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# Photolability of nitrofurazone in aqueous solution I. Quantum yield studies

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**Abstract**

Equipment was developed to study the quantum yield for nitrofurazone in aqueous solutions. Various factors including the wavelength of irradiation, the pH of the medium, the presence of surfactants, polyethylene glycols or ultraviolet light absorbers influenced the photolability of the drug. The quantum yield decreased with increasing wavelength of incident radiation or pH of the medium. However, the quantum yield in surfactants was markedly higher than that in either polyethylene glycol or aqueous solution. The enhanced photodecomposition of drug in polyethylene glycol and surfactant solutions as compared to simple aqueous solution, is likely to be caused by the association of nitrofurazone with the surfactants and polyethylene glycol in the dark (ground state). There is a linear relationship between the molar uptake and quantum yield. The increase of quantum yield in the presence of ultraviolet light absorbers suggests that the compounds were acting as photosensitizers.

*Keywords:* Nitrofurazone; Quantum yields; UV radiation; Photodegradation; UV absorbers

## 1. Introduction

The effect of light is often considered an important factor in drug stability. However, there is little information on the light stability of nitrofurazone although the various official compendia state that nitrofurazone formulations should be stored in light resistant containers. Nevertheless, some stability studies were made (Spross, 1953; Uriach and Pozo, 1966; Iwahara et al., 1966) by following the change in extinction at the wavelength of maximum absorbance of the drug. Separation of intact drug from its photodecomposition products by paper chromatography (Wunderlich, 1958; Shahjahan, 1979; Shahjahan and Enever, 1979) and identification of photolysis products on a reverse phase high performance liquid chromatography column (Quilliam et al., 1987) were

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also reported. In a previous publication (Shahjahan and Enever, 1991), the solubilization of nitrofurazone and ultraviolet light absorbers in polyethylene glycols and nonionic surfactants and determination of the possible site of incorporation of the drug and absorbers within the micelle has been studied. So far, the quantitative photostability studies of nitrofurazone using a stability-indicating assay method has not been reported.

The most readily available source of radiant energy is sunlight but it is hardly necessary to point out the unsuitability of sunlight as a source of light for quantitative photochemical studies. It is better to use a light source that can be more readily controlled as to its intensity and wavelength, as it is recognized that photochemical reactions depend on the intensity of the light and its wavelength (Lin and Lachman, 1969; Allwood and Plane, 1986). The results of a photochemical process are frequently expressed by means of the quantum efficiency or quantum yield. The quantum yield is defined as the number of molecules reacting per quanta of energy absorbed. The experimental determination of the quantum yield constitutes one of the main aspects of the study of photochemical changes. The number of moles of light absorbing substance that react in a given time can be determined by a suitable analytical procedure. In a previous publication (Shahjahan and Enever, 1992) a paper chromatographic method for the determination of nitrofurazone in presence of its decomposition products was established. The method was successfully applied in this study to investigate the stability behaviour of nitrofurazone in solutions. The measurement of quanta, i.e. the energy, absorbed requires further consideration. Since the value of energy depends on the wavelength, i.e. monochromatic light or light falling within a narrow range of wavelengths, should be used. Much of the earlier photochemical research work is of little value because of failure to observe this condition.

The energy of the monochromatic radiation is determined most accurately by means of a thermopile. For many purposes, the accuracy of the thermopile is not required, and the energy of the absorbed light is determined by means of an actinometer. This technique uses a photochemical reaction to estimate the absorbed energy. Many possible actinometer systems have been suggested through the years. The uranyl oxalate actinometer (Leighton and Forbes, 1930) has been very widely used and is both reasonably easy to use and sensitive if a procedure other than titrimetric analysis is adopted. In the present investigation the uranyl oxalate actinometer with spectrophotometric procedure (Pitts et al., 1955) has been chosen since its wavelength range is that required for the study. Although the procedure of Porter and Volman (1962) may be much more sensitive than that of differential absorption spectrophotometry, the sensitivity and convenience of the latter seems to be adequate for this work.

In the present work the following areas have been investigated:

(1) A study of factors influencing the photolability of the drug, i.e. the influence of the wavelength of light, pH of the medium, nature of surfactant or polyethylene glycol, presence of ultraviolet light absorbers on the quantum yield.
(2) In order to carry out such photolability experiments it was necessary to design an instrument that produced monochromatic radiation and was capable of measuring the amount of light absorbed by a system.

## 2. Materials and methods

### 2.1. Materials

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

Citric acid, urea, ceric sulphate, oxalic acid, sulphuric acid were of analar grade while uranyl sulphate were of reagent grade (BDH, UK). Double distilled water was prepared from an all glass distilation unit (QVF, Stoke-on-Trent, UK).

### 2.2. Instrumentation

The apparatus described here, based on a commercial ultraviolet light source with optical filters and a chemical actinometer, was designed for this purpose. Important design considerations were as follows:

(1) The achievement of a reasonable intensity of light.
(2) Monochromatic radiation.
(3) An optical system which provides completely uniform illumination of both the sample and the blank.
(4) Temperature control.

#### 2.2.1. Light source

The key requirement for the source in this application is stability of light output. In designing the present apparatus, a 'UV 100' ultraviolet irradiating system (Catalogue No. 17097, Engelhard Hanovia Lamps, Bucks., UK) was used as the source. The equipment comprised a 100 Watt compact high pressure mercury arc lamp which provided an effective point source of ultraviolet light. Excess heat radiated from the source was removed from the system by circulating water through the jacket. To achieve monochromatic radiation from this light source, 25 mm diameter interference filters, obtained from Barr and Stround, Glasgow, were used (their characteristics are given in Table 1). In operation, the intensity of the lamp decreased linearly at the rate of 1% per 10 h running for which correction was made.

Table 1
Characteristics of interference filters

| Wavelength (nm) at peak transmission | Peak transmission (%) | Band width at half peak (nm) |
|---|---|---|
| 281.3 | 22.5 | 14.4 |
| 312.0 | 21.8 | 17.0 |
| 362.8 | 20.1 | 14.5 |
| 407.5 | 28.8 | 16.0 |
| 436.5 | 33.8 | 13.3 |

#### 2.2.2. Cell holder

It accommodated—in two compartments—two pairs of stoppered rectangular 1 and 2 cm standard silica spectrophotometric cells in a block of overall dimensions 2.9 cm × 4 cm × 3.4 cm. Good contact with the cell holder walls as well as between them was accomplished by contact of the non-optical cell faces.

The cell holder was placed in a hollow rectangular box with a recess in the upper surface to receive the holder. The dimensions were such that the light aperture in the cell holder was coaxial with the light beam and the front of the 1 cm cells was exactly 12 cm from the light source. A constant temperature of $25 \pm 0.5$°C was maintained by rapid circulation of water through the jacket from a thermostated water bath. This whole rectangular box, with the cell holder inside, was covered by a lid to exclude extraneous light.

### 2.3. Quantum yield determination of nitrofurazone systems

#### 2.3.1. Determination of energy absorbed by the drug

Drug solution (2.5 ml) ($2 \times 10^{-3}$ m $l^{-1}$ concentration in the case of surfactant or polyethylene glycol solution and $7 \times 10^{-4}$ m $l^{-1}$ for aqueous solutions) and the appropriate solvent were placed in the two 1 cm silica cells. Actinometer solution (5 ml) (prepared in dim light by mixing equal volumes of aqueous solutions of 0.1 M oxalic acid and 0.02 M uranyl sulphate) was placed into each of the 2 cm cells using the same pipette. These cells were placed into the cell holder and irradiated for a definite length of time using the appropriate wavelength interference filter.

After irradiation, 2.5 ml of actinometer solution was pipetted from the cell behind the drug solution into a 25 ml volumetric flask containing 10 ml of 0.0255 M ceric sulphate in 0.5 N sulphuric acid. After cleaning and drying, the same pipette was used to deliver 2.5 ml of the unexposed actinometer solution into another 25 ml volumet-

ric flask. This was treated similarly in order to produce a blank for analyzing this actinometer solution behind the drug cell.

Of the actinometer solution 0.5 ml from the cell behind the cell containing solvent was pipetted into a 25 ml volumetric flask containing 2 ml of 0.0255 M ceric sulphate in 0.5 N sulphuric acid and 2 ml of 2 N sulphuric acid. A blank was similarly prepared by taking 0.5 ml of unexposed actinometer solution for analyzing the solution behind the solvent cell.

These four volumetric flasks were heated in a water bath at 70°C for 10 min in darkness, cooled to room temperature, and then made up to the mark with distilled water. The absorbance were measured at 320 nm using 1 cm path length silica cells with the respective blank in the reference compartment. If the absorbance reading was greater than the spectrophotometric scales, both the blank and sample solution were further diluted with 0.2 N sulphuric acid to maintain the final acidity in both flasks between 0.1–0.3 N sulphuric acid. Duplicate samples were taken to check the error in pipetting. The average of the two readings for each sample was taken. The amount of oxalate decomposed was calculated from this absorbance reading by referring to a calibration curve prepared for the absorbance values for known amount of oxalate decomposed. The total amount of oxalate decomposed in the 5 ml of actinometer solution was then calculated by the use of corresponding dilution factor.

From the difference in the number of molecules of oxalate decomposed in the two actinometer cells, an estimate of the amount of energy absorbed by the drug was made by dividing this difference by the known quantum yield for the disappearance of oxalate at that wavelength. The quantum yield data for oxalate photodecomposition nearest to the wavelengths used in this study were obtained from published work (Leighton and Forbes, 1930).

### *2.3.2. Determination of the amount of drug decomposed*

Duplicate samples of 0.2 ml of irradiated drug solution were analyzed by the stability-indicating paper chromatographic method described earlier (Shahjahan and Enever, 1992). The average of two readings was taken and the concentration of drug was determined by reference to a known standard. From the difference between the control and irradiated samples, the amount of drug decomposed (in $\mu$g) in 0.2 ml volume could be obtained. The number of molecules of drug decomposed in 2.5 ml solution could be determined by multiplying the amount of drug decomposed (in $\mu$g) by a factor of $3.8 \times 10^{16}$.

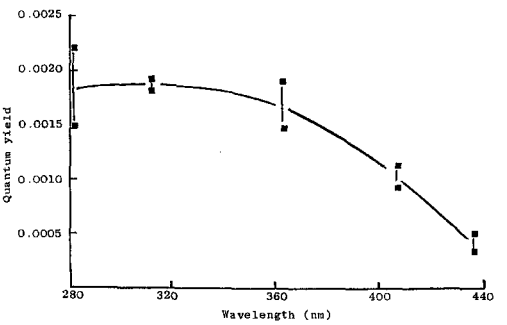


Fig. 1. Effect of wavelength on the quantum yield for disappearance of nitrofurazone in pH 6.0 buffer solution.

### *2.3.3. Calculation of quantum yield*

The quantum yield for the disappearance of nitrofurazone was obtained by dividing the number of molecules of drug decomposed in a given time by the number of quanta absorbed in that time. The experiment was repeated three times and the mean was taken as the quantum yield for the disappearance of nitrofurazone in a given system at that particular wavelength.

## 3. Results

### *3.1. Effect of wavelength of light on the quantum yield of nitrofurazone in pH 6.0 buffer*

The effect of wavelength of irradiation on the quantum yield of nitrofurazone disappearance in McIlvaine's pH 6.0 buffer solution is shown in Fig. 1. The quantum yield decreased with increasing wavelength and this effect becomes more prominent with increase in wavelength. This is to be expected since, the drug in aqueous solution

exhibits wavelength of maximum absorption of approximately centered at 260 and 375 nm and is likely to be more susceptible to decomposition in these regions. In addition, as has been known, light of shorter wavelength has greater energy than that of longer wavelength. Similar results were reported for photolytic decomposition of methyl cobalamin, coenzyme $B_{12}$ and sulphitocobalmin (Bond et al., 1972). Further studies on the quantum yield were carried out at 362.8 nm, the best approximation available to the 375 nm peak since the earth's atmosphere filters out radiation below 290 nm.

### 3.2. Effect of pH on the quantum yield for nitrofurazone at 362.8 nm

Fig. 2 shows the effect of pH in the range studied with McIlvaine's buffers on the quantum yield at 362.8 nm of nitrofurazone disappearance in aqueous solution. It can be seen from the results that the quantum yield decreased with increasing pH. The fall in quantum yield was most marked when changing the pH of the solution from pH 2.2 to pH 4.0. This result agrees with the previous observation of Spross (1953) that light sensitivity of nitrofurazone is more pronounced in acid solutions. Since the drug is mainly used for topical application and the pH of the skin is normally between pH 5 and pH 6 further studies were carried out in solutions buffered at pH 6.0.

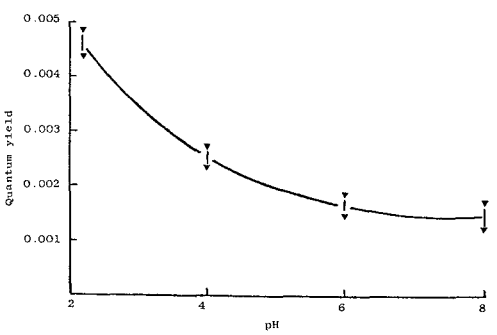


Fig. 2. Effect of pH on the quantum yield for disappearance of nitrofurazone when irradiated at 362.8 nm.

Table 2
Quantum yield data for the drug in different aqueous solution at 362.8 nm

| Aqueous solution buffered at pH 6 containing | Quantum yield |
|---|---|
| No surfactant or polyethylene glycol | $0.0017 \pm 0.0002$ |
| Brij 35 (0.1 M) | $0.0258 \pm 0.0028$ |
| Texofor A1P (0.1 M) | $0.0217 \pm 0.0021$ |
| Texofor A30 (0.1 M) | $0.0230 \pm 0.0048$ |
| Polyethylene glycol 1000 (0.25 M) | $0.0053 \pm 0.0007$ |

### 3.3. Effect of nature of surfactant and polyethylene glycol on the quantum yield for nitrofurazone at 362.8 nm

The quantum yield data for the disappearance of nitrofurazone in different surfactant solutions (0.1 M concentration) and polyethylene glycol (0.25 M concentration) solution buffered at pH 6.0 are given in Table 2.

It can be seen from this table that the quantum yield obtained for the three surfactants is not appreciably different and may be within the range of experimental error. However, the quantum yield in surfactants is markedly higher than that in either polyethylene glycol or aqueous solution. The lowest quantum yield is obtained with the aqueous solution.

### 3.4. Effect of ultraviolet light absorbers on the quantum yield for nitrofurazone at 362.8 nm

#### 3.4.1. Surfactant solutions

Fig. 3a shows the effect of Uvinul N-35 concentration on the quantum yield for the disappearance of the drug in Texofor A30 (0.1 M) solution buffered at pH 6.0. The quantum yield did not change significantly up to a concentration of $3.6 \times 10^{-4}$ m $l^{-1}$, but subsequently the quantum yield increased rapidly with concentration. These results indicate that incorporation of Uvinul N-35 in the surfactant solution increases the susceptibility of the drug to light. When the ratio of the quantum yields in the absence and presence of Uvinul N-35 is plotted against Uvinul N-35 concentration (Fig. 3b) a curve with an overall negative slope was obtained. This suggests that Uvinul

N-35 does not exert any quenching effect on the reaction but rather it has sensitizing effect on nitrofurazone decomposition.

In attempting to determine the effect of Uvinul D-50 on the quantum yield of nitrofurazone, it was found that more light was transmitted through the solution containing the drug and Uvinul D-50 than through the solvent system containing Uvinul D-50 alone, i.e. an apparent negative quantum yield was obtained. There are two possible explanations for this anomaly. One may be that the Uvinul D-50 acting as a sensitizer transferred energy to the drug molecules which subsequently transmitted energy at a different wavelength to the actinometer solution. Secondly, the light absorbing properties of Uvinul D-50 may be modified in the presence of the drug in surfactant solution. However, the second possibility is considered to be less likely by the fact that the differential spectra of Uvinul D-50 in Texofor A30 (0.1 M) solution in the presence of the drug before and after irradiation remains the same.

### *3.4.2. Polyethylene glycol solutions*

Uvinul N-35 was not soluble in polyethylene glycol solution and its effect on the quantum yield in this system could not be evaluated. Fig. 4a shows the effect of concentration of Uvinul D-50 on the quantum yield of nitrofurazone disappearance. The quantum yield increased slowly with the increase in concentration of the absorber up to

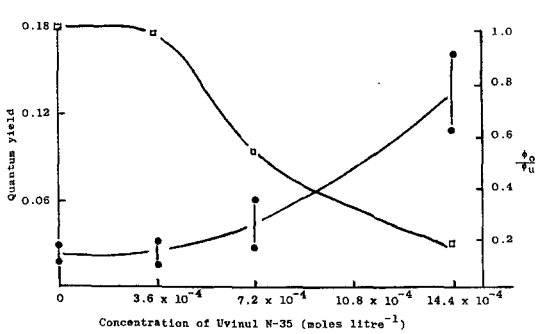


Fig. 3. Effect of concentration of Uvinul N-35 (a) on the quantum yield for the disappearance of nitrofurazone in Texofor A30 (0.1 M) solution buffered at pH 6.0 at 362.8 nm (left ordinate). (b) on $\frac{\phi_o}{\phi_u}$ in Texofor A30 (0.1 M) solution (right ordinate).

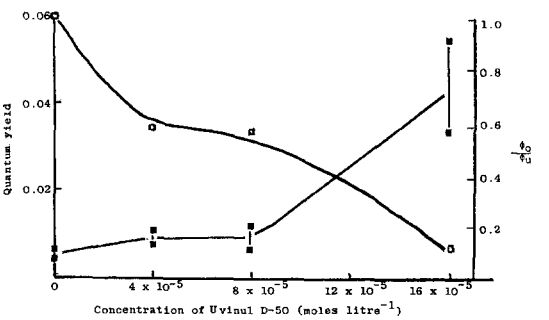


Fig. 4. Effect of concentration of Uvinul D-50 (a) on the quantum yield for the disappearance of nitrofurazone in polyethylene glycol 1000 (0.25M) solution buffered at pH 6.0 at 362.8 nm (left ordinate). (b) on $\frac{\phi_o}{\phi_u}$ in polyethylene glycol 1000 (0.25 M) solution (right ordinate).

$8 \times 10^{-5}$ m $l^{-1}$. Thereafter, there was a sharp rise in quantum yield with further increase in concentration. The ratio of the quantum yields with and without Uvinul D-50 has been plotted against concentration of Uvinul D-50 in Fig. 4b. Again a curve with an overall negative slope—similar to that of Uvinul N-35—was obtained, which signifies that Uvinul D-50 also acts as a photosensitizer.

## 4. Discussion

Solubility studies have shown (Shahjahan and Enever, 1991) that nitrofurazone associates with the surfactants and polyethylene glycols in the dark (ground state). Many drugs which interact with macromolecules in such a way, and are subject to photodecomposition, exhibit decreased light stability (Kostenbauder et al., 1971). The enhanced photodecomposition of drug in polyethylene glycol and surfactant solutions, as compared to simple aqueous solution, is thus likely to be due to this association, since the associated drug will be in media of markedly different polarity to that of water. 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, whereas the polyethylene glycols are hydrophilic in nature,

this would also offer an explanation for the difference in photolability of the drug in these two media. If the drug was distributed only in the polyoxyethylene region of the micelle there would not be such a great difference in its photolability relative to polyethylene glycol. The higher quantum yield in the surfactant solutions may be a result of increased approximation of excited state and ground state nitrofurazone species in the micellar phase. Kostenbauder et al. (1971) found that malachite green was not photoreduced in the presence of the mild reducing agent ascorbic acid in aqueous solution, but when it was bound to the nonionic surfactant, polysorbate 80, it underwent rapid photodecomposition. Table 3 shows a comparison of the molar uptake of the drug in surfactant (0.1 M) and in polyethylene glycol 1000 (0.25 M) solutions. It is evident that the molar uptake in surfactant solution is higher than in polyethylene glycol solution and this parallels the more pronounced photodecomposition in the surfactant solutions. In fact, there is a linear relationship between the molar uptake and quantum yield (Fig. 5).

The quantum yield data for the disappearance of drug in different formulations without the ultraviolet light absorbers (Table 2) showed values of the order of $15 \times 10^{-4}$–$28 \times 10^{-3}$ indicating that deactivation processes are more significant than chain reactions (Bond et al., 1972). The low quantum yield obtained for the decomposition of nitrofurazone may be due to:

(1) Loss of absorbed energy through collisions of drug molecules with solvent molecules, and/or

Table 3
Ratio of moles of nitrofurazone solubilized per mole of surfactant and polyethylene glycol 1000 at 25°C

| Additives | Ratio of moles of drug solubilized per mole of additive |
|---|---|
| Nil | 0 |
| Polyethylene glycol 1000 (0.25 M) | 0.005 |
| Brij 35 (0.1 M) | 0.022 |
| Texofor A1P (0.1 M) | 0.028 |
| Texofor A30 (0.1 M) | 0.029 |

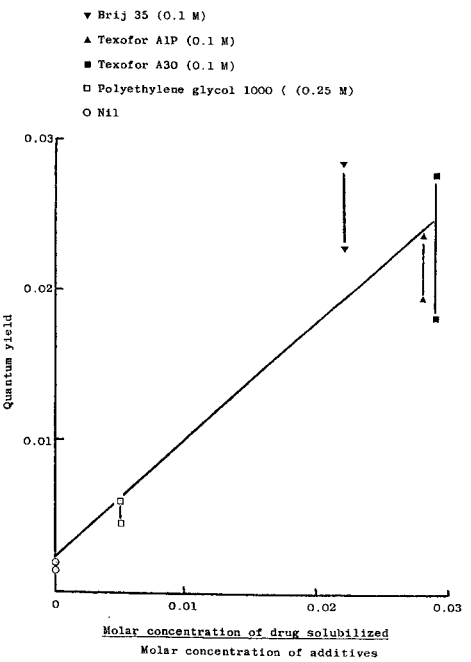


Fig. 5. Relationship between the quantum yield at 362.8 nm and ratio of moles of drug solubilized per mole of additives.

(2) the gain of an electron by the photoproduced radical, resulting in the reformation of nitrofurazone.

In the present investigation, comparison of the quantum yield data in Table 2, shows that a simple aqueous solution of the drug would be the most suitable formulation from a stability point of view. However, because of its low aqueous solubility, it is not possible to obtain a sufficiently high concentration of the drug in simple aqueous solution to produce a clinically effective product.

The increase of quantum yield in the presence of ultraviolet light absorbers suggests that the compounds were acting as photosensitizers. Benzophenone itself is the parent compound for Uvinul D-50, and a commonly used sensitizer (Evans, 1969). Sensitization of photochemical reactions by Uvinul N-35 has also been reported by Thomas (1966). Further studies on the photochemical reaction kinetics of the drug are being conducted and will be reported in a future communication.

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