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Original Research

The effect of Ultraviolet-B irradiation on the photodegradation of ciprofloxacin and norfloxacin as inhibitors of bacterial DNA replication and cell division in urea medium

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Abstract: Ciprofloxacin hydrochloride and Norfloxacin are second-generation fluoroquinolone antibiotic against bacterial DNA gyrase, which reduces DNA strain throughout replication. As DNA gyrase is essential through DNA replication, subsequent DNA synthesis and cell division are inhibited. Direct photolysis of fluoroquinolones was studied by using UV irradiation in the presence or absence of other substances that generate free radicals. This study aimed to assess the effect of Ultraviolet B (UVB) irradiation in removing ciprofloxacin and norfloxacin by using a simulating model of wastewater contained urea at pH 4. A known concentration of ciprofloxacin and norfloxacin were prepared in an appropriate aqueous solution in presence or absence 0.2M urea and adjusted at pH 4. The dissolved drugs were irradiated with UVB-lamp in a dark place for 60 minutes. The percent of removal and the rate of elimination (*k*) of each drug were calculated. The direct photolysis effect of UVB irradiation was observed with ciprofloxacin which amounted to 24.4% removal compared with12.4% removal of norfloxacin after 60 minutes of irradiation. The effect of UVB irradiation was enhanced by urea to reach 38.9% and 15% for ciprofloxacin and norfloxacin. The calculated *k* of ciprofloxacin has amounted to three folds of that of norfloxacin. Direct photolysis of ciprofloxacin and norfloxacin can be achieved simply by using a simulation model of 0.2 M urea and UVB irradiation at pH 4. UVB is highly effective in removing ciprofloxacin compared with norfloxacin by 2-3 folds.

Key words: Ultraviolet B irradiation; Photolysis; Ciprofloxacin; Norfloxacin; Urea.

Introduction

Drugs are likely to be disposed of in water sources, and their concentrations were estimated and classified according to the chemical properties (1). Drug concentration in water sources was based upon the number of prescriptions that administered to the patients (2). On the other hand, drugs prescribed to the animals also shared in the contamination of water sources. It is mentioned that the concentrations of antimicrobials in untreated wastewater were ranged between 3.9 ng/L and 27µg/L (3). The presence of antimicrobials in the aquatic environment indicated that these compounds are stable and resisted the photodegradation or their fate by biotransformation or sorption was limited. Ciprofloxacin among the fluoroquinolone is the most likely to be present in the wastewater effluent. Hospital wastewater effluent showed higher concentration (1 ng/L - 1µg/L) of ciprofloxacin and potentially impacts a high risk of contamination in both municipal and hospital effluent (4). In one study, the concentrations of fluoroquinolones including ofloxacin, levofloxacin, norfloxacin, and ciprofloxacin were detected in high concentrations in the hospital wastewater effluent to reach 12.11 µg/L for norfloxacin and 9.60 µg/L for ciprofloxacin (5). One of the several factors that play a role in the removal of these compounds from the aquatic environments is the pH of the media. The elimination rates of ciprofloxacin and norfloxacin increased significantly with the increase of pH while ofloxacin exhibited the highest reactivity with available free available chlorine under the pH of 7 (6). Ciprofloxacin is the only fluoroquinolone that significantly removed from the wastewater treatment plants after removing the nitrogen (7). Ciprofloxacin was oxidized in a solution with high urea concentration and successfully removed by electrochemical oxidation at an optimum of pH 3. Previous studies clarified that ciprofloxacin and ofloxacin (OFX) in aqueous solution were suspected to photodegradation by ultraviolet A radiation up to one hour (8). The rationale of this study is related to the removal of the quinolones (e.g. Nalidix acid) and fluoroquinolones (e.g. Ciprofloxacin and Norfloxacin) from the wastewater after treatment with chemical substances and ultraviolet radiation are varied. Therefore, this study aims to assess the effect of Ultraviolet B (UVB) irradiation in removing ciprofloxacin and norfloxacin by using a simulating model of wastewater contained urea at pH 4.

Materials and Methods

This study was done in the laboratories of the Department of Pharmacology, College of Pharmacy, Haweler Medical University, in Erbil-Iraq. This study was appro-

ved by the Institutional Scientific Committee. Ciprofloxacin (500mg tablet) and Norfloxacin (400 mg tablet) were purchased from local pharmacies. The dissolution tests of both tablets were carried on according to the instruction of the United States Pharmacopeia (USP). In brief, the powder 20 tablets of ciprofloxacin were dissolved in 900 mL 0.01N hydrochloric acid and the mixture was stirred at 50 rounds per minute for 30 minutes, and then the mixture was filtered through a 0.45-µm membrane filter. The peak spectra of ciprofloxacin were detected at a wavelength of 276 nm by using a UV-Visible spectrophotometer. Regarding the norfloxacin, the powder of 20 tablets was mixed with a 900 mL water containing 2.86 mL of glacial acetic acid and 1.0 mL of a 50% (w/w) solution of sodium hydroxide and the pH of the mixture adjusted to 4. The mixture was stirred at 50 rounds per minute for 30 minutes, and then the mixture was filtered through a 0.45-µm membrane filter. The peak spectra of ciprofloxacin were detected at a wavelength of 278 nm by using a UV-Visible spectrophotometer. Standard curves of absorbance-concentration at a wavelength of 276 nm (for ciprofloxacin) and 278 nm (for norfloxacin) were constructed and the equation of regression is used to calculate the drug concentration (Fig.1). A solution of urea was prepared by dissolving a known volume of urea in distilled water to get a final concentration of 0.2 M that approximate the normal levels in urine and the pH was adjusted to 4.

A primary stock solution of 250 µg/mL was prepared by diluting the dissolved ciprofloxacin or norfloxacin solution with 0.9 % isotonic sodium chloride, and the pH values of all the solutions without other additives were adjusted to 4.0 with lactic acid. A series of ciprofloxacin and norfloxacin solutions were prepared in the presence of urea (0.2M, pH 4). Each of the above solutions was exposed to the ultraviolet light-B (UVB) radiation in a dark room for 30 minutes. The source of the UVB light is the EL series ultraviolet lamps. The lamp utilizes 8 watts, wavelength 302nm, dual bi-pins tube, plugged into the service outlet located on the top of the cabinet of 20cm x 8cm x 15 cm, of six samples for each treatment. The samples were exposed to UVB irradiation for several tie intervals (15, 30, 45, and 60 minutes). Each experiment was repeated 6 times.

Statistical analysis

The data are expressed as number, percentage and mean ±SD. The rate of elimination (-*k*) was calculated using the following equation:

-*k* = (In concentration at 45 min. *minus* in concentration at 60 min) / time at 60 min. *minus* time at 45 min.

The results were analyzed using unpaired and paired Student's t-test, simple correlation test and regression analysis taking the p-value ≤ 0.05 as the lowest limit of significance.

Results

Tables 1 and 2 showed the mean ± SD of the concentrations of ciprofloxacin and norfloxacin after treatment with 0.2 M urea or UVB irradiation or both. Each drug in aqueous media was stable at pH 4 and tended to lysis after 60 minutes by 4.4% and 5% for ciprofloxacin and norfloxacin which did not significantly differ. The presence of 0.2M urea allowed the drug to lose its stability to reach the concentrations of 225.2 ± 4.7 µg/ml for ciprofloxacin and 220.2 ± 4.2 µg/ml for norfloxacin. The photolysis effect of UVB irradiation is well observed and reached to 189.0±9.3 µg/ml for ciprofloxacin 219.2±4.4 µg/ml for norfloxacin (Tables 1 and 2). The

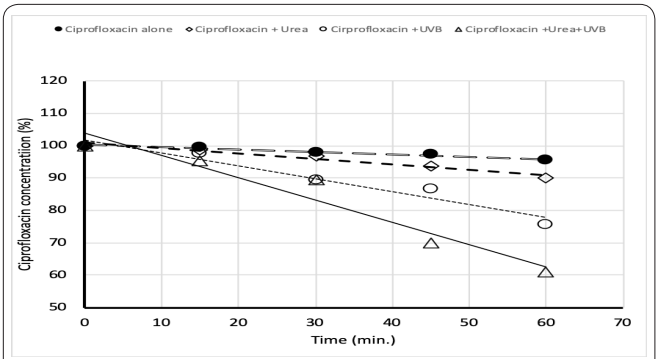

Figure 1. The remaining percentage of ciprofloxacin concentration: y= 100.36-0.0747x (ciprofloxacin alone); y=100.8-0.1653x (ciprofloxacin in 0.2M urea); y=101.8-0.3973x (Ciprofloxacin irradiated with UVB); and y=103.7-0.6867x (ciprofloxacin in 0.2M and irradiated with UVB). The y represents the percentage of ciprofloxacin concentration and x represents the time (min.).

Table 1. Effect of UVB irradiation on the degradation of ciprofloxacin (250 µg/ml) in a simulation model of the aquatic environment using 0.2M urea.

Treatment	Time (min)				
	0	15	30	45	60
Drug alone	250±0.0	249.3±0.7 (0.28) P=0.058	245.1±2.4† (0.98) P< 0.001	243.2±2.2 (0.90) P< 0.001	238.9±2.3 (0.96) P< 0.001
Drug +0.2M Urea	250±0.0	246.4±1.1 (0.45) P< 0.001	242.3±1.7 (0.7) P< 0.001	234.0±4.0 (1.71) P< 0.001	225.2±4.7 (2.08) P< 0.001
Drug irradiated with UVB	250±0.0	243.9 ±3.8 (1.56) P< 0.001	223.6±3.6 (1.61) P< 0.001	216.9±7.9 (3.64) P< 0.001	189.0±9.3 (4.92) P< 0.001
Drug +0.2M Urea+ irradiated with UVB	250±0.0	238.0±2.7 (1.13) P< 0.001	224.1±5.9 (2.63) P< 0.001	175.2±11.9 (6.79) P< 0.001	152.7±5.6 (3.66) P< 0.001

The results expressed as mean ± SD (CV) of (*n*=6) observations. P represents the probability of the significance difference at the time = 0 by using paired student's t test.

Table 2. Effect of UVB irradiation on the degradation of norfloxacin (250µg/ml) in a simulation model of the aquatic environment using 0.2M urea.

Treatment	Time (min.)				
	0	15	30	45	60
Drug alone	250±0.0	248.6±1.1 (0.44) P< 0.001	245.0±1.0 (0.41) P< 0.001	241.6±1.3 (0.54) P< 0.001	237.5±1.4 (0.59) P< 0.001
Drug +0.2M Urea	250±0.0	246.7±1.5 (0.61) P< 0.001	241.4±1.2 (0.5) P< 0.001	236.0±0.9 (0.38) P< 0.001	230.6±2.1 (0.91) P< 0.001
Drug irradiated with UVB	250±0.0	243.5 ±1.7 (0.7) P< 0.001	237.0±2.8 (1.2) P< 0.001	229.6±1.9 (0.83) P< 0.001	219.2±4.4 (2.0) P< 0.001
Drug +0.2M Urea+ irradiated with UVB	250±0.0	240.0±2.8 (1.16) P< 0.001	230.6±7.3 (3.16) P< 0.001	222.8±3.9 (1.75) P< 0.001	212.4±5.8 (2.73) P< 0.001

The results expressed as mean ± SD (CV) of (*n*=6) observations. P represents the probability of the significant difference at the time = 0 by using paired student's t-test.

photolysis effect of UVB irradiation was significantly (p< 0.001) higher with ciprofloxacin than norfloxacin. The presence of urea 0.2M synergistically enhanced the removal of ciprofloxacin and norfloxacin by UVB irradiation and the effect against norfloxacin was significantly (p < 0.001) less than ciprofloxacin (Tables 1 and 2).

Figures 1 and 2 show the regression analysis of drug removal by urea or UVB irradiation or both. The slopes of ciprofloxacin removal were -0.0746, -0.1653, -0.3979 and -0.6867 percent per min. (Figure 1) while the slopes of norfloxacin were less than corresponding values of ciprofloxacin which accounted -0.853, -0.1313, -0.2013 and -0.2460 percent per min. (Figure 2). The removal of each drug was observed after 30 minutes of incubation or irradiation with UVB. Therefore, the elimination rate was calculated at an interval of 45 and 60 minutes. The elimination (-*k*) rates of ciprofloxacin in aqueous solution, in addition to 0.2M urea, irradiated with UVB and irradiated solution of ciprofloxacin with 0.2M urea were -0.0012, -0.0026, -0.0092, and -0.0092 µg/ml/min. while the corresponding values of norfloxacin were -0.0011, -0.0015, -0.0031and 0.0032 µg/ml/min. Therefore, the elimination rate of ciprofloxacin is approximately equal to three folds of the corresponding value of norfloxacin in the aquatic environment.

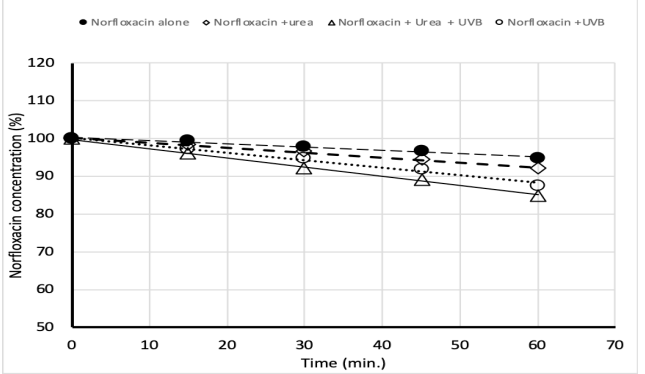

Figure 1. The remaining percentage of norfloxacin concentration concerning the regression equation of degradation. The equations of regression are: y= 100.36-0.0853x (ciprofloxacin alone); y=100.36-0.1313x (ciprofloxacin in 0.2M urea); y=101.38-0.2013x(Ciprofloxacin irradiated with UVB); and y=99.84-0.2460x (ciprofloxacin in 0.2M and irradiated with UVB represents the percentage of ciprofloxacin concentration and x represents the time (min.).

Discussion

Due to weak biodegradability, alternative processes including adsorption, biodegradation, chemical oxidation, and photodegradation can efficiently eliminate fluoroquinolone antibiotics from wastewater (9-12). The photodegradation is an approved process to degrade this family of antibiotics, due to their sensitiveness to light (13).

Albini and Monti suggested possible Hydrogen abstraction either through an excited state or by •OH arising through direct water oxidation and/or residual O_2 activation as trigger points in the fluoroquinolone photodegradation (14); nonetheless, no consistent information is found regarding its mechanism (15). Chen and Chu (16), however, tried to determine the active species formed through simulated solar light mediated by Bismuth Tungstate (SSL/Bi2WO6) in a medium with norfloxacin; they indicated that •OH is the main active species in the SSL/Bi2WO6 process (contribution rate = 79.3%); because when •OH radicals were fully exhausted by a quenching material like methanol, the norfloxacin removal efficiency was decreased from 83.7% to 32.4% in 20 min; so they related this retardation to the •OH oxidation of methanol. Other active species determined by Chen and Chu are e^- (the direct product of photolysis with the contribution rate of 15.0%) and oxidative photo-hole (contribution rate = 5.7%) (16).

pH changing affects the degradation process by generating •OH as an oxidizer and either hydrated electrons (e_{aq}^-) or hydrogen atoms (•H) as reducers (17). An et al. calculated the frontier electron densities (FEDs) of Ciprofloxacin to predict the reaction positions for electron extraction and •OH attack (17). According to Frontier Orbital Theory, an electron can be extracted at a site with higher values of $2FED^2_{HOMO}$, whereas •OH addition is generally at a site with a higher $FED^2_{HOMO} + 2FED^2_{LUMO}$ value (18) (HOMO = the highest occupied molecu-

lar orbital; LUMO = the lowest unoccupied molecular orbital). Accordingly, An et al. (17) proposed the direct photo-hole (h+) oxidation and hydroxylation as two important pathways for Ciprofloxacin degradation; for the former, according to An et al. (17), C4 on quinolone ring or N12 on piperazynilic ring are the first sites of the electron extraction; N12 is probably the main initial position for direct photo-hole oxidation. The loss of CO2 and H2O from the quinolone's carboxylate group due to the complete and partial eliminations, respectively, of the piperazynilic ring from the Ciprofloxacin after hole attack on N12 might be included (18-19). For the latter, •OH attacks most probably to C10 and C5 on the quinolone ring. An et al. depicted possible mechanisms for the oxidation and hydroxylation of Ciprofloxacin (17).

In another study, An et al. (20) introduced elimination of piperazynilic ring (as the first; so that the partial and complete piperazynilic ring elimination was observed for all three drugs), •OH attack to quinolone ring (as the second), and ipso attack at the Fluorine atoms on the aromatic ring by •OH (as the third) as three possible oxidative mechanisms of norfloxacin, levofloxacin, and lomefloxacin. They indicated that the reaction occurs predominantly at the quinolone ring. As well, the solvated electron reacts predominantly with the quinolone rings.

Regarding pH-dependency through photodegradation, Torniainen et al. (19) showed that the photodegradation enhances from 15% loss of the ciprofloxacin at pH 3.0 and 4.0 towards the maximum at pH 8.6 with remaining 15% of the drug. At pH 10.6 the rate resembles the level at pH 6.0 (19). Ciprofloxacin seems to be most sensitive to photodegradation in zwitterionic form at slightly basic status, but its maximum stability is at pH 3.0 to 4.0, where the COOH group is not ionized and the basic nitrogen completely protonated (19). An et al (17) gained nearly the same results, so that the rate constants of ciprofloxacin increased from 0.06 min^{-1} at pH 3.0 to 0.38 min^{-1} at pH 9.0, and then decreased to 0.07 min^{-1} at pH 11.0. On the other hand, the half-time decreases from 10.9 min at pH 3.0 to 1.9 min at pH 9.0, and then increases to 9.4 min at pH 11.0. In our results, we expected such pH-dependent photodegradation would be repeated, as it has been demonstrated that urea increases the measured pH of aqueous solutions (21).

The results of this study show that UVB irradiation in removing the fluoroquinolones from a simulating model of an aquatic environment. The photolysis effect of UVB irradiation on the ciprofloxacin is approximately 3 folds of that observed with norfloxacin. In this study, UVB-irradiation is used to remove the contaminants of ciprofloxacin as this compound carried a high risk of contamination of the aquatic environment in both municipal and hospital effluent (4). The results of this study are in agreement with a recent study that showed effective removal of ciprofloxacin with UV irradiation (22). Snowberger et al (23) found that irradiation of fluoroquinolones, including ciprofloxacin and norfloxacin with UV light of 253.7 nm wavelength resulted in the removal of these compounds with the generation of their metabolites that having antibacterial effects. In this study, ciprofloxacin was subjected to UVB and at pH solution of 4 by which the ciprofloxacin is stable while in the Snowberger et al study, the fluoroquinolones were subjected to UVC and at pH 2-12 by which these compounds in these media were unstable. In this, the effect of UVB irradiation upon norfloxacin is less than that of ciprofloxacin. Santos et al found that the direct photolysis effect of UV was not effective in the degradation of the norfloxacin which amounted to 85%. The mechanism by which the photolysis effect of UV irradiation is attributed to the generation of the hydroxyl radical and singlet oxygen (24). It is important to mention here that the pH of aqueous media was 4 and the direct photolysis effect of UV irradiation is beyond the quinolone ring, that is, cleavage of the cyclopropane ring and fluorine solvolysis (25). Another study suggested that the removal of fluoroquinolone by direct photolysis is pH depended and the optimum effect can be obtained at a strongly acidic pH and sunlight exposure (26). Therefore, the results of this study highlight the importance of using UVB irradiation and a fixed pH of 4 in order to remove the contaminant of the water surface or hospital effluent with antibiotics. It's not just the use of antibiotics that disrupts the DNA replication system in bacteria; The same can be done with genetic methods such as RNA intervention and genome editing (27) systems.

In conclusion, direct photolysis of ciprofloxacin and norfloxacin can be achieved simply by using a simulation model of 0.2 M urea and UVB irradiation at pH 4. UVB is highly effective in removing ciprofloxacin compared with norfloxacin by 2-3 folds.

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