action against a number of Gram-negative and Gram-positive bacteria. It is used as a local application for superficial wounds, burns, ulcers and skin infections. The drug is very slightly soluble in water and the commercial preparations available are a cream, an ointment and a solution usually of 0.2% w/v strength in a polyethylene glycol formulation. The various official compendia state that the drug formulations should be stored in light-resistant containers and exposure to direct sunlight and excessive heat should be avoided. Ultraviolet light is a high energy component of sunlight that can initiate photodegradation. Thus protection against ultraviolet light is essential if photolabile products are to be stored for any length of time.

The incorporation of ultraviolet light absorbers in certain concentrations has been reported to substantially decrease photodegradation rates of reserpine solution (Asker et al., 1971). If ultraviolet light absorbers are to be incorporated, into a pharmaceutical product itself, it is essential that

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those selected are of low toxicity with respect to the particular route of administration of the preparation. Certain of the substituted benzophenones and acrylonitriles appear to have suitably low toxicities. For example, 2,2′,4,4′-tetrahydroxybenzophenone (Uvinul D-50) and ethyl-2-cyano-3,3-diphenyl acrylate (Uvinul N-35) would be likely ultraviolet light absorbers for incorporation into topical products containing photolabile drugs as these compounds exhibit very low toxicity in oral, eye irritation and skin tests on animals (GAF Technical Bulletin, 1965). A major difficulty with using such compounds, however, is that they have relatively low aqueous solubilities. Thus, if they are to be incorporated into pharmaceutical products, vehicles must be used in which appreciable quantities of the absorbers can be dissolved. One approach would be to solubilize them with surfactants.

Many pharmaceutical substances, which are sparingly soluble in water have been formulated in conjunction with surfactants to produce solubilized systems. Mulley (1964) gave a list of drugs together with that of the surfactants that have been formulated as solubilized systems. It is essential that, at the concentration employed, the surfactant be non-toxic, miscible with the solvent and compatible with the material to be solubilized. Toxicity is of paramount importance and for this reason most solubilized systems in pharmacy are based on nonionic surfactants, which are generally far less toxic than anionic and cationic compounds. An important factor in choosing a nonionic surfactantant is the comparative solubilizing efficiency of the wide range of surfactants available, which is controlled by such structural features as the alkyl chain length and the length of the ethylene oxide chain.

The nature of the solubilizate, the presence of additional polar or nonpolar substrates, and the temperature are parameters influencing solubilization in addition to the nature of the surfactant and the solvent. The solubilization of a compound in micelles results in a change in its environment, which can lead to altered activity. In order to gain a greater understanding of the mechanism of solubilization it is valuable to have a knowledge of the location of solubilizate in the micelle.

In the present work, the solubilization of nitrofurazone and ultraviolet light absorbers in nonionic surfactants, and determination of the possible site of incorporation of the drug and absorbers within the micelle has been investigated. In addition, the solubility of these compounds in polyethylene glycol has been determined. The aim was to evaluate the use of ultraviolet light absorbers in protecting the drug in such formulations.

Materials and Methods

Materials

Nitrofurazone (human grade), batch No. 6B5017, was obtained from Smith Kline and French Laboratories Ltd, Welwyn Garden City, Herts. Ultraviolet light absorbers (Uvinul D-50 and Uvinul N-35) were obtained from GAF (Great Britain) Ltd, Chemical Division, Manchester, U.K. The commercial nonionic surfactants, Texofor A14, A1P and A30 were obtained from ABM Chemicals Ltd, Stockport, Cheshire, U.K. and Brij 35, from Honeywill-Atlas Ltd, Surrey. Texofors of the A series are polyoxyethylene ethers of cetyl alcohol, represented by the formula $CH_3(CH_2)_{15}(OCH_2CH_2)_nOH$, where n is approx. 14, 24 and 30 for A14, A1P and A30 respectively. Brij 35 is a polyoxyethylene ether of lauryl alcohol, represented by the formula $C_{12}H_{25}(OCH_2CH_2)_nOH$, where n is approx. 23. The nonionic surfactants used were partially purified from contaminated polyethylene glycols by partitioning between ethyl acetate and an aqueous solution of sodium chloride in a manner similar to that of Weibull (1960). Polyethylene glycols were obtained from Koch-Light Laboratories Ltd, Colnbrook, Bucks, U.K. Concentrated stock solutions were prepared, stored in the dark, and diluted as required. Double-distilled water was obtained from an all glass distillation unit (QVF, Stoke-on-Trent). All solvents used were of 'Analar' grade (BDH, U.K).

Solubility determinations

Solubilities were determined by stirring excess of substance in medium (water, surfactant or polyethylene glycol solution of known concentration where appropriate) taken into a series of screw

cap vials. The vials were closed with Teflon lined caps and attached to a wheel rotating at 7 rpm immersed in a water bath maintained at 25 ± 0.2°C. The water bath was covered with aluminium foil to protect the drug from light. The resultant solutions at equilibrium (after 72 h) were filtered through 0.45 μm Millipore membrane filters, suitably diluted with a 2:1 v/v ethanol-water mixture and assayed spectrophotometrically. Solubility determinations for each compound were carried out five times and the mean values were taken as equilibrium solubilities.

Z value determinations

Spectral measurements were carried out in various solvents with a Pye Unicam SP 1800 recording spectrophotometer using matched 1 cm path length silica cells. Absorption by the solvent system was eliminated by using it in the comparison cell in all cases. λ_{max} values of the three determinations were averaged. Repeated observations showed that this method gave maxima of ±0.5 nm precision. With the exception of polyethylene glycol solutions of Uvinul N-35, the concentration of compounds used for this study was 0.008 mg cm^{-3}. It was not practical to obtain such concentrated solutions with Uvinul N-35. The energy of transition (E_T) was calculated from the λ_{max} value through the use of the equation:

$$E_T = \frac{11.97 \times 10^4}{\lambda_{max}(nm)} \text{kJ mol}^{-1} \quad (1)$$

The Z value of each compound in surfactant solution was obtained by reference to a calibration curve constructed for each compound using solvents of known Z values. The Z values for the solvents used in this study were obtained from published work (Bjaastad and Hall, 1967).

Results and Discussion

Solubility in nonionic surfactants

The solubilities of Uvinul D-50, Uvinul N-35 and nitrofurazone in the partially purified surfactants Texofor Al 4, Al P and A30 are shown in Fig. 1a–c, respectively. In each case the solubilities were proportional to surfactant concentrations. In the Texofor series, since each surfactant has the same hydrocarbon chain length, increased in solubility on ascending the series from A14 to

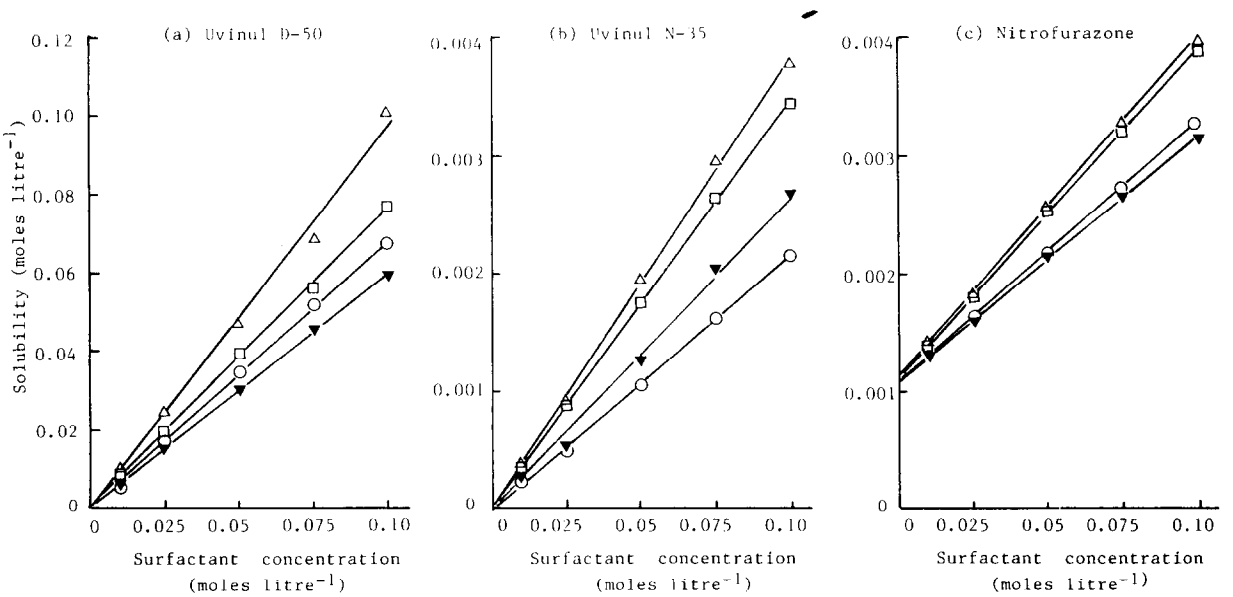

Fig. 1. Solubilities in aqueous surfactant solutions of varying polyethylene and hydrocarbon chain length at 25°C. (▼) Texofor A14, (□) Texofor A1P, (△) Texofor A30, (○) Brij 35.

A30 for a given surfactant concentration can be attributed to the increase in the number of ethylene oxide units in the surfactant molecule. The solubilizing efficiency of the surfactants, as indicated by the slopes of solubility plots, increased as the polyoxyethylene chain length increased, i.e. the more hydrophilic surfactants appeared more efficient. Similar observations have been reported (Barry and El Eini, 1976) for solubilization of other drugs by polyoxyethylene surfactants. The solubilizing efficiency of a particular surfactant was in the order Uvinul D-50 > Uvinul N-35 > nitrofurazone.

The effect of variation in hydrocarbon chain length of surfactant on solubilization was examined by comparing the solubilities of the ultraviolet light absorbers and nitrofurazone in Texofor A1P and Brij 35. These surfactants have similar ethylene oxide chain lengths (24 and 23, respectively), but Brij 35 has a C_{12} hydrocarbon chain whilst Texofor A1P has a C_{16} hydrocarbon chain. From the solubility curves (Fig. 1a–c) it is apparent that, for any given surfactant concentration, the solubility of each solubilizate is greater in Texofor A1P, i.e. in the surfactant with the longer hydrocarbon chain. The relative increase in efficiency was found to be in the order Uvinul N-35 > nitrofurazone > Uvinul D-50.

These results, together with those concerning the effect of variation in polyoxyethylene chain length on solubility, suggest that all three solubilizers are distributed between both the hydrophilic and hydrophobic regions of the micelles. However, Uvinul D-50 appears to be located more deeply in the hydrophilic region than nitrofurazone or Uvinul N-35. Uvinul N-35, in fact, appears to be almost exclusively located in the hydrocarbon region.

Solubility in polyethylene glycols

Fig. 2 shows the solubilities of the compounds in solutions of polyethylene glycol 1000. The solubility of each compound increases with molar concentration of the glycol but the effect was much less than in the surfactant solutions. It can be seen that polyethylene glycol exhibited the lowest solubilizing capacity (ratio of moles solubilizing per mole of polyethylene glycol) with Uvinul

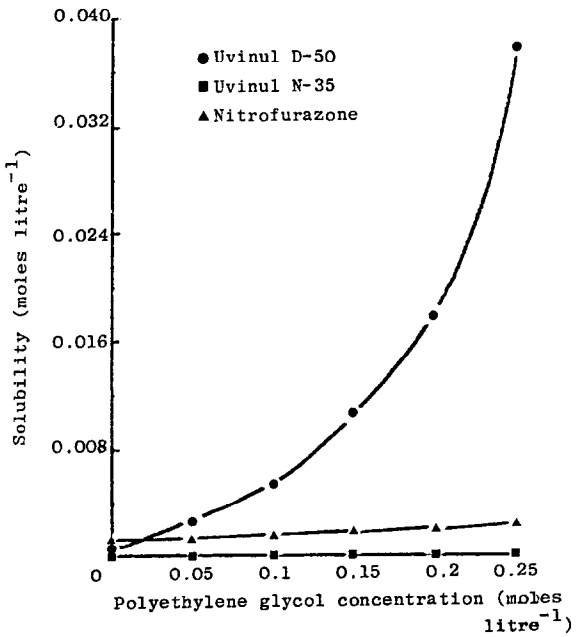

Fig. 2. Solubilities in aqueous solutions of polyethylene glycol 1000 at 25°C.

N-35 . For a particular concentration of polyethylene glycol, the solubilizing capacity was approx. 500 and 30 times higher for Uvinul D-50 and nitrofurazone, respectively, than that for Uvinul N-35. The solubilizing capacities of Texofor A1P and polyethylene glycol 1000 (having approximately 24 and 22 ethylene oxide units respectively) for each compound at 0.1 molar concentration are compared in Table 1.

From this comparison it is evident that solubilizing capacity of surfactant for each compound is much higher than that of a similar concentration of polyethylene glycol. In fact, it is approx. 16, 425 and 8 times higher for Uvinul D-50, Uvinul

TABLE 1

Comparison of ratio of moles solubilized per mole of polyethylene glycol 1000 and Texofor A1P

Solubilizates	Polyethylene glycol 1000	Texofor A1P
Uvinul D-50	0.0471	0.768
Uvinul N-35	0.00008	0.034
Nitrofurazone	0.0035	0.028

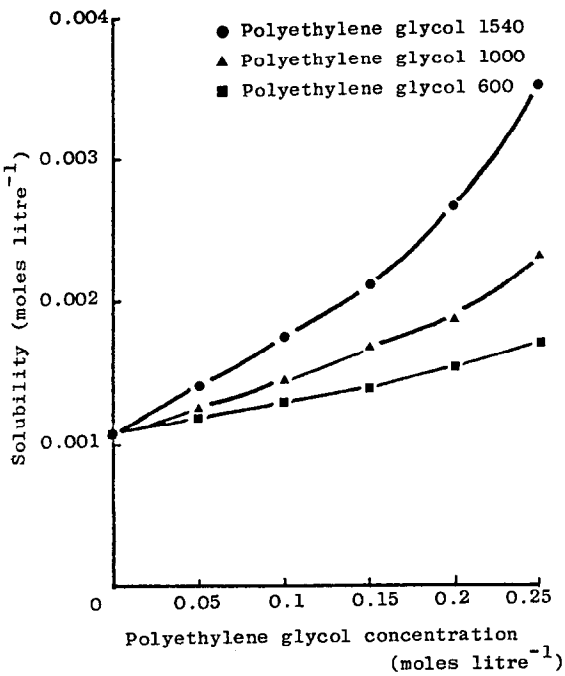

Fig. 3. Solubilities of nitrofurazone in aqueous solutions of polyethylene glycols of varying molecular weight at 25°C.

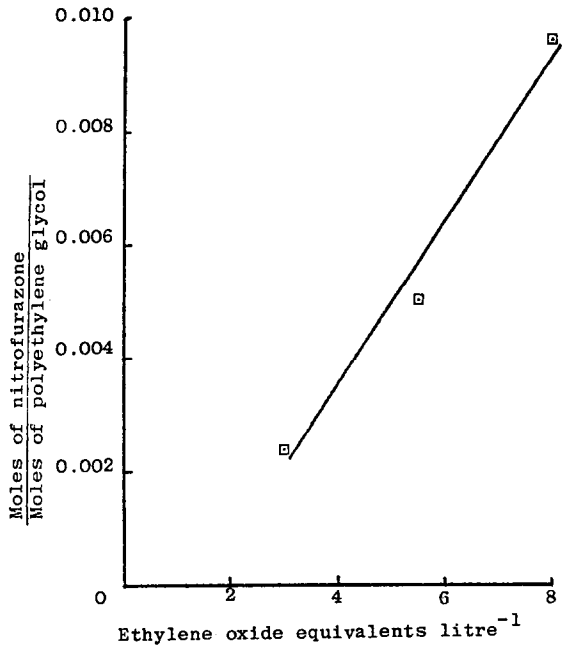

Fig. 4. Solubility data of nitrofurazone in polyethylene glycols at 0.25 M concentration, plotted as moles of nitrofurazone per mole of polyethylene glycol against ethylene oxide equivalents.

N-35 and nitrofurazone, respectively. It is interesting to note that although the uptake of Uvinul N-35 is much less than that of nitrofurazone in polyethylene glycol, the situation becomes reversed in the presence of surfactant. This may be due to the fact that Uvinul N-35 is located within the hydrocarbon portion of the micelle.

Fig. 3 shows the solubilities of nitrofurazone in aqueous solutions of polyethylene glycols of different molecular weights. Solubility increased with molar concentration of glycol and with increase in the molecular weight of polyethylene glycol. The uptake of nitrofurazone per mole of polyethylene glycol 600 is roughly independent of concentration while that in polyethylene glycol 1000 and 1540 increases with concentration. When the uptake of nitrofurazone at 0.25 M concentration is plotted against concentration of polyethylene glycols expressed as equivalents of ethylene oxide l^{-1} (polyethylene glycol 600, 1000 and 1540 having per mole ethylene oxide units 12, 22 and 32, respectively) a straight line is obtained with a correlation coefficient of 0.987 (Fig. 4). Thus, it appears that solubilization of nitrofurazone in nonionic surfactants does depend to some extent on location of at least a portion of the molecule in the polyoxyethylene region.

TABLE 2

Distribution of solubilizate between core and mantle of polyoxyethylene-cetyl micelles

Solubilizates	r	a (equivalent/ equivalent)	b (equivalent/ (equivalent)	y	a'
Uvinul D-50	0.944	0.023200	0.258573	2.153	0.002140
Uvinul N-35	0.999	0.000689	0.017315	0.955	0.000004
Nitrofurazone	0.978	0.000593	0.012549	1.134	0.000161

Assessment of the distribution of the solubilizate between the hydrocarbon core and polyoxyethylene mantle of the surfactant micelles

Table 2 shows the values of intercept a representing the solubilization in the mantle (equivalent of solubilizate per equivalent of ethylene oxide group) and the slope b representing the solubilization in the core (equivalent of solubilizate per equivalent of cetyl group) and the correlation coefficient, r, for linear regression of a plot of micellar solubility in mol l^{-1} of a solubilizate at 0.1 M surfactant concentration per equivalent of ethylene oxide group against the mole ratio of cetyl to ethylene oxide portions of the molecule for the Texofor surfactants. A 0.1 M concentration of Texofor A14, A1P and A30 would represent 1.4, 2.4 and 3 ethylene oxide equivalents per l respectively. The cetyl-ethylene oxide mole ratios used here for calculations are 0.1/1.4 for Texofor A14, 0.1/2.4 for Texofor A1P and 0.1/3 for Texofor A30.

Considering the uncertainties in the exact distribution of ethylene oxide chain lengths in these commercial surfactants, the correlation coefficients are satisfactory. The a and b values of Table 2 can now be used to calculate the distribution of the solubilized material between the core and the mantle of the micelles for any particular surfactant composition. The parameter y in Table 2 is the ratio of the amount in the mantle to the amount in the core calculated for Texofor A1P micelles, by multiplying a/b with 2.4/0.1 (C_{EO}/C_R). The values of y calculated therefrom for the ultraviolet light absorbers and drug show excellent qualitative correlations with the structure of the solubilizate as regards the distribution of the polar moiety in the molecule. Thus, Uvinul D-50 with polar hydroxyl groups in the molecule, as expected, has a relatively lower solubility in the micellar core whilst the interaction with the polyoxyethylene mantle is more pronounced, presumably because this interaction with the ethylene oxide groups involves hydrogen bonding. Nitrofurazone, having polar groups in the molecule less favourably positioned, accounts for a lower value of y than Uvinul D-50. On the other hand, Uvinul N-35 has weaker polar groups in the molecule with a bigger non-polar moiety and is a more hydrophobic molecule. As a result, the degree of association with the polyoxyethylene mantle is relatively small, whereas the solubility in the core is much greater.

It is interesting to compare the values of y for the micellar systems with the corresponding values of the solubilities in polyethylene glycol itself. For this purpose, the latter quantity termed a' was calculated and is also given in Table 2. The parameter a' is defined as equivalents of solute bound per equivalent of ethylene oxide groups calculated for polyethylene glycol 1000 at 0.1 M concentration by dividing the solubility data (corrected for water solubility) in moles l^{-1} by the concentration as equivalents of ethylene oxide per litre (0.1 M concentration of polyethylene glycol 1000 would represent 2.2 ethylene oxide units). A plot of y vs a' for these solubilizates is linear which indicates a direct relationship exists between their solubility trend in polyethylene glycol and distribution tendencies within the polyoxyethylene mantle of the surfactants.

The comparison of a and a' values indicates that the ability of the polyoxyethylene mantle of the micelles to associate such molecules is substantially higher than that of polyethylene glycol 1000 at similar molar concentrations.

Considering the structure of the micellar interface in detail, this effect does not seem unreasonable. Polyethylene glycol exists approx. as a random coil. In comparison, because of the geometrical arrangements imposed by the micelle core, the ethylene oxide groups close to the hydrocarbon core are forced to be in close proximity (Mukerjee, 1971). The ethylene oxide groups in this region are expected, therefore, to have much higher local concentrations of ethylene oxide groups than polyethylene glycols, and the solubilization is likely to be facilitated by multiple interactions with neighbouring chain elements.

Ultraviolet spectroscopic method of investigation of solubilization sites

The λ_{max} values of Uvinul D-50, Uvinul N-35 and nitrofurazone in a wide range of solvents are given in Table 3.

The plots of E_T vs Z for Uvinul D-50, Uvinul N-35 and nitrofurazone were made and Table 4

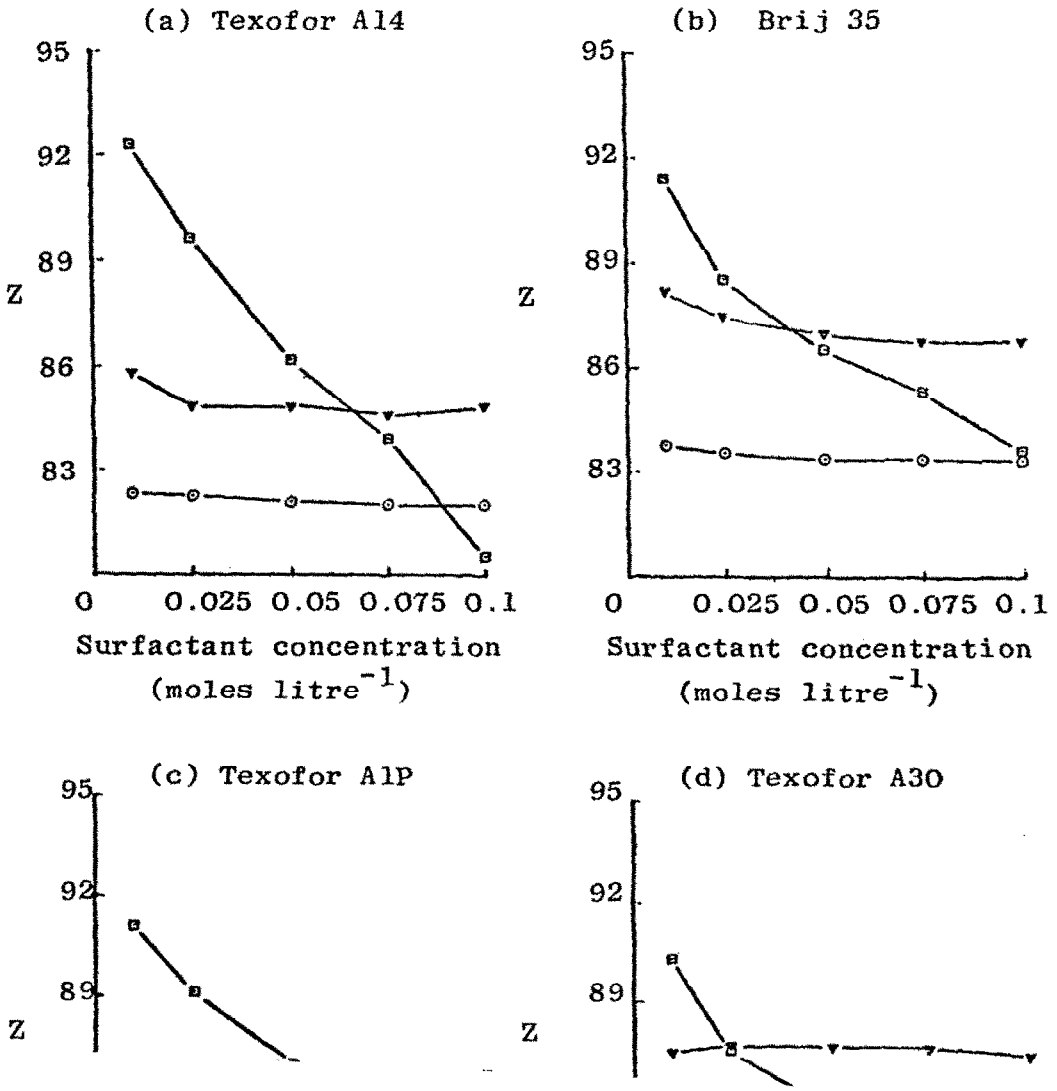
(a) Texofor A14
95
92
89
86
83
Z
0
0.025
0.05
0.075
0.1
Surfactant concentration
(moles litre^{-1})
(b) Brij 35
95
92
89
86
83
Z
0
0.025
0.05
0.075
0.1
Surfactant concentration
(moles litre^{-1})
(c) Texofor A1P
95
92
89
Z
(d) Texofor A30
95
92
89
Z

TABLE 3

Spectral properties of the different solubilizates in solvents of varying polarity

Solvents	Z value	λ_{max} (nm)			
		Uvinul D-50	Uvinul N-35	Nitrofurazone	
Water, distilled	94.6	336.0	–	260.5	375.1
56% v/v methanol	90.9	339.2	307.6	260.2	372.7
80% v/v methanol	87.1	342.3	305.4	262.3	369.2
90% v/v methanol	85.5	344.2	304.3	263.1	367.5
Methanol	83.6	345.9	302.2	263.9	365.8
80% v/v ethanol	84.8	349.1	305.1	264.0	371.2
90% v/v ethanol	82.5	350.4	304.3	264.2	369.5
95% v/v ethanol	81.2	352.8	303.9	264.3	368.4
Ethanol	79.6	354.5	302.5	265.1	367.4

indicates the results of least-squares regression analysis of the data.

Except for a chromophore (375 nm) of nitrofurazone the correlation coefficients seem satisfactory. The z values of surfactant solutions were determined by reference to the appropriate plots.

Fig. 5a–d shows the relationship among the Z values for the solubilizates in different surfactant concentrations of Texofor A14, Brij 35, Texofor A1P and Texofor A30, respectively. The Z values for nitrofurazone in Fig. 5 were based on the 260 nm chromophore.

Determination of the relative regions of solubilization in the micelle by comparing the changing Z value fits well with the data obtained from the solubility measurements for Uvinul D-5O and nitrofurazone. The Z value for nitrofurazone in 0.01 M surfactant solution showed an environment with a polarity between that of water and 56% v/v methanol, indicating that significant quantities of the drug were not included in the micellar phase. This is in agreement with the fact that the solubility of nitrofurazone is not appreciably greater in 0.01 M concentration of all four surfactants than in water at 25°C. With increasing surfactant concentration, the Z value decreased, indicating an environment of decreasing polarity and at 0.1 M concentration approximated to that of 75–96% v/v ethanol (Kosower, 1958a). The behaviour was similar for all the surfactants. As Bjaastad and Hall (1967) have pointed out, decreasing polarity might be explained by an increase in concentration and organization of micelles as the concentration of surfactant is increased.

In the case of Uvinul D-50, at 0.01 M concentration of surfactant, the comparatively low Z value indicates inclusion of significant quantities in the micellar phase and this is supported by the solubility results as well. Above this concentration the Z value does not change appreciably showing an environment of same polarity throughout and at 0.1 M concentration approximates to that of 92–85% v/v ethanol. The behavior is similar for all the surfactants.

Uvinul N-35 possessing a very low water solubility would be expected to be included in the hydrocarbon interior of the micelles, but the Z values of the surfactant solutions appear to indicate that it was situated in a more polar environment than either Uvinul D-50 or nitrofurazone. This is contradictory to the results obtained by the previous solubility method.

Reigelman (1960) suggested that if the nonionic surfactant concentration is increased the char-

TABLE 5

λ_{max} values of solubilizates in different concentrations of polyethylene glycol 1000

% w/v polyethylene glycol 1000 in water	λ_{max} (nm)			
	Uvinul D-50	Uvinul N-35	Nitrofurazone	
5		309.8	261.2	375.2
10		309.9	261.5	375.3
15		310.0	261.7	375.7
20		310.0	261.9	376.0
30			261.8	376.0
40	349.1		261.3	376.5
50	350.3		261.7	376.8
60	352.5			

ylene glycol 1000 solution in water are given in Table 5.

It can be seen from Table 5 that Uvinul D-50 has a λ_{max} value in the surfactant solutions that is close to the λ_{max} value in approx. 40–50% w/v mixture of polyethylene glycol 1000 and water. This indicates that this compound is located mainly within the polyoxyethylene portion of the micelle. In the case of nitrofurazone, only one chromophore (375 nm) shows a significant shift in polyethylene glycol solution. This may indicate that the molecule is oriented in such a way that one chromophore (260 nm) lies away from the polyoxyethylene portion of the micelle while the other (375 nm) is located within the polyoxyethylene mantle. The λ_{max} value, due to the latter chromophore in surfactant solution is similar to that of 5–20% w/v mixture of polyethylene glycol 1000 and water. Thus, relative to Uvinul D-50, this portion of nitrofurazone molecule may be less deeply embedded within the polyoxyethylene portion of the micelle. With Uvinul N-35, it was found that the λ_{max} does not shift significantly in a mixture of polyethylene glycol 1000 and water. The λ_{max} values of Uvinul N-35 in aqueous polyethylene glycol solution does not correspond with λ_{max} in surfactant solutions. Therefore, it does not appear that Uvinul N-35 could be in the polyoxyethylene portion of the micelle. This would support the previous assessment from the solubility data of location in the hydrocarbon interior of the micelle. The reason for the apparent anomalous Z value results with Uvinul N-35 in surfactant solutions is not clear.

The use of more than one experimental technique for the investigation of solubilization sites in aqueous micelle is clearly desirable and due caution is needed in analyzing the data.

From the solubility studies it has been seen that incorporation of Uvinul D-50 Into both nonionic surfctant and polyethylene glycol is possible while Uvinul N-35 cannot be included in the polyethylene glycol system. The relatively low solubilities of the solubilizates in polyethylene glycol solutions, in particular Uvinul N-35, as compared to those in the surfactants emphasises the advantage of using the phenomenon of micelle formation to increase the solubility of these slightly water-soluble compounds. Thus if it is intended to make use of ultraviolet light absorber to protect the solution, then the nonionic surfactant systems have the great advantage in that both water-soluble and oil-soluble ultraviolet light absorbers may be incorporated.

The ultraviolet spectra of nitrofurazone In various aqueous solutions possess two absorption bands located in the region of 260 nm and 375 nm respectively. Solvent effects may be used to assign transitions such as $n \rightarrow \pi^*$ or $\pi \rightarrow \pi^*$. It can be seen from Table 4, that a plot of of E_T vs Z gave a straight line of positive slope for the 260 nm chromophore of the drug, while for the 375 nm chromophore a negative slope was obtained. A positive slope indicates an $n \rightarrow \pi^*$, and a negative slope indicates a $\pi \rightarrow \pi^*$ transition (Kosower, 1958b). For a $\pi \rightarrow \pi^*$ transition, the excited state is more polar than the ground state (Cowan and Drisko, 1976). The fact that the 375 nm absorption maximum shows a shift to shorter wavelength in a less polar solvent indicates an increase in the energy of the excited state relative to the ground state. On the other hand, for the $n \rightarrow \pi^*$ transition, the excited state is less polar than the ground state, and a decrease in solvent polarity produces a shift of the 260 nm maximum to longer wavelengths indicating a decrease in energy of the excited state relative to the ground state. It is therefore to be expected that nitrofurazone would show differences in degree of photolability in media of different polarity.

Further studies on the photolability of the drug in polyethylene glycol and surfactant solutions are being conducted and will be reported in a future communication.

Acknowledgement

The award of a Commonwealth Scholarship to one of us (M.S.) by the Association of Commonwealth Universities, U.K., for financial support of this research work is gratefully acknowledged.

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