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Investigation of the nature of the interaction of nitrofurazone with urea

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Summary

The effect of urea on the solubility of nitrofurazone in pH 4.0 buffer was studied. The solubility was found to increase with increase in the urea concentration as well as with a rise in temperature. The thermodynamic parameters for the process of dissolution of nitrofurazone in urea tend to rule out a complexation mechanism. Analysis of the spectral properties of the system also suggests that no interaction takes place between nitrofurazone and urea.

Nitrofurazone is a topical antibacterial agent possessing relatively low aqueous solubility characteristics. In a preceding paper (Shahjahan and Enever, 1992a), the solubility at 25°C is reported to be 215 mg/l in distilled water. The effect of urea on the aqueous solubility of organic compounds has been widely studied (Feldman and Gibaldi, 1967; Chen et al., 1976). In another preceding report (Shahjahan and Enever, 1992b), a description is given of the use of 10% w/v urea solution in McIlvaine's pH 4.0 buffer as an immobile phase in the paper chromatographic determination of nitrofurazone. Similar use of urea solutions for paper chromatographic determination of oxytetracycline (Sina et al., 1971) and formation of a slightly soluble tetracycline-urea complex has also been reported (Youssef et al., 1973). Urea is a relatively nontoxic compound and scientific data are still needed concerning the action of urea as a complexing agent. Therefore, it was of interest to study the consequences of the interaction between urea and nitrofurazone as manifested by the effects of particular urea concentrations and temperature on the solubility of nitrofurazone.

Nitrofurazone (Human Grade; Batch No. 6B5017) was obtained from Smith Kline and French Laboratories Ltd (Herts, U.K.). All solvents and laboratory reagents were of 'Analar' grade (BDH, U.K.). Double-distilled water was prepared using an all-glass distillation unit (QVF, Stoke-on-Trent).

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The solubility of nitrofurazone in pH 4.0 buffer containing different concentrations of urea was determined at various temperatures using the procedure described earlier (Shahjahan and Enever, 1992a).

The method of difference spectroscopy (tandem technique), as described by Chen et al. (1976), was used to investigate the possible interaction between nitrofurazone and urea. Equal volumes of nitrofurazone (0.008 mg/ml) dissolved in buffer at pH 4.0 were placed in both reference and sample cells (1 cm path length) of a Unicam SP 1800 recording spectrophotometer and the baseline established by scanning at 2 nm/s between 230 and 450 nm. To the sample cell was added, in 0.2-ml portions, 1 ml of a solution containing 0.008 mg/ml of nitrofurazone dissolved in 30% w/v urea solution in pH 4.0 buffer. At the same time, similar volumes of urea solution (30% w/v) in pH 4.0 buffer were added to the reference cell. The spectrum was recorded after each addition.

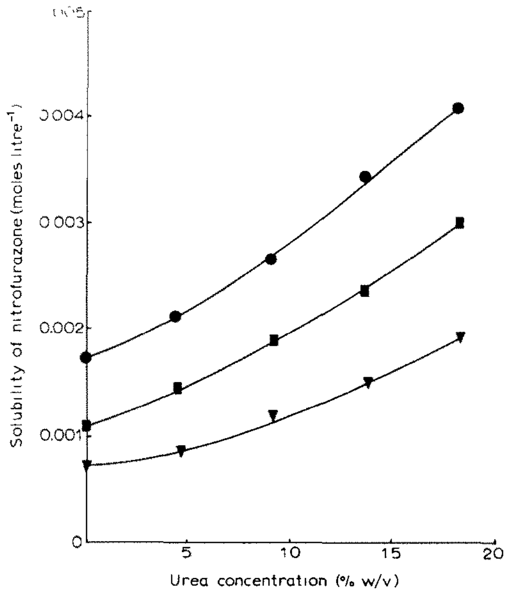

Fig. 1. Solubility of nitrofurazone in urea solution at pH 4.0 at various temperatures: (▼) 15°C, (■) 25°C, (●) 35°C.

Fig. 1 summarises data concerning the effect of urea on the solubility of nitrofurazone in pH 4.0 buffer. The solubility was found to increase with increasing urea concentration as well as with rising temperature. Urea has been shown to increase the aqueous solubility of chloramphenicol (Goldberg et al., 1966) and of benzoic and salicylic acids (Bolton, 1963; Altwein et al., 1965). Altwein et al. (1965) stated that the interaction of salicylic acid and urea involved the formation of complexes. Feldman and Gibaldi (1967), however, concluded that the enhanced solubility of benzoic and salicylic acids in urea did not involve complexation, but occurred via the 'breaking up' of water clusters surrounding these relatively nonpolar molecules. This increased the entropy of the system and produced a 'driving' force for solubilization.

To determine the thermodynamic parameters for the process of dissolution of nitrofurazone in urea, the values of log N/N_0 of nitrofurazone at each concentration of urea were plotted against $1/T$. N and N_0 represent the respective values for the mole fraction solubility of nitrofurazone in pH 4.0 buffer with and without urea present. The enthalpy of the process (ΔH) was calculated from the slopes of such plots. The free energy

TABLE 1

Thermodynamic parameters for the solution of nitrofurazone in urea at pH 4.0

Urea (mol l^{-1})	ΔG (J mol^{-1})			ΔH (J mol^{-1})	ΔS (J mol^{-1} K^{-1})
	15°C	25°C	35°C		
0.833	−498	−833	−636	+0.0243	+2.09
1.665	−1369	−1524	−1294	−0.0515	+4.61
2.498	−2081	−2223	−2043	−0.0666	+7.12
3.330	−2751	−2885	−2592	−0.0477	+9.21

(ΔG) of the solution process was evaluated using the relationship:

$$\Delta G = -2.303RT\ \log(N/N_0) \tag{1}$$

The change in entropy (ΔS) associated with this process was determined according to the following relationship:

$$\Delta S = \frac{\Delta G - \Delta H}{T} \tag{2}$$

These thermodynamic parameters are listed in Table 1. It can be seen from Table 1 that the change in enthalpy is exceedingly small. The variation in ΔH with concentration of urea showed no trend and appeared to be due to experimental error. The type of complexation most frequently described in the pharmaceutical literature involves the formation of hydrogen bonds. The enthalpy for the formation of a hydrogen bond is between 12.6 and 20.9 kJ/mol (Feldman and Gibaldi, 1967), well above the low ΔH values noted in this investigation. Moreover, the free energy values determined in the present work also tend to rule out a complexation mechanism in that the ΔG values of complexation are usually in the range of 8.4–20.9 kJ/mol (Feldman and Gibaldi, 1967). Since the increased solubility of nitrofurazone in urea does not appear to involve a complexation mechanism, the possibility remains that urea is somehow 'disrupting' the water structure and thereby bringing about an increase in solubility of the compound. The value of ΔS in Table 1 certainly supports the concept of an increase in entropy upon dissolution of nitrofurazone.

The formation of a complex in solution can often alter the spectral properties of a substance. It is for this reason that the spectral properties of the system were studied. It is generally recognised that several experimental problems associated with the detection and measurement of spectral changes can be greatly simplified by using a difference spectral technique. Instead of comparing the spectrum of nitrofurazone with that of a mixture of nitrofurazone and urea, their difference spectra were recorded and are com-

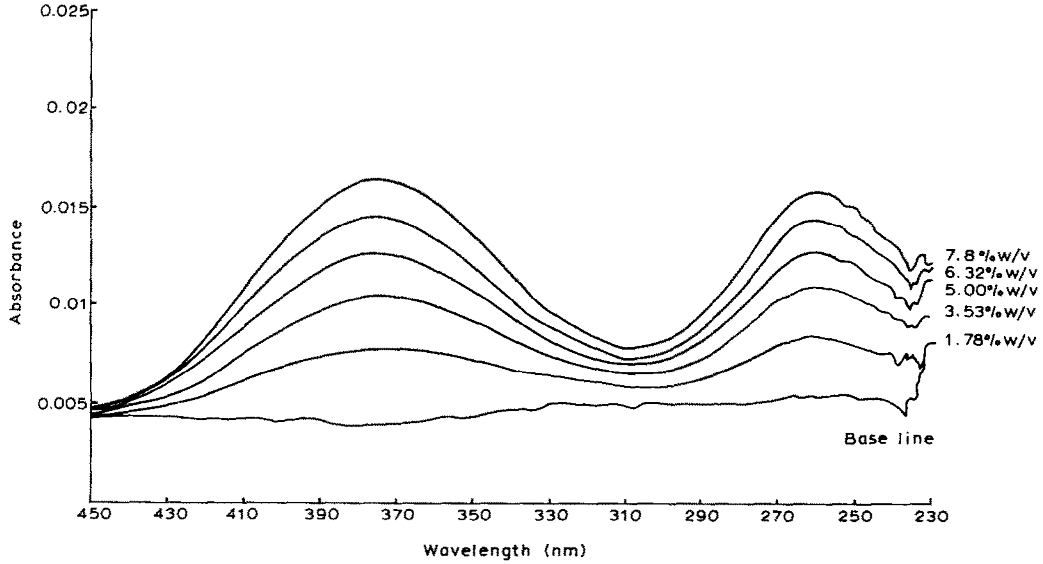

Fig. 2. Difference spectra of nitrofurazone-urea in pH 4.0 buffer solution.

pared in Fig. 2. Analysis of the spectra suggests that no interaction takes place between molecules of nitrofurazone and urea since no spectral changes are evident.

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