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Photo-isomerization of fluvoxamine in aqueous solutions

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Abstract

The hydrolysis and photolysis of fluvoxamine, a selective serotonin reuptake inhibitor, in aqueous buffer solutions (pH 5, 7, and 9), in synthetic humic water, and lake waters were investigated in the dark and in a growth chamber outfitted with fluorescent lamps simulating the UV output of sunlight at 25 °C. No significant hydrolytic degradation/isomerization was observed for 30 days in all aqueous solutions. However, fluvoxamine was moderately isomerized to its (*Z*)-isomer by simulated sunlight. The photo-isomerization occurred in two stages. The photo-isomerization occurred rapidly within the first 7 days and slowly thereafter with a rate constant of 0.12–0.19 day^{-1} for the first stage and 0.04–0.05 day^{-1} for the second stage. Photosensitized rate constants in synthetic humic water and in lake waters were approximately 6–7 times faster than that in pH 9 buffer with the rate constants of 1.15–1.34 day^{-1} in the first stage. The (*Z*)-isomer of fluvoxamine was the only product detected in all aqueous solutions and was identified using LC–ESI-MS.
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Keywords: Hydrolysis; Photolysis; Fluvoxamine; Photo-isomerization; Selective serotonin reuptake inhibitor

1. Introduction

Fluvoxamine maleate, 5-methoxy-4′-(trifluoromethyl)-valerophenone (*E*)-*O*-(2-aminomethyl)-oxime maleate, is one of the recently developed selective serotonin reuptake inhibitors (SSRIs) for the treatment of certain affective disorders. It is the only achiral SSRI currently on the market, selectively inhibiting the neuronal uptake of serotonin. Ruijten et al. [1] has reported that fluvoxamine is completely metabolized in rats, hamsters, and mice, and to about 90% in dogs. In their study, the major metabolite in dogs, rats, and hamsters was the carboxylic acid formed by oxidative elimination of the methoxy group. Fluvoxamine exhibits non-linear elimination kinetics in the therapeutic dose range [2]. Many researchers have reported the mean elimination half-lives of fluvoxamine in man to be 15–20 h [3,4] and 10–14 h [5,6]. Recent research has recently reported the photo-isomerization of fluvoxamine in only pure water to give a geometric isomer of fluvoxamine and the isomer was identified by nuclear magnetic resonance (NMR) and mass spectrometry (MS) [7].

Recently, two papers have reported the occurrence of some SSRIs in US streams [8,9], indicating SSRIs are widely used and are potentially present in wastewater treatment effluent released into water bodies and drinking water sources. The persistence of them or their degradation products may cause adverse impacts on aquatic organisms.

Foda et al. [10] have cited a number of LC analysis methods for the determination of fluvoxamine and some methods are also reported such as high-performance liquid chromatography (LC) [1,11–13], gas chromatography [14–16], and capillary electrochromatography [17].

In this investigation, hydrolysis and photolysis experiments were initiated not only buffer solutions but also in natural waters to determine the potential for fluvoxamine to be degraded by photolysis and hydrolysis, to identify degradation products, and to estimate the importance of hydrolysis and photolysis to the fate of fluvoxamine residues that may enter aquatic environments from wastewater treatment plants.

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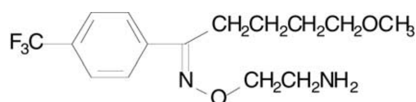

Fig. 1. Molecular structure of fluvoxamine.

2. Experimental

2.1. Chemicals and solvents

Fluvoxamine maleate was purchased from Sigma–Aldrich (St. Louis, MO, USA) or extracted with chloroform and purified by recrystallization with diethyl-ether from LUVOX® (Solvay Pharmaceuticals Inc., Baudette, MN, USA). Purified fluvoxamine was injected onto an LC and the chromatographic response was monitored at 210 nm to determine purity. Its purity was more than 99%. Its identity was confirmed by liquid chromatography–electrospray ionization-mass spectrometry (LC–ESI-MS) and was compared to a purchased authentic standard. The molecular structure of the compound is given in Fig. 1. Standard buffer solutions used to calibrate the pH meter electrode and all salts used to prepare buffer solutions were reagent grade or better and obtained from Fisher Scientific (Pittsburgh, PA, USA). All solvents were LC grade and were also obtained from Fisher Scientific. Humic acid (sodium salt) was obtained from Aldrich (Milwaukee, WI, USA) and de-ionized water was used to prepare the buffer solutions.

2.2. Preparation of fluvoxamine maleate standard solution, buffer solutions, and synthetic humic water

A stock solution (1000 mg l^{-1}) containing fluvoxamine maleate was prepared in methanol. Buffers consisted of sodium acetate buffer (pH 5) of CH_3COONa (0.01 M) and CH_3COOH (0.01 M), sodium phosphate buffer (pH 7) of Na_2HPO_4 (0.01 M) NaH_2PO_4 (0.01 M), and sodium borate buffer (pH 9) of H_3BO_3 (0.01 M) and NaOH (0.01 M). Synthetic humic water (SHW) was made according to US Environmental Protection Agency (US EPA) guidelines [18] and a previously published paper [19]. Also two lake waters were collected from Mississippi State University (Mississippi State, MS, USA) and Chocktaw Lake (Ackerman, MS, USA), filtered using a 0.2 μm filter and then stored in a refrigerator at 4 °C. The pH values of all solutions were measured using a Beckman phi 390 pH meter (Fullerton, CA, USA). The pH and absorbance values at 370 nm were 7.60 and 7.25, and 3.50×10^{-2} and 2.00×10^{-2} a.u., respectively.

2.3. Photolysis and hydrolysis experiments

Photolysis and hydrolysis experiments were conducted at a concentration of 5 mg l^{-1}. For photolysis, a 0.5 ml aliquot of the stock solution was added to 100 ml of each solution, thus the final test solutions contained 0.5% methanol. Samples were prepared in 2 ml, capped clear borosilicate glass vials and irradiated in a temperature controlled growth chamber outfitted with fluorescent lamps (Light Sources FL40T12-/BL, Milford, MA, USA) simulating the ultraviolet (UV) output of sunlight at 25 °C. These lamps did not emit wavelengths below 290 nm. This system has been used in previous experiments to investigate the photodegradation of chemicals in aqueous solutions [19–22] and the spectral output is reported in other published works [14]. The light intensity was measured before starting an experiment and twice a week over the experimental period using an EPP2000 Miniature Fiber Optic Spectrometer and SpectraWiz (version 2.1) software (StellarNet, Tampa, FL, USA). Control samples (hydrolysis samples), having the same initial concentration as photolysis samples, were kept in the dark at the same temperature. Samples were withdrawn to analyze the amounts remaining in solutions at 0, 1, 3, 5, 7, 10, 22, and 30 days for buffer solutions; 0, 0.125, 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, and 8 days for synthetic humic water; 0, 0.25, 0.5, 1, 1.5, 2, 4, 8, and 16 days for two lake waters of treatment. Experiments were performed in duplicate. The rate constants were calculated by linear regression analysis of a plot of the natural logarithm (ln C/C_0) of residual fluvoxamine concentration versus time, where C_0 is the initial concentration and C the concentration at a certain time. The quantum yield was calculated according to the following equation

$$\Phi = \frac{k_{300-400}}{\sum I_\lambda \varepsilon_\lambda}$$

where Φ is the quantum yield, k the degradation rate constant, I_λ the irradiance, and ε_λ the molar absorptivity. Because it was polychromatic radiation, $\sum I_\lambda \varepsilon_\lambda$ was calculated as sum of $I_\lambda \times \varepsilon_\lambda$ at each wavelength from 300 to 400 nm.

2.4. UV–vis spectrophotometer and LC analysis

The UV–vis absorption spectrum of fluvoxamine was recorded with a Model 8453 UV–vis spectrophotometer (Hewlett-Packard GmbH, Waldbronn, Germany). The test solutions were the unirradiated mixtures at pH 5, 7, and 9, which were 1×10^{-5} M fluvoxamine maleate. The amount of fluvoxamine remaining in solution was measured by direct injection of the water sample onto a Waters 2695 LC with UV detection using a Waters (Model #996, Milford, MA, USA) photodiode-array detector. Data were processed using MassLynx (version 3.4) software. The degradation products were separated from the parent compound using a Waters Nova-Pak® C18 (150 mm × 3.9 mm i.d.) analytical column. The mobile phase used was composed of acetonitrile-aqueous triethylamine (10 mM) (42:58, v/v), with the pH adjusted to 4.8 by addition of 85% phosphoric acid. The flow rate was 1.0 ml min^{-1}. For each solution, the amount of fluvoxamine remaining was calculated as a percentage of concentration prior to incubation (zero time). The amount of degradation products generated was calculated as a percentage of peak

area for the parent compound as standards for degradation products were not available.

2.5. LC–ESI-MS analyses

LC–ESI-MS in positive mode was performed on a Micromass quattro micro mass spectrometer (Micromass, Manchester, UK), operating at a capillary voltage of 3 kV, cone voltage of 40 kV, source temperature of 80 °C, cone temperature of 240 °C, cone gas flow of 60 l h^{-1}, and desolvation gas flow of 609 l h^{-1}. The entire column eluents of samples exposed to light for 8 days in pH 9 buffer were directly introduced into the mass spectrometer through the ESI interface. The MS scan range was *m/z* 120–400. Degradation products were separated on a Phenomenex Luna 5 μm phenyl-hexyl (25 mm × 2 mm i.d., Torrance, CA, USA) column. Elution was carried out with acetonitrile (A)–ammonium acetate (10 mM) (B). The solvent gradient began at A:B (10:90, v/v) for 2 min and proceeded to A:B (90:10, v/v) over 30 min. The flow rate was 0.2 ml min^{-1}.

3. Results and discussion

3.1. UV spectrum of fluvoxamine

Fluvoxamine showed a maximum absorbance (λ_{max}) at 245 nm in all aqueous solutions (Fig. 2). Spectral data indicated that fluvoxamine absorbed light at wavelengths over 290 nm and would thus be capable of absorbing the UV energy of sunlight. This fact suggests that natural sunlight could be responsible for the direct photo-degradation/photo-isomerization of fluvoxamine in aquatic environments.

3.2. Kinetics of isomerization

In hydrolysis experiments, no degradation/isomerization was observed over 30 days, suggesting that fluvoxamine is quite stable to hydrolysis at pH values normally found in aquatic habitats. Similarly, Olszanowski and Krzyzanowska

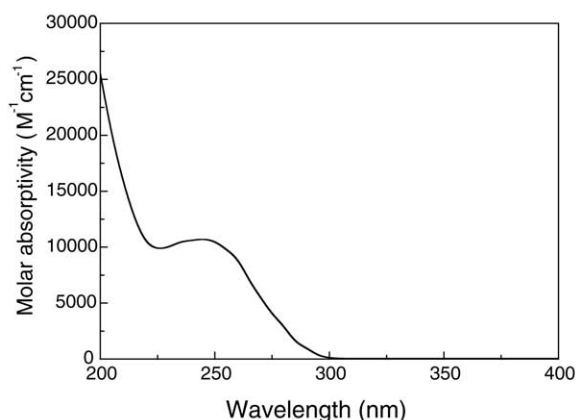

Fig. 2. UV absorption spectrum of fluvoxamine in pH 7 buffered solution.

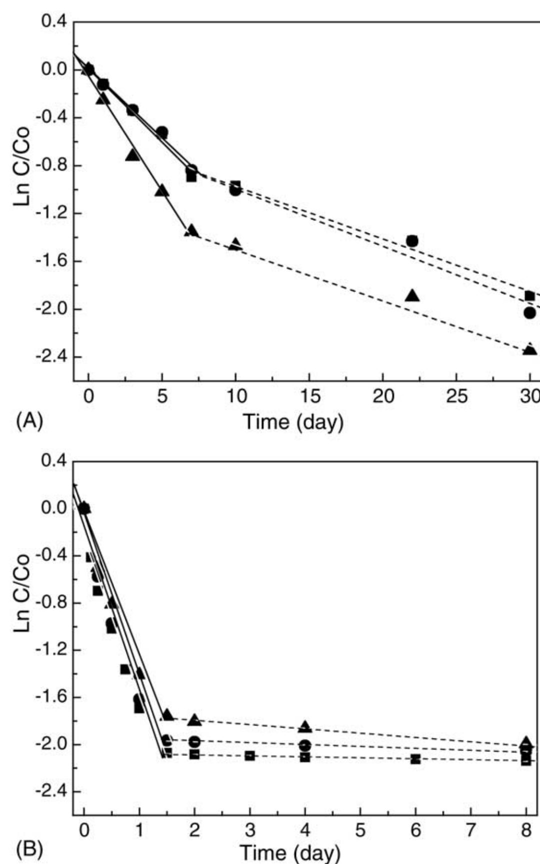

Fig. 3. Photo-isomerization of fluvoxamine by two stages of pseudo-first order kinetic in pH buffer buffers (panel A: (■) pH 5; (●) pH 7; (▲) pH 9) and in SHW and two lake waters (panel B: (■) SHW; (●) lake water I; (▲) lake water II). The solid lines indicate the degradation in the first stage and dashed lines indicate the degradation in the second stage.

[23] have reported that 2-hydroxy-5-methylbenzophenone (*E*)- and (*Z*)-oximes (active substances of commercial copper extractants) which have similar structures to fluvoxamine, kept in the dark did not degrade over a 60 day period, indicating that oxime compounds are generally stable in the dark conditions. However, fluvoxamine was moderately isomerized to the (*Z*)-isomer by irradiation in all pH buffers tested. Interestingly, the isomerization pattern was divided into two stages, occurring rapidly within the first 7 days and slowly thereafter as shown in Fig. 3A. In the first stage (from 0 to 7 days), the rate constants were 3.0, 2.4, and 4.8 times higher than those in the second stage (from 7 to 30 days) in pH 5, 7, and 9 buffer, respectively. The rate constants and quantum yields of fluvoxamine photo-isomerization are shown in Table 1. The rate constants were calculated by linear regression analysis. The r^2 values ranged from 0.9865 to 0.9906 in the first stage and from 0.9717 to 0.9891 in the second stage. In Table 1, the results indicated that the highest rate was at pH 9 in the first stage, but, in the second stage, much smaller differences were observed between buffers. The half-lives ranged from 3.6 to 6.0 days and from 14 to 17 days in the first and in the second stage, respectively. All rate constants followed pseudo-first order kinetics.

Table 1
Kinetic parameters of fluvoxamine photodegradation in different aqueous media

Media	First stage		Second stage	
	Degradation rate (day^{-1})	Quantum yield (Φ, $\times 10^{-3}$)	Degradation rate (day^{-1})	Quantum yield (Φ, $\times 10^{-3}$)
pH 5 buffer	0.12	5.51	0.04	1.91
pH 7 buffer	0.12	5.16	0.05	2.19
pH 9 buffer	0.19	8.55	0.04	1.87
SHW	1.34	–	0.01	–
Lake water I	1.28	–	0.02	–
Lake water II	1.15	–	0.03	–

Like buffer solutions, two stage isomerization patterns were also observed in SHW and the two lake waters (Fig. 3B). In the first stage (from 1 to 1.5 days), the rate constants were 134, 64, and 38 times higher than those in the second stage (from 1.5 to 8 days) in SHW, lake waters I, and II, respectively. These rate constants are also shown in Table 1 and the half-lives were 0.5–0.6 days and 26–70 days in the first and in the second stage, respectively. There were two different isomerization patterns observed between buffer solutions and solutions containing humic material (SHW) or natural water materials (two lake waters). One pattern is the rate constants between two types of solutions in the first stage of each and the second is the rate constants between the first and the second stage in two types of solutions. The first patterns can be explained by photosensitized isomerization. Humic materials or natural water materials played a role in isomerization of fluvoxamine under photolysis, with approximately 6–7 times enhancement compared to pH 9 buffer. The second patterns may be explained by changes in the pH of solutions and/or by photoproducts formed during the experiment. During the experimental period, changes in pH in aqueous solutions were recorded at regular intervals in three buffers, SHW and lake water I as seen in Fig. 4. No significant changes were observed in buffers and SHW, indicating that much lower degradation rates in the second stages were not related to pH changes. However, lake water I showed a decrease in 0.74 unit of pH

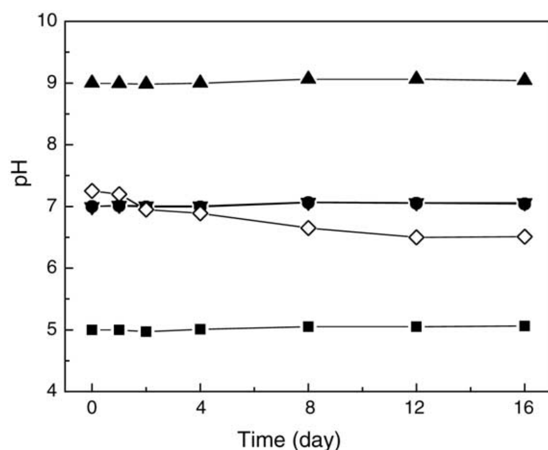

Fig. 4. Change in pH of aqueous solutions during the photo-isomerization: (■) pH 5 buffer; (●) pH 7 buffer; (▲) pH 9 buffer; (▼) SHW; (◇) lake water I.

at 16-day after treatment. It is likely that the pH of the lake water was changed not by photoproducts formed, but presumably by degradation products of organic materials present in water during the irradiation. Two stages of pseudo-first-order decay of DDT in an UV/surfactant system were also reported by Chu [24].

Miolo et al. [7] have previously reported the photoisomerization of fluvoxamine in only water, showing the same photoproduct of the [*Z*]-isomer of fluvoxamine. The half-life of fluvoxamine by photolysis in this paper was much shorter than ours although the concentration (ca. 4340 $mg\,l^{-1}$) in aqueous solution is much higher than our solution (5 $mg\,l^{-1}$). The differences in half-lives are likely due to different light sources. That is, they have used a UVB light with a wavelength range of 290–320 nm, emitting mainly at 312 nm. However, a wavelength range of 290–400 nm, emitting mainly at 340 nm, was used in our experiments.

3.3. Characteristics of the photoisomer

The mass spectrum of the parent showed an exact $[M+H]^+$ of *m/z* 319. This spectrum exhibits ion peaks at *m/z* 200 $[M-CH_2CH_2CH_2OCH_3-CH_2CH_2NH_2-H]^+$, *m/z* 226 $[M-OCH_2CH_2NH_2-OCH_3-H]^+$, *m/z* 258 $[M-OCH_2CH_2NH_2]^+$, and *m/z* 360 $[M+H+CH_3CN]^+$ (Fig. 5B). Over the experimental period, only one photoproduct was detected regardless of the types of aqueous solutions though there were differences in amounts of the photoproduct. This photoproduct was detected at *m/z* 319 $[M+H]^+$ leading to a molecular mass of 318 (Fig. 5C). This mass spectrum was exactly identical to that of parent compound as seen in Fig. 5B and C, indicating that the photoproduct has the same molecular weight and identical chemical structure to the parent compound and that the photoproduct is the [*Z*]-isomer of the parent compound. As mentioned above, the same photoproduct was previously detected and identified [7]. A paper has reported that the (*Z*)-isomer of fluvoxamine accounted for 3% in original standard [1]. Before this experiment we confirmed that no (*Z*)-iosmer of fluvoxamine was present. The same authors have also elucidated that the (*Z*)-isomers of some metabolites in animals occurred along with the (*E*)-compound and the (*E*) to (*Z*) ratio of fluvoxamine was 1:4 in the dog, indicating that the (*E*)-isomer can isomerize to the (*Z*)-isomer. From the above report, it is likely that the one photoproduct produced in this investigation is

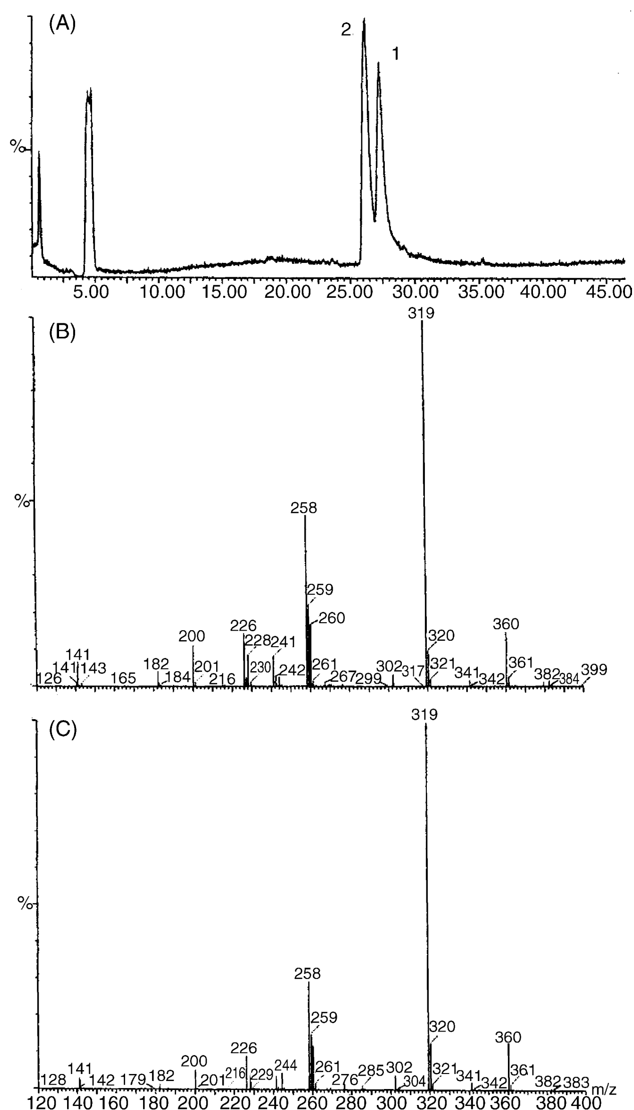

Fig. 5. The total ion chromatogram obtained from a sample irradiated in pH 9 buffer for 5 days (A) and their mass spectra of parent (B, peak #1 in A) and photoproduct (C, peak #2 in A).

also (*Z*)-isomer by isomerization of oxime moiety of fluvoxamine. Ruijten et al. [1], however, has reported 11 different metabolites of fluvoxamine in the four animals and has also reported that most of the metabolites contain both (*E*)-isomer and (*Z*)-isomers. The oxime isomerization can be induced by temperature, light, H^+ and OH^- ions, and a solvent [25]. Examples of photo-isomerization of compounds, 2-hydroxy-5-methylbenzophenone (*E*)- and (*Z*)-oximes with the oxime moiety in their structures exposed to a full spectrum of UV light were reported [23,26]. During the irradiation, the (*E*)- and (*Z*)-isomers of individual compounds were converted to (*Z*)- and (*E*)-isomers, respectively. Unlike this investigation, however, in their experiments, photo-degradation also occurred in addition to photo-isomerization.

The retention time of the photoproduct was slightly shorter than that of the parent compound, suggesting that the photoproduct is a more polar compound than the parent compound

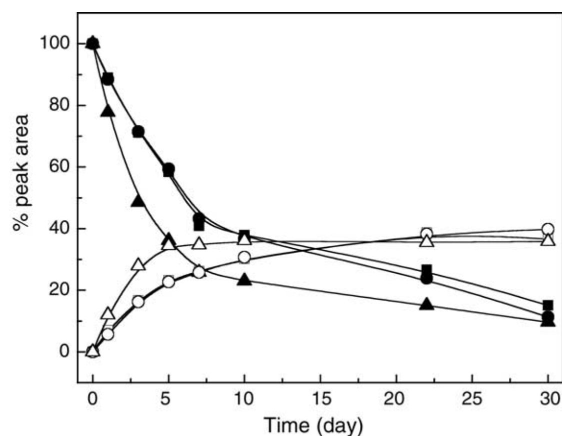

Fig. 6. Changes in amounts of the parent and the photoproduct as a function of time. Symbols: parent—(■) pH 5 buffer; (●) pH 7 buffer; (▲) pH 9 buffer and photoproduct—(□) pH 5 buffer; (○) pH 7 buffer; (△) pH 9 buffer.

(Fig. 5A). The photo-isomerization profiles of fluvoxamine under the different pH conditions are illustrated in Fig. 6. This figure shows the photo-isomerization of fluvoxamine and the formation of (*Z*)-isomer as a photoproduct. During the experimental period of 30 days, the amount of the photoproduct formed gradually increased until 4 days and then maintained constancy through the rest of the experimental period at pH 9. However, at pH 5 and 7, it gradually increased through 30 days, indicating it is quite stable to further hydrolysis and photolysis at all pH levels (Fig. 6). The same stability was reported by Miolo et al. [7]. They also reported that the [*Z*]-isomer produced during the photolysis loses capacity to inhibit serotonin uptake. The similar stability was shown in SHW and lake waters, but a slight decrease was seen after 4 days in SHW and after 8 days in natural waters (data not shown), suggesting that the [*Z*]-isomer may be slowly changed to other product in real aqueous environments. Using a diode array detector, the UV spectrum of the photoproduct was compared with that of the parent compound (Fig. 7). The UV spectrum of the photoproduct is somewhat different from that of the parent compound. The UV spectrum of

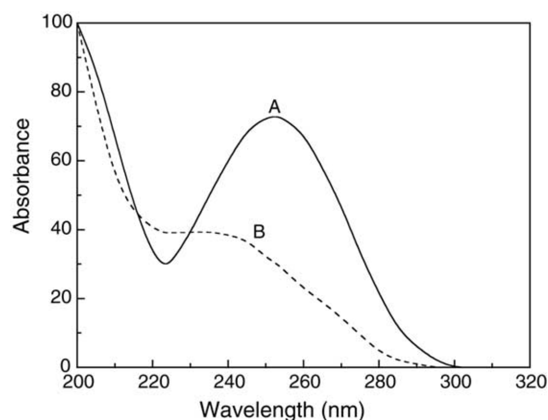

Fig. 7. UV absorption spectra of parent compound (A) and photoproduct (B) obtained by on-line diode array detector.

the photoproduct showed a maximum absorbance at approximately 235 nm instead of at 245 nm and had a lower absorption than the parent compound at wavelengths above 290 nm. This spectrum supports the observation that the photoproduct is relatively stable to direct photolysis. As previously mentioned, however, this photoproduct started to degrade after 8 days in SHW and lake waters, suggesting that indirect photolysis by humic materials or natural water materials may be occurring. These results appear to be similar to those observed for 2-hydroxy-5-methylbenzophenone (*E*)- and (*Z*)-oximes. When exposed to light, the UV spectrum of the (*Z*)-isomer produced by photo-isomerization is quite different from that of the (*E*)-isomer. Also the (*E*)-isomer had a λ_{max} at 259 and 316 nm, while the (*Z*)-isomer had a λ_{max} at 249 nm [23].

4. Conclusions

Fluvoxamine, a selective serotonin reuptake inhibitor, was found to be relatively persistent to chemical degradation, other than isomerization by UV irradiation, in aqueous solutions: the photo-isomerization to the (*Z*)-isomer was the main dissipation process during the UV irradiation. It was also shown that the photo-isomerization rates in SHW and in natural waters was up to seven times faster than in buffer solutions, indicating that fluvoxamine can be isomerized by sunlight in real aqueous environments.

The isomer was hydrolytically and photolytically quite stable during the experimental period of 30 days in buffer solutions used. However, it is shown that the isomer can be dissipated in SHW and natural waters, suggesting the possibility of disappearance in real aqueous environments.

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