

## Photodegradation of norfloxacin in aqueous and organic solvents: A kinetic study



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### ABSTRACT

The kinetics of photodegradation of norfloxacin (NF) on UV irradiation in aqueous solution (pH 2–12) and in organic solvents has been studied using a validated HPLC method. The apparent first-order rate constants ( $k_{\text{obs}}$ ) for the reaction in aqueous solution range from 0.28 (pH 2) to  $5.19 \times 10^{-3} \text{ min}^{-1}$  (pH 10) and in organic solvents from 0.34 (1-butanol) to  $0.80 \times 10^{-3} \text{ min}^{-1}$  (acetonitrile). The rate–pH profile for the photodegradation of NF shows an initial slow increase in the rate up to pH 6, followed by a rise in the rate to form a bell-shaped curve with  $\text{pH}_{\text{max}}$  around 10. It represents the involvement of cationic, zwitterionic and anionic species of NF undergoing photodegradation at variable rates in acid, neutral and alkaline regions. The increase in rate in the pH range 6–10 is due to the participation of zwitterionic and anionic species and may largely result from the hydrolytic degradation of piperazine side chain in the higher pH range. The decrease in rate above pH 10 is due to low reactivity of anionic species which are less susceptible to photodegradation. The role of excited triplet states of NF species to influence the rate of photodegradation has been highlighted. The photodegradation of NF in organic solvents is a linear function of the dielectric constant and an inverse function of the viscosity of the medium. Five photodegraded products of NF have been identified by LC–MS/MS analysis and schemes for the photodegradation pathways of NF in acid, neutral and alkaline solutions are presented.

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### 1. Introduction

Norfloxacin [1-ethyl-6-fluoro-1,4-dihydro-4-oxo-7-(1-piperazinyl)-3-carboxylic acid] (NF) (Fig. 1) was the first fluoroquinolone antibiotic to be used clinically [1]. It is effective in the treatment of bacterial infections of the respiratory and urinary tracts and exhibits activity against both Gram positive and negative organisms [2–4]. NF is available in the form of tablets and eye drops for clinical treatment.

NF is sensitive to light [5], and its photodegradation in the aqueous solution [3,6–14] and in the solid state [14,15] has been studied to identify the photodegraded products. Albin and Monti [16] have presented an excellent review on the photochemistry of fluoroquinolones and discussed the effect of chemical structure and medium on the degradation process. The photodegradation

pathways of NF and other piperazine side chain containing fluoroquinolones in aqueous and organic solvents have been suggested by Albin and Monti [16] and other workers [11,17–19]. The UV and visible light mediated  $\text{TiO}_2$  photocatalytic degradation of NF has also been studied [20,21]. The determination of NF in photodegraded solutions has been carried out by HPTLC [15], HPLC [6–11,13], UPLC [22], UV spectrometry [12] and spectrofluorimetry [3]. Some photodegraded products of NF have been identified by GC, HPLC, UPLC, NMR and MS/MS techniques [8–11,15]. An earlier study has shown the formation of ethylenediamine and formylpiperazine derivatives on the photodegradation of NF at neutral pH [6]. The photodegradation reaction of NF in aqueous solution follows first-order kinetics [7,13,23], and leads to the formation of a number of products by different pathways [8,16,19]. The present investigation involves a detailed study of the kinetics of photodegradation of NF over a wide range of pH that has not been carried out so far. The rate–pH relation would enable to establish the pharmaceutically useful pH range with optimum stability for the formulation of NF preparations. It is intended to observe the effect

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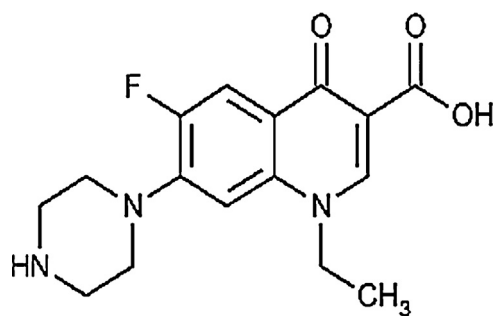


Fig. 1. Chemical structure of NF.

of variations in protolytic equilibria of NF species and hence their excited triplet states on the rates of photodegradation in acid, neutral and alkaline regions. Reaction pathways would be proposed in the light of previous studies [16–19], on the basis of the photodegraded products identified in different pH regions by LC–MS/MS analysis. A systematic study of the photodegradation of NF in organic solvents and the correlation of rate constants with solvent parameters, i.e., dielectric constant and viscosity would facilitate the understanding of the effect of solute–solvent interaction and its influence on the rates of degradation of the antibiotic.

## 2. Materials and methods

NF (99%) was purchased from Sigma–Aldrich (USA) and was used without further purification. All chemicals and solvents were of HPLC grade and obtained from Sigma–Aldrich (USA). Deionized water having 16.5 MΩ resistance from Milli-Q pore system (Bedford, USA) was used throughout the study. The solvents and solutions were filtered through a Millipore filtration unit and degassed before use. The buffer systems used in this study were: KCl–HCl (pH 2.0); citric acid–Na<sub>2</sub>HPO<sub>4</sub> (pH 2.5–8.0); Na<sub>2</sub>B<sub>4</sub>O<sub>7</sub>–HCl (pH 8.5–9.0); Na<sub>2</sub>B<sub>4</sub>O<sub>7</sub>–NaOH (pH 9.5–10.5); NaHPO<sub>4</sub>–NaOH (pH 11.0–12.0); the ionic strength was set as 0.02 M in each case.

The experimental work was carried out in a dark chamber under subdued light. All the solutions of NF were freshly prepared for the reactions and protected from light to avoid the effect of any chemical or photochemical change.

### 2.1. HPLC assay

The HPLC system (model LC-10 ATVP, Shimadzu, Japan) used in this study was equipped with a UV detector (model SPD-10 AVP) connected to a micro system. The analytical column used was Purospher RP-8 endcapped (5 μm). The HPLC analysis was carried out at room temperature (25 ± 1 °C) using isocratic condition. The mobile phase consisted of a mixture of water and acetonitrile (50:50, v/v) with 0.3% triethylamine at pH 3.3, adjusted with phosphoric acid. The volume of injection was 20 μl, and the flow rate was 1.0 ml min<sup>-1</sup>. All the solutions and the mobile phase were sonicated for 20–25 min before use. The NF was detected at the wavelength of 290 nm. The validation of the assay method was carried out under the conditions used in this study prior to its application to the photodegradation studies of NF [24].

### 2.2. Photolysis

A 5 × 10<sup>-5</sup> M aqueous solution of NF was prepared, and the pH was adjusted in the range of 2.0–12.0 using an appropriate buffer solution. The solution was placed in a 100 ml beaker (Pyrex) and

immersed in a water bath maintained at 25 ± 1 °C. The solution (100 ml) was irradiated using a Philips 30 W TUV tube (50% emission at 274 nm, major absorption maximum of NF), in a dark chamber. The tube was fixed horizontally at a distance of 25 cm from the center of the beaker. Samples were withdrawn at various intervals for HPLC assay. The same procedure was used for the photolysis of NF (5 × 10<sup>-5</sup> M) in various organic solvents. For the identification of photodegraded products in acid and alkaline solutions, 1 mg ml<sup>-1</sup> (3.1 × 10<sup>-3</sup> M) solutions of NF were irradiated under the same condition for 20–25 h and used for LC–MS/MS analysis.

### 2.3. Light intensity measurement

The measurement of the intensity of Philips 30 W TUV tube was carried out by potassium ferrioxalate actinometry [25], and a value of 5.52 ± 0.11 × 10<sup>18</sup> quanta s<sup>-1</sup> was obtained.

### 2.4. LC–ESI–QqTOF–MS/MS analysis

The standard NF was dissolved in 0.1 M hydrochloric acid solution and its photodegraded products of acidic and alkaline medium were diluted in a mixture of 1:1 acetonitrile and water,

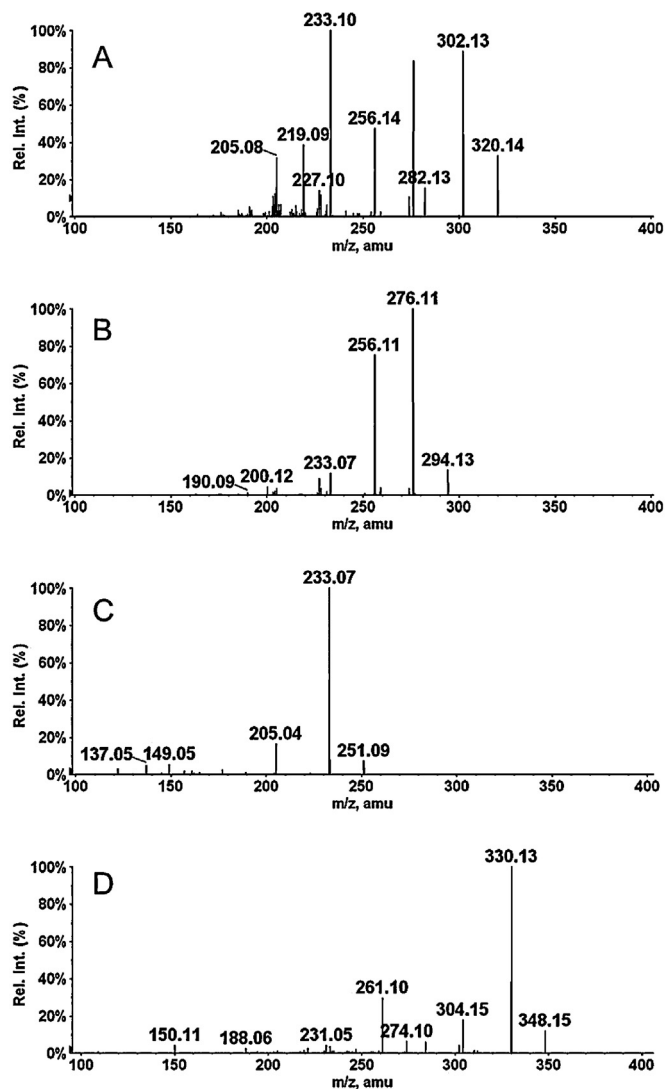


Fig. 2. Mass spectra of norfloxacin (A) and its photodegraded products, NFP-2 (B), NFP-4 (C) and NFP-5 (D), at collision energy of 25 eV.

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