Photolability of nitrofurazone in aqueous solution II. Kinetic studies

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Abstract

The effect of ultraviolet radiation on the photolability of nitrofurazone in aqueous solutions was followed by a stability-indicating paper chromatographic method. Various factors including the pH of the medium, the presence of surfactants, polyethylene glycols, metal ions or ultraviolet light absorbers influenced the rate of photodecomposition of the drug. The photodecomposition of nitrofurazone in aqueous solution followed apparent zero-order kinetics. In the polyethylene glycol or aqueous solution the rate was much lower than that in the surfactants. The process of photodecomposition was accelerated by ferric ions while slightly inhibited by cupric ions. It was found that the rate constant increased initially with the incorporation of a small amount of the ultraviolet light absorbers. Subsequently, the rate constant decreased with increasing concentration of ultraviolet light absorber. Uvinul D-50 shows a higher stabilizing effect than Uvinul N-35. There was little thermal degradation of the drug in comparison to the decomposition by irradiation with ultraviolet light at the temperature of the study. Thermal degradation followed a first order rate process.

Keywords: Nitrofurazone; Reaction kinetics; UV radiation; Photodegradation; UV absorbers; Thermal stability

1. Introduction

It is recognised that light is an important external factor in drug instability. Pharmacopoeias and licensing agencies have taken this into account by specifying appropriate storage instructions. The photostability of drugs is one of those areas largely ignored by pharmaceutical science, although the number of drugs known to be sensitive to light is on the increase (Thoma and Klimek, 1991).

In a number of recent papers, however, the photochemical degradation of a drug substance has been described, and the rate of photodegradation has been quantified in terms of a rate con-

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stant (Al-Turk et al., 1988; Suleiman et al., 1989). Moore (1990) pointed out that some caution must be exercised in the interpretation of a rate constant derived from the study of photochemical reactions. The rate of a photochemical reaction is critically dependant on the wavelength and intensity of the irradiating source as well as the shape and position of the reaction vessel in relation to light source. In other words, the number of quanta of the relevant wavelength region being absorbed per unit time is one of the two factors which determines the rate at which a photochemical reaction occurs. The other factor is the photochemical efficiency or quantum yield of the reaction. In earlier works no attempt was made to restrict the wavelength employed for irradiation. Ultraviolet lamps were employed without using filters or monochromators. None of these works served to establish a quantum efficiency or mechanism for the photodegradation.

Nitrofurazone, an antibacterial drug was found to be susceptible to photodecomposition (Shahjahan, 1979; Shahjahan and Enever, 1979; Quilliam et al., 1987). The incorporation of ultraviolet light absorbers in certain concentrations has been reported to substantially decrease photodegradation rates (Asker et al., 1971). In a previous publication (Shahjahan and Enever, 1996) we investigated photodecomposition of nitrofurazone under carefully controlled conditions to evaluate the quantum efficiency at 362.8 nm (nearest to the absorbance peak). The results of the quantum yield studies have shown the complexity of the photodecomposition pathway of nitrofurazone in aqueous solution in the presence of ultraviolet light absorbers.

The aim of the present study was to collect further qualitative and quantitative data in order to obtain more detailed information on the decomposition of nitrofurazone in aqueous solution. Since a photochemical process is a chemical reaction which takes place only under the influence of light, the investigation should be restricted to the temperature for which negligible thermal reaction occurs in the dark during the time necessary for the photochemical run. Therefore, another study was undertaken to investigate the thermal stability of the drug in various solutions kept in darkness

at 25°C. In this communication we report the reaction kinetics of nitrofurazone degradation in aqueous solution and evaluate the potential impact of ultraviolet light absorbers on the photodegradation.

2. Materials and methods

2.1. Materials

Nitrofurazone (Human Grade), Batch No. 6B5017; m.p. 220–224°C (with decomp) was obtained from Smith Kline and French Laboratories (Herts., UK). Uvinul D-50 and Uvinul N-35 obtained from GAF (UK). The nonionic surfactants used were partially purified samples of Texofor A14, A1P and A30 (ABM Chemicals, UK) containing approximately 14, 24 and 30 m of ethylene oxide as well as Brij 35 (Honeywill Atlas, Surrey) containing 23 m of ethylene oxide (Shahjahan and Enever, 1991). Polyethylene glycols obtained from Koch-light Laboratories, Colnbrook, Bucks, UK.

Citric acid, ferric chloride hexahydrate, urea were of analar grade while cetyl alcohol, ethylenediaminetetra-acetic acid (disodium salt) were of reagent grade (BDH, UK). Cupric sulphate (analar) was supplied by Hopkin and Williams, Chadwell Heath, Essex. Double distilled water was obtained from an all glass distilation unit (QVF, Stoke-on-Trent, UK).

2.2. Photostability studies

Drug solution (2.5 ml) (2×10^{-3} m l^{-1} concentration in the case of surfactant and polyethylene glycol 1000 solution in pH 6.0 buffer and 7×10^{-4} m l^{-1} in the case of aqueous buffer solutions) was pipetted into the 1 cm silica cells. The cell was placed in the cell holder of an irradiation assembly (maintained at 25 ± 0.5°C) consisting of a 100 Watt compact high pressure mercury arc lamp as the light source and interference filters to achieve monochromatic radiation as reported earlier (Shahjahan and Enever, 1996) and irradiated at 362.8 nm for a given length of time. At various time intervals 0.2 ml of each solution was assayed

in triplicate by using a paper chromatographic procedure (Shahjahan and Enever, 1992a) which employed Whatman no. 4 chromatographic paper previously impregnated with 10% w/w urea in McIlvaine's pH 4.0 buffer and ethyl acetate: n-butanol: benzene (3:2:1) saturated with urea as the mobile phase. The experiment was repeated and the mean value of the two results was taken.

2.3. Thermal stability studies

2 ml of nitrofurazone solution $(7 \times 10^{-4} \text{ m l}^{-1})$ in McIlvaine's buffer of varying pH values and also different surfactant or polyethylene glycol 1000 solutions of the drug $(2 \times 10^{-3} \text{ m l}^{-1})$ buffered at pH 6.0 were pipetted into 10 ml colourless neutral glass ampoules and the necks of the ampoules sealed. These ampoules were then stored at $25 \pm 0.1°C$ in a water bath. In order to ensure constant temperature control in the heating of the ampoules, these were fitted with ampoule holders made from copper tubing 2.5 cm long and 2 cm internal diameter which had been constricted at one end. Complete immersion of the ampoules in the water bath thus maintained throughout the experiment. One ampoule of each solution was withdrawn at various time intervals and was analyzed by taking triplicate samples for paper chromatographic analysis as described earlier. The mean value of the three results was taken.

3. Results and discussion

Photodegradation of pharmaceuticals often follows zero order kinetics. This would be expected, since such rate is independent of concentration and is set by some outside limiting factors such as the absorption of light (Asker et al., 1971). For this reason, and also because no other order of reaction gave a better fit of the data, the results were represented graphically as percentage drug decomposed vs. time (h). Linear relationships were assumed and the slopes of the best straight lines were determined by the method of least squares. The apparent zero order rate constants were given by the slope values.
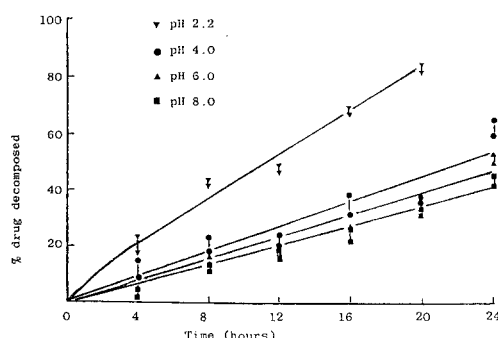

Fig. 1. The effect of pH on the photodecomposition of nitrofurazone $(7 \times 10^{-4} \text{ m l}^{-1})$ in aqueous solution.

3.1. Effect of pH on the photodecomposition of nitrofurazone in solution

It can be seen from Figs. 1 and 2 that, at higher pH values in the range studied with McIlvaine's buffers, nitrofurazone decomposed at a lower rate. Between pH 4.0 and pH 8.0 there seemed comparatively little difference in the decomposition rates when compared with those between pH 4.0 and pH 2.2. Greatest instability was observed at pH 2.2 probably due to increased hydrogen ion concentration of the solution. Similar effect has been shown on the phototransformation of ergot alkaloids (Lin and Lachman, 1969). These results agree with the results obtained with quantum yield studies (Shahjahan and Enever, 1996) in that the fall in quantum yield was most marked when changing the pH of the solution from pH 2.2 to
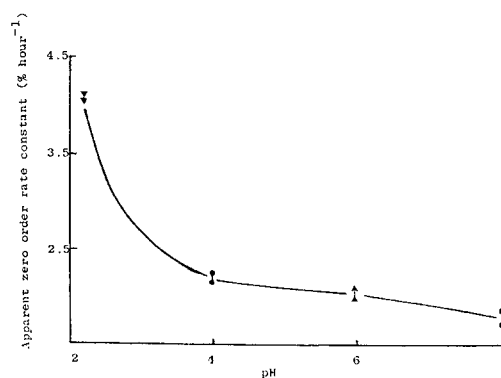

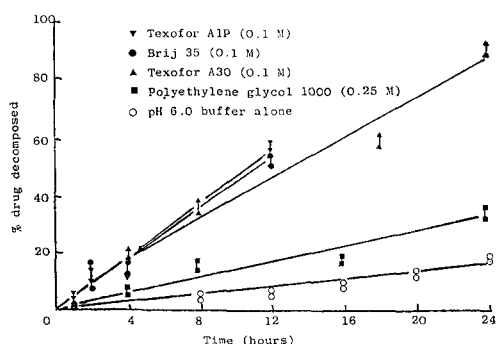Fig. 2. The effect of pH on the apparent zero order rate constant of photodecomposition.

Fig. 3. The effect of surfactants and polyethylene glycol on the photodecomposition of nitrofurazone (2×10^{-3} m 1^{-1}) in solution buffered at pH 6.0.

pH 4.0. It also agrees with the previous observation of Spross (1953) that the light sensitivity of nitrofurazone is more pronounced in acid and neutral solutions than in alkaline solution.

Since the drug is mainly used for topical application and the pH of the skin is normally between pH 5 and pH 6 further rate studies were carried out in solutions buffered at pH 6.0.

3.2. Effect of the nature of surfactants and polyethylene glycol on photodecomposition of nitrofurazone in solution

The results shown in Fig. 3 indicate that the rate of decomposition in the surfactants (0.1 M concentration at pH 6.0 buffer) is highest for the solution in Texofor A1P and lowest for Texofor A30. This suggests that the rate of photodegradation decreased as the polyoxyethylene chain length increased. By comparing the rates in Texofor A1P and Brij 35 it can be seen that the rate was possibly marginally increased in the surfactant solution having the longer hydrocarbon chain length. However, the difference in the decomposition rate between these surfactants is small in comparison with the difference between the surfactants and either polyethylene glycol 1000 (0.25 M concentration) or aqueous solution buffered at pH 6.0. (The data for the latter solution have been recalculated from results obtained using a 2×10^{-3} m 1^{-1} solution on the basis that the degradation is a zero order process).

In the polyethylene glycol or aqueous solution the rate is much lower than that in the surfactants. These former solutions, having highest hydrophilicity, thus confer greater photostability. In surfactants, the solute is considered to be solubilized by the less polar micellar pseudophase and this type of solubilization has been shown to affect the chemical and biological properties of the solubilizate (Bjaastad and Hall, 1967). Indeed, since the surfactants possess regions of opposing hydrophilic and lipophilic solvent tendencies, and, since the drug has been shown to be distributed between both regions of the micelle (Shahjahan and Enever, 1991), whereas polyethylene glycols are hydrophilic in nature, this would be a possible reason for the difference in photostability of the drug. A similar pattern of results were reported for the effect of solvent on the photodecomposition rate of a nitrofuran derivative (Fujioka et al., 1973). They found that the reaction rate became much greater when the solvent was changed from water to ethyl acetate.

In the present investigation, by comparing the rates for these formulations (Table 1) it can be seen that aqueous solution would be the most suitable formulations from a stability point of view. This is in agreement with the quantum yield study results in that aqueous formulations are most stable with respect to irradiation. A plot of apparent zero order rate constant versus quantum yield for the drug in aqueous, polyethylene glycol and Texofor A30 solutions is linear (Fig. 4) which indicates a direct relationship between the parameters. This adds support to the postulate that the decomposition upon irradiation is a zero

Table 1
Comparison of apparent zero order rate constants in different formulations

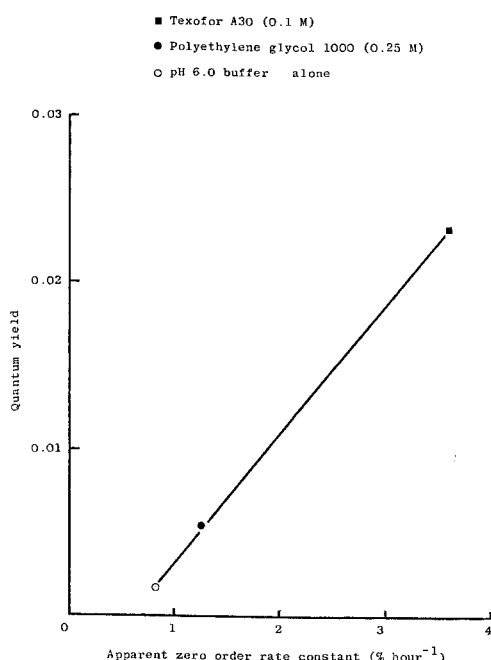| Formulations	Apparent zero order rate constant (%h^{-1})
Brij 35 (0.1 M)	4.516
Texofor A1P (0.1 M)	4.841
Texofor A30 (0.1 M)	3.581
Polyethylene glycol 1000 (0.25 M)	1.257
Aqueous solution (pH 6.0)	0.818

Fig. 4. Relationship between the quantum yield and apparent zero order rate constant for nitrofurazone in solutions buffered at pH 6.0.

order process. Although aqueous formulations are most stable with respect to photostability, however, it is not possible to obtain sufficient quantities of the drug in simple aqueous solution to produce a clinically effective product because of its low solubility.

Since it was observed that, for a given compound, the highest solubility was achieved in 0.1 M concentration of Texofor A30 and a similar amount could be dissolved in 0.25 M polyethylene glycol 1000 solution, further rate studies were carried out in these solutions buffered at pH 6.0.

3.3. Effect of ultraviolet light absorbers upon the photodecomposition rate of nitrofurazone in solution

3.3.1. Surfactant solution

The effect of the concentration of ultraviolet light absorbers on the zero order photodecomposition rate constant is shown in Fig. 5. It is evident that the rate constant increased initially with the incorporation of a small amount of the

ultraviolet light absorbers. Subsequently, the rate constant decreased with increasing concentration of ultraviolet light absorbed. Previous quantum yield studies (Shahjahan and Enever, 1996) indicated that incorporation of Uvinul N-35 in the surfactant solution increased the susceptibility of the drug to light and thus Uvinul N-35 did not exert any quenching effect on the reaction, but rather it had a sensitizing effect on nitrofurazone decomposition.

In effect, although Uvinul N-35 absorbed the majority of radiation and hence protected the drug from decomposition, some of the energy was transferred to the drug and produced greater sensitizing of the drug to light. Thus, Uvinul N-35 has two effects—a sensitizing effect and light absorbing effect. At low concentrations of absorber, the sensitizing effect is more prominent since, as can be seen in Fig. 5, there was an increase in the apparent zero order rate constant for decomposition of the drug. However, as the concentration of absorber was increased further, the light absorbing properties predominated over its sensitizing effect and thereby produced an overall protective effect on the drug as shown by the rate studies results.

When the zero order rate constants were compared for the two ultraviolet light absorbers at a given molar concentration, the rate constant was found to be always lower with Uvinul D-50. For a similar concentration of 0.16×10^{-3} m l^{-1} the rate constant in Uvinul D-50 was approximately 60% of that in Uvinul N-35. Thus, Uvinul D-50
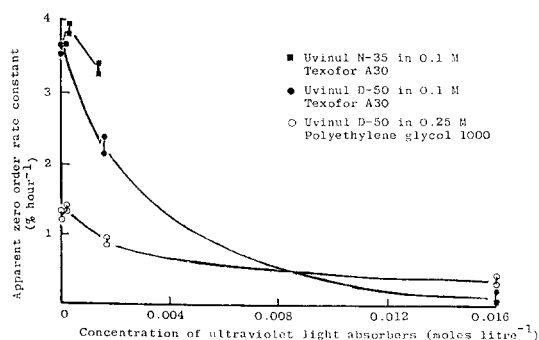

Fig. 5. Effect of concentration of ultraviolet light absorbers on the photodecomposition rate of nitrofurazone (2×10^{-3} m l^{-1}) in solution buffered at pH 6.0.

Table 2
Comparison of the effect of concentration of Uvinul D-50 on the apparent zero order rate constants for nitrofurazone decomposition in polyethylene glycol and in surfactant solution

Concentration of Uvinul D-50 (m l^{-1})	Ratio of rate constant to aqueous solution at pH 6.0	
	Polyethylene glycol solution	Surfactant solution
0	1.537	4.378
0.16 × 10^{-3}	1.720	4.451
1.6 × 10^{-3}	1.106	2.771
16 × 10^{-3}	0.441	0.125

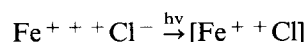shows a higher stabilizing effect than Uvinul N-35.

3.3.2. Polyethylene glycol solution

As Uvinul N-35 was not soluble in polyethylene glycol solution, the experimental results were limited to those with Uvinul D-50. It can be seen, from Fig. 5, that a similar initial rise in the apparent rate constant was observed when a low concentration of Uvinul D-50 was employed. Subsequently, as with the surfactant solution, there was a decrease in rate with increasing Uvinul D-50 concentration. The ratio of apparent rate constant in water to that in polyethylene glycol solutions for a given concentration of Uvinul D-50 when compared with that in surfactant solution (Table 2) was lower up to a concentration of 1.6 × 10^{-3} m l^{-1}, but at 16 × 10^{-3} m l^{-1} concentration the situation was reversed. In other words Uvinul D-50 exerts a higher degree of protection in surfactant solution than in polyethylene glycol solution as the concentration is increased. The higher quantum yield (Shahjahan and Enever, 1996)—and yet simultaneous higher protective action shown in rate studies with higher concentration of Uvinul D-50—can be explained in the same manner as for Uvinul N-35.
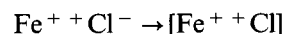
3.4. Effect of metal ions on the photodecomposition of nitrofurazone in aqueous solution

It is known that di- and trivalent metal ions frequently catalyze reactions by favouring the for-

mation of free radicals (Spross, 1953). Therefore, an experiment was carried out to determine the effect of ferric and cupric ions upon the rate of nitrofurazone decomposition. These ions were chosen since transition elements are normally more effective in catalyzing reactions. The results are shown in Fig. 6. The process of photodecomposition was accelerated by ferric ions while slightly inhibited by cupric ions. The effect of metal ions on a chemical reaction is complex as both acceleration and inhibition by metal ions has been reported. Ferric chloride itself in solution is known to undergo photoreduction.

$$Fe^{+++}Cl^- \xrightarrow{hv} [Fe^{++}Cl]$$

followed by numerous reactions of this intermediate, including dissociation

$$Fe^{++}Cl^- \rightarrow [Fe^{++}Cl]$$

In the present study the accelerating effect of Fe^{+++} ion on the photodecomposition of nitrofurazone may be due to radical formation through the processes analogous to the above, as $Fe^{+++}Cl^-$ ion pairs have been found capable of photochemically initiating polymerization of vinyl compounds by radical formation. (Evans et al., 1951). The decrease in the rate of photodecomposition of the drug in the presence of cupric ions may be due to the quenching effect of cupric ions which could be attributed to a dark reaction between ground state nitrofurazone molecule and
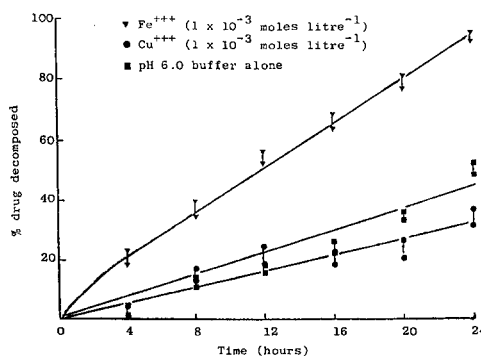

Fig. 6. The effect of metal ions on the photodecomposition of nitrofurazone (7 × 10^{-4} m l^{-1}) in pH 6.0 buffer solution.
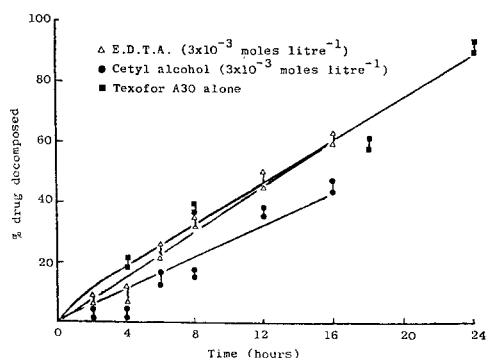
Fig. 7. The effect of additives on the photodecomposition of nitrofurazone $(2 \times 10^{-3}$ m $1^{-1})$ in Texofor A30 (0.1 M) solution buffered at pH 6.0.

cupric ion (Spross, 1953). This quenching of the excited state may be due to an electronic effect resulting from complexation between nitrofurazone molecules and cupric ions. The essential condition for this type of complex is that suitable groups are sterically available for coordination, e.g. $- NH_2$ which is present within the nitrofurazone molecule (Turney, 1965).

3.5. Effect of additives upon the photodecomposition of nitrofurazone in surfactant solution

Although the commercial surfactants used in the present study were freed from contaminating polyethylene glycol, they might contain trace impurities such as the synthetic precursor, cetyl alcohol or metal ions which may be introduced during manufacture. From the earlier experiment since it was shown that photodecomposition was accelerated by the presence of ferric ions in aqueous solution, it seemed possible that the increased rate of decomposition in surfactant solutions compared with water may be due to the presence of these trace impurities. Metal complexing agents such as ethylenediaminetetra-acetic acid (EDTA) have been known to exert a protective effect by removing heavy metal contaminants. Fig. 7 shows the result of an experiment carried out using 3×10^{-3} m 1^{-1} of EDTA (disodium salt) and cetyl alcohol. The results indicate that EDTA has no appreciable effect on the rate while cetyl alco-

hol has a protective effect on the photodecomposition of the drug in surfactant solution. Thus, the increased photodecomposition in surfactant solution is unlikely to be due to the presence of metallic ions or cetyl alcohol impurities.

3.6. Thermal stability of nitrofurazone at 25°C

The results shown in Fig. 8 indicate that the thermal decomposition of nitrofurazone in different solutions at 25°C approximates to a first order rate process. The effect of pH on the rate constant for thermal decomposition in aqueous solution is shown in Table 3 and shows that the drug is quite stable in these solutions, relative to their light sensitivity. The variation of rate constant with pH of the solution does not appear to be significant and may be due to experimental error. These results are similar to those of Spross (1953) with the exception that he found thermal decomposition is slightly enhanced at pH 2. However, Spross used the absorbance values of degraded solutions at 260 and 375 nm as a measure of
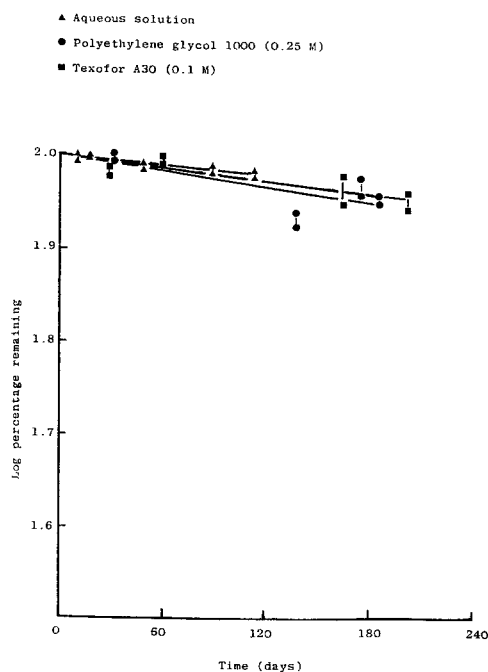

Fig. 8. First order plots of thermal degradation of nitrofurazone in different solutions buffered at pH 6.0 at 25°C.

Table 3
Effect of pH on the first order rate constant for the thermal decomposition of nitrofurazone at 25°C and comparison of decomposition with respect to irradiation

pH	First order rate constant day^{-1} for thermal decomposition	% Thermal decomposition in 20 h	% Photodecomposition in 20 h
2.2	3.6×10^{-4}	Not detectable	82
4.0	4.5×10^{-4}	Not detectable	44
6.0	4.0×10^{-4}	Not detectable	41
8.0	3.8×10^{-4}	Not detectable	36

intact nitrofurazone. As has been shown, this method is not specific for the drug in the presence of its decomposition products.

Table 4 shows the effect of surfactant or polyethylene glycol on the rate constant for thermal decomposition of the drug at 25°C. The results suggest that the surfactant and polyethylene glycol do not have a drastic effect on the thermal decomposition process as compared with their effects on the photodecomposition.

From the results in Tables 3 and 4, it is evident that photostability studies of the drug at 25°C are not significantly affected by thermal decomposition of the drug over the same time period. The higher quantum yields found in the presence of ultraviolet light absorbers and yet their simultaneous protective effect may seem inconsistent. In fact, the highest concentration of ultraviolet light absorbers used in the quantum yield study was of the same order of magnitde as the concentration at which no protective effect was shown in the kinetic studies (Fig. 5). Besides this, since the molecular extinction coefficient of nitrofurazone

Table 4
Effect of surfactants and polyethylene glycol on the rate constant of thermal decomposition of nitrofurazone at 25°C in aqueous solution buffered at pH 6.0

Aqueous solution buffered at pH 6.0	First order rate constant day^{-1}
No surfactant or polyethylene glycol	4.0×10^{-4}
Polyethylene glycol 1000 (0.25M)	6.4×10^{-4}
Texofor A1P (0.1M)	4.5×10^{-4}
Texofor A30 (0.1M)	5.5×10^{-4}

at both 260 and 375 nm (Shahjahan and Enever, 1992b) was greater than those of the ultraviolet light absorbers, incorporation of small quantities of the absorbers showed the sensitizing effect rather than protective effect giving rise to higher apparent rate constants than in the absence of ultraviolet light absorbers.

The protective effect at higher concentrations of the absorbers was due to their light absorbing properties predominating over their sensitizing effects. When the protective effects of the two ultraviolet light absorbers are compared for a given molar concentration of absorbers, it was found that Uvinul D-50 was more effective. This is to be expected, since Uvinul N-35 has an absorption maximum at 305.7 nm in a Texofor A30 (0.1 M) solution, whilst with Uvinul D-50 this occurs at 349.8 nm, which is much closer to the absorption maximum of the drug. In selecting an ultraviolet light absorber, Thomas (1966) suggested that it is important to choose one which has an absorption maximum at, or near, the wavelength or wavelengths at which the photolabile compound is most sensitive. Moreover, it can be seen from the previous results (Shahjahan and Enever, 1992b) that the molecular extinction coefficient of Uvinul D-50 at 375 nm is much higher than that of Uvinul N-35.

For Uvinul D-50, there is a relatively greater increase in the protective effect with increasing concentration in Texofor A30 (0.1 M) solution when compared with the polyethylene glycol 1000 (0.25 M) solution (Table 2). The molecular extinction coefficient of Uvinul D-50 at 375 nm is very similar in both media and its Wavelength$_{max}$ is only slightly closer to that of the drug in surfactant solution than in polyethylene glycol solution.

Thus, these relatively minor changes alone would not be the sole cause for the more rapid alteration in the rate constant with the concentration of Uvinul D-50 observed in the surfactant solution. The difference ·in the protective effect with Uvinul D-50 in these two media may therefore be attributed to differences in sensitizing efficiency. It is not possible to postulate a detailed mechanism for the difference of sensitization by Uvinul D-50 in these two systems, as several types of photosensitized reactions are recognised with benzophenone, the parent compound (Calvert and Pitts, 1966).

The photodecomposition rate of nitrofurazone in Texofor A30 and polyethylene glycol 1000 solution was found to be 4 and 1.5 times higher than that in simple aqueous solution. The value of using nonionic surfactants in the nitrofurazone system is not based on the greater increase of solubility in such systems because the drug is more photolabile in these systems. However, incorporation of 16×10^{-3} m 1^{-1} of Uvinul D-50 into Texofor A30 and polyethylene glycol 1000 solutions has shown that it is possible to protect the drug by more 8- and 2-fold with respect to its photodecomposition in simple aqueous solution. Uvinul N-35 could not be incorporated in the polyethylene glycol systems and the solubility in Texofor A30 (0.1 M) was not enough to achieve an effective concentration to protect the drug. The solubility data suggest that nonionic surfactants with higher alkyl chain length may be suitable in achieving such a concentration. Thus, if it is intended to make use of ultraviolet light absorbers 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.

Acknowledgements

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