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Low Pressure UV Photolysis of the Pharmaceutical Compounds Acetaminophen, Atenolol, Bezafibrate, Diclofenac and Ibuprofen

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Abstract: Pharmaceutically active compounds (PhACs) are continuously introduced into the environment by human and livestock excretion, hospital sewage and pharmaceutical effluents. While the performance of UV photolysis regarding PhACs degradation may be limited by low quantum yields, it may be efficient when the contaminants significantly absorb UV radiation. In this work, the direct photolysis under 254 nm UVC radiation of acetaminophen (ACT), atenolol (ATL), bezafibrate (BZF), diclofenac (DIC) and ibuprofen (IBU), isolated and in mixture, was investigated. The results showed that PhAC photolysis followed apparent first-order kinetics, with removals ranging from 32% to 99% after 60 min, while all the compounds exhibited lower photolysis rates when mixed in solution. Less than 13% mineralization was achieved. The toxicity of irradiated solutions of *Vibrio fischeri* remained the same or slightly decreased for ATL, BZF and IBU, increased for ACT, and notably decreased for DIC; nevertheless, the solution of mixed PhACs became very toxic following irradiation, showing the need for oxidant addition for removing residual toxicity.

Keywords: photolysis; pharmaceutically active compounds; toxicity; advanced water treatment; pharmaceutical facility effluents; wastewater treatment

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1. Introduction

Different classes of pharmaceutically active compounds (PhACs) have been found and quantified in surface waters, groundwater, drinking water sources and wastewater throughout the world [1–4]. PhACs are continuously introduced into environmental compartments by human and livestock excretion, hospital sewage and effluents from pharmaceutical facilities [5].

The concentration of PhACs found in surface waters is usually in the range ng L^{-1}–µg L^{-1} [6,7]. Even though the levels of these compounds found in the environment are much lower than therapeutically effective doses, it is known that some compounds may disrupt key processes in sensitive non-target organisms, including certain human populations such as children and pregnant women [8]. Moreover, the literature shows examples of wastewaters generated in the pharmaceutical industry (which mainly includes production and formulation facilities) with extremely high concentrations of various pharmaceutical residues in the order of mg L^{-1} [9,10]. Acetaminophen (ACT), atenolol (ATL), bezafibrate (BZF), diclofenac (DIC) and ibuprofen (IBU) are among the PhACs frequently detected in natural water bodies and wastewater. For example, these PhACs were found in the Billings Reservoir, an important water basin in the metropolitan region of ãSao Paulo, Brazil [11].

There is a great concern in the scientific community regarding water and sewage treatment processes, which, except in very particular cases, have no treatment operations suited to completely degrade, eliminate or remove PhACs from aqueous effluents [3,12]. Thus, it is an emerging issue in environmental science and engineering to achieve the effective removal of these compounds, along with other priority pollutants, before discharging treated wastewater [13]. For these reasons, alternative treatments, such as photochemical advanced oxidation technologies (AOTs), constitute an attractive alternative for converting these pollutants into less toxic and/or more readily biodegradable compounds [14].

AOTs involve mainly (but not exclusively) the generation and use of hydroxyl radicals, which can react with low selectivity with the majority of organic substances and, therefore, oxidize organic pollutants to CO_2, water and inorganic salts of heteroatoms other than oxygen [15]. These radicals can be obtained through different routes, with or without the use of UV-visible radiation. Common examples of photoirradiated AOTs are H_2O_2/UV, TiO_2/UV and photo-Fenton.

A large number of AOTs have been considered for eliminating different PhACs from water [16–20]. Nevertheless, most of them have investigated the degradation of individual drugs dissolved in water, without considering the potential effects of PhAC mixtures on the performance of treatment processes [13]. Photolysis promoted by UV radiation is a key process, concomitantly occurring in photo-irradiated AOTs, which can eventually be used alone for treating or sterilizing wastewater [21]. However, in most cases, the performance of UV photolysis in water and effluent treatment processes is limited by the low photon absorption and/or low quantum yields. Nevertheless, there are cases in which the contaminant significantly absorbs UV radiation, making the photolysis process efficient [21].

In this context, the goal of the present study was to investigate direct photolysis under UVC radiation at 254 nm of acetaminophen (ACT), atenolol (ATL), bezafibrate (BZF), diclofenac (DIC) and ibuprofen (IBU), isolated and in mixture, which may help understand the behavior of these PhACs in different UVC-driven photochemical degradation treatment processes. In this study, high concentrations of PhACs and acid pH were considered since effluents from pharmaceutical facilities can exhibit such conditions [9,10,22–24]. Since direct photolytic reactions can result in the formation of degradation products more toxic than the parent compounds, the toxicity of aqueous solutions of *Vibrio fischeri* was also characterized for non-irradiated and irradiated solutions.

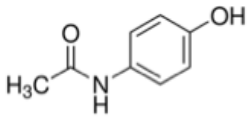
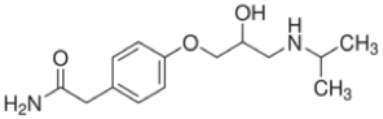
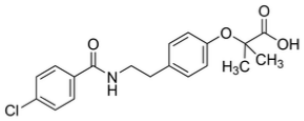
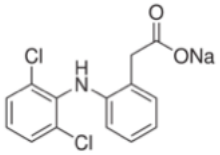
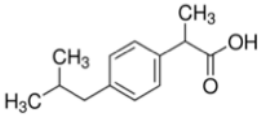
The study of this PhAC mixture on the performance of low-pressure UV photolysis, combined with the study of toxicity removal, is not usually found in the literature and therefore forms an original contribution. This information is critical for assessing the potential of photo-irradiated AOTs applied for the degradation of these micropollutants in wastewater treatment.

2. Materials and Methods

2.1. Chemicals

All solutions were prepared using pure water (18.2 MΩ cm) from a Milli-Q® Direct-Q system (Merck Millipore from Molsheim/France). For HPLC analysis, methanol (HPLC grade) and glacial acetic acid (100%) were purchased from Merck. The PhACs acetaminophen (ACT), atenolol (ATL), bezafibrate (BZF), diclofenac (DIC) and ibuprofen (IBU) were purchased from Sigma-Aldrich, their CAS number, purity, molar weight, molecular and structural formulas are presented in Table 1.

Table 1. CAS-number, purity, molar weight, molecular and structural formulas of the PhACs selected.

PhACs (CAS-Number)	Purity	Molecular Formula (Molar Weight)	Structural Formula
Acetaminophen (103-90-2)	≥99%	$C_8H_9NO_2$ (151.16 g mol^{-1})	
Atenolol (29122-68-7)	≥98%	$C_{14}H_{22}N_2O_3$ (266.34 g mol^{-1})	
Bezafibrate (41859-67-0)	≥98%	$C_{19}H_{20}NClO_4$ (361.82 g mol^{-1})	
Diclofenac (15307-79-6)	≥99%	$C_{14}H_{10}NNaCl_2O_2$ (318.13 g mol^{-1})	
Ibuprofen (15687-27-1)	≥98%	$C_{13}H_{18}O_2$ (206.28 g mol^{-1})	

2.2. Equipment and Procedures

2.2.1. pKa

The values of pKa of each PhAC were determined from ten aqueous solutions of the same concentration (5 mg L^{-1}) with pH between 2 and 11. UV-visible absorption spectra were obtained for each solution. The pKa values were obtained at the wavelengths corresponding to the maximum absorbance of the protonated and deprotonated forms.

2.2.2. Molar Absorption Coefficients

The spectral molar absorption coefficient (ε) of each PhAC was calculated according to Equation (1), where A is the absorbance, c is the PhAC molar concentration (mol L^{-1}), ε is the molar absorption coefficient (L mol^{-1} cm^{-1}), and l is the path length (1 cm). The slope of the absorbance curves as a function of concentration was determined for the wavelength range 200–340 nm.

$$A = \varepsilon cl \quad (1)$$

2.2.3. Photolysis Experiments

Hydrolysis experiments were carried out in the dark, using 20 mL of each PhAC solution. The flasks were kept in a shaker, at 25 °C and pH 3, 5, 7, 9, for 24 h.

Photochemical degradation experiments were performed in batches in a tubular photochemical reactor (Figure 1), consisting of a borosilicate glass tube equipped with a concentric low-pressure mercury vapor lamp (TUV Philips 75 W from Poland), emitting short-wave UV radiation with a peak at 253.7 nm, at a rate of 2.75×10^{19} photons s^{-1}. A circulation vessel was connected to the photochemical reactor, from which samples (1 mL) were withdrawn and immediately analyzed. The total and irradiated volumes were 5.0 and 3.9 L, respectively.

All the experiments were performed at 25 °C and pH 2, which was adjusted at the beginning of the experiments but not controlled over time. This acid pH was selected based on studies that report effluents from the pharmaceutical industry showing acidic character [22,23]. The solution was recirculated at a flow rate of 0.4 L min^{-1} through the

reactor and the vessel by means of a centrifugal pump. The vessel was loaded with an aqueous solution containing each PhAC individually, at 5 mg L^{-1} initial concentration, or with a solution containing the five PhACs at an initial concentration of 5 mg L^{-1} each. Three replicates of the experiments at each experimental condition were performed.

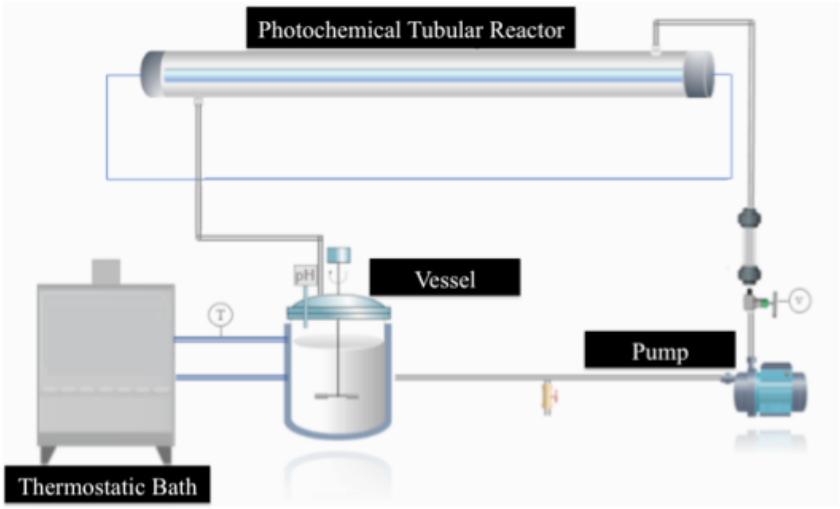


Figure 1. Simplified scheme of the experimental apparatus used in the photodegradation experiments.

2.3. Analyses

2.3.1. UV-Visible Spectrophotometry

UV-Vis absorption spectra were measured with a Varian Cary 50 UV-Vis spectrophotometer using a 1 cm path-length quartz cuvette.

2.3.2. TOC

The total organic carbon (TOC) was measured with Shimadzu TOC-5000A equipment. The TOC was determined indirectly by the difference between the total carbon (TC) and inorganic carbon (IC) contents of the sample.

2.3.3. High-Performance Liquid Chromatography (HPLC)

An HPLC system (Shimadzu, LC20 model, Kyoto/Japan), equipped with a two-solvent delivery pump, UV/VIS diode array detector (SPD 20A model) and an autosampler, was used to follow PhACs concentration–time profiles. The compounds were analyzed using a C18 column (Phenomenex, 250 mm × 4.6 mm; 5 µm from Molsheim/France), the eluent consisted of a mixture of water (A) and methanol (B), both containing 0.2% of glacial acetic acid at a flow rate of 1 mL min^{-1}. The gradient method detailed in Table 2 was used. The detection wavelengths were 225 nm (ATL, BZF and IBU) and 254 nm (ACT and DIC). The retention times were 11.1, 5.8, 14.9, 16.9 and 17.4 min for ACT, ATL, BZF, DIC and IBU, respectively.

Table 2. Gradient elution used for PhACs quantification by HPLC analysis.

Time (min)	Phase A	Phase B
0.01	90	10
7	90	10
10	20	80
30	20	80
32	90	10
35	90	10

2.3.4. Toxicity Assays

Samples taken at 0 and 120 min during photolysis experiments were examined for acute toxicity using the luminescent bacteria *Vibrio fischeri*, according to the Brazilian ABNT Standard [25]. *V. fischeri* bioluminescence was measured using the Microtox® test protocol, using a Microtox Model 500 analyzer and MicrotoxOmni v. 4.2 software (Modern Water, Inc., New Castle, DE, USA). The pH of irradiated solutions was previously corrected to 7.0, and four sample dilutions were measured after 15 min exposure time. The EC_{50} values were calculated using standard statistical procedures.

3. Results

3.1. pKa Measurements

The values of pKa found are shown in Table 3 and are in perfect agreement with the literature. For the degradation experiments, the solution's pH was adjusted to obtain all PhAC molecules entirely in one of their forms (neutral, protonated or deprotonated); at pH $\leq$ 2, ACT, BZF, DIC and IBU are totally in their neutral form, while ATL is totally protonated. Moreover, acidic conditions can be found in wastewater from pharmaceutical facilities, as aforementioned.

Table 3. Experimental values of pKa for the PhACs used in the experiments.

PhAC	pKa	Reference
ACT	9.0	[26]
ATL	9.3	[27]
BZF	3.5	[28]
DIC	4.0	[29]
IBU	4.7	[29]

The molar absorption coefficient (ε) measures the probability that a compound will absorb light at a certain wavelength (λ) [30]. Direct photolysis is only effective when the contaminant absorption spectrum overlaps the emission spectrum of the UV lamp and when the direct photolysis quantum yield is reasonably large [9]. Table 4 shows the molar absorption coefficients of ACT, ATL, BZF, DIC and IBU at 254 nm and pH 2. ATL and IBU showed the lowest molar absorption coefficients ε, which were approximately eight times lower than those exhibited by ACT, BEZ and DIC on average.

Table 4. Molar absorption coefficients (ε) of ACT, ATL, BZF, DIC and IBU at 254 nm and pH 2.

PhAC	ε (L mol^{-1} cm^{-1})
ACT	8989
ATL	724
BZF	7403
DIC	5374
IBU	1022

3.2. Photolysis Experiments

The stability of the PhACs in aqueous solution in the absence of light has been previously reported [31–34]. In fact, dark control experiments performed in aqueous solution at 25 °C showed that the hydrolysis of PhACs was found to be insignificant over 4 h, regardless of pH and medium (isolated or mixed). Consequently, PhAC degradation occurred only by the effect of UVC radiation in the photodegradation experiments described therein.

PhAC removal by UVC photolysis followed pseudo-first-order decay during the first 60 min, as indicated by the linear time behavior of ln([PhACs]/[PhACs]$_0$) over time. Figure 2a shows the results for each isolated PhAC at an initial concentration of 5 mg L^{-1}, while Figure 2b shows the results obtained for the compounds mixed in solution at 5 mg L^{-1}. Direct photolysis at 254 nm allows fast degradation of DIC and BZF; however,

for the other PhACs, a long exposure time is necessary. ATL exhibited negligible degradation in all cases, in accordance with its low molar absorption coefficient (Table 4). Similar results were found by [19]. On the other hand, ACT degradation was less important than that observed for DIC and BZF, despite its higher molar absorptivity, suggesting that ACT photolysis occurs with a low quantum yield at 254 nm.

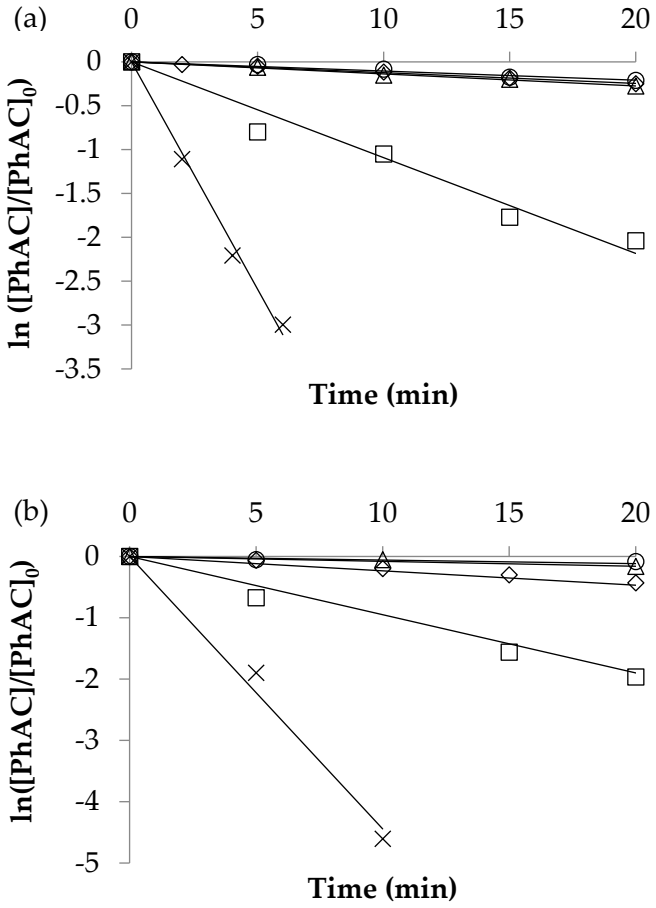


Figure 2. UVC photolysis of ◇ ACT, ○ ATL, □ BZF, △ IBU, × DIC: (**a**) isolated, $[PhAC]_0$ = 5 mg L^{-1}; (**b**) mixed, $[PhAC]_0$ = 5 mg L^{-1}.

Table 5 summarizes the results obtained in the photolysis experiments. PhACs removals ranged from 32% to 99% after 60 min of irradiation. Nevertheless, all the compounds exhibited lower photolysis rate constants when mixed in the solution as a result of the higher amount of degradation by-products formed upon irradiation, i.e., the competition for incident photons increased.

Table 5. Results of photolysis experiments: k, pseudo-first-order rate constant (min^{-1}); $t_{1/2}$, half-life time (min); removal %, percent removal after 60 min of irradiation; and R^2.

	Isolated PhACs (5 mg L^{-1})				**Mixed PhACs (5 mg L^{-1})**			
	k (min^{-1})	$t_{1/2}$ (min)	**Removal %**	R^2	k (min^{-1})	$t_{1/2}$ (min)	**Removal %**	R^2
ACT	0.013	53	62%	0.99	0.022	32	85%	0.98
ATL	0.012	58	54%	0.96	0.005	134	32%	0.99
BZF	0.103	6	93%	0.96	0.099	7	99%	0.98
DIC	0.518	1	99%	0.99	0.460	2	99%	0.99
IBU	0.014	47	57%	0.99	0.013	54	38%	0.95

Finally, nonetheless, there were good photolysis removals for all conditions studied, and the time evolution of TOC revealed less than 13% PhACs mineralization, with the formation of persistent degradation products.

Although a long period is required for the degradation of the studied PhACs by low-pressure UV photolysis, this is a viable alternative to apply in treatment systems as a polish process since most organic micropollutants, such as PhACs, are not biodegradable—they are resistant to biological treatment and are not removed by conventional wastewater treatment. In addition, it is important to remember that low-pressure UV irradiation can be combined with auxiliary oxidants that can make the degradation process faster and more effective.

3.3. Toxicity Assays

Irradiated PhAC solutions were examined for acute toxicity using the test organism *V. fischeri*. According to the classification presented by [35], samples are considered toxic (EC_{50} < 10%) or very toxic (EC_{50} < 1%), with the toxicity inversely proportional to EC_{50}, given in *v/v* %.

Figure 3 presents the results of the toxicity assays for the experiments carried out with $[PhACs]_0$ = 5 mg L^{-1}, isolated and in mixture. The high toxicity of the untreated solution of mixed PhACs is remarkable compared with those of isolated PhACs. Furthermore, for most isolated PhACs (ATL, BZF and IBU), the toxicity of treated solutions remained the same or slightly decreased after prolonged UVC irradiation. An important increase in solution toxicity was observed for ACT, while for DIC, the solution toxicity notably decreased. Finally, the assay conducted with mixed PhACs showed that after UVC irradiation, the solution became very toxic, with an EC_{50} equal to 0.5%, despite the fast and almost complete PhAC removal in some cases, as a result of the formation of persistent degradation products more toxic than the parent compounds.

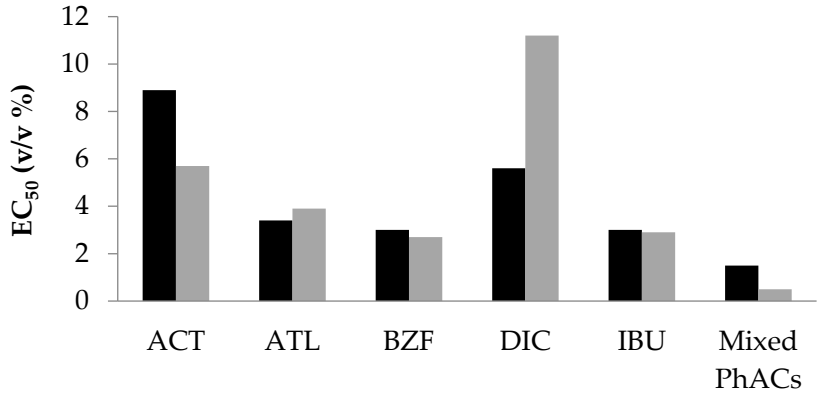


Figure 3. Values of EC_{50} (*v/v* %) determined through acute toxicity assays with *V. fischeri* for experiments performed with solutions of isolated or mixed PhACs. ■ Untreated solutions. ■ Solutions irradiated at 254 nm over 120 min.

The results of toxicity tests reveal that the isolated use of low-pressure UV radiation is not effective in the treatment of water contaminated by the studied PhACs. These results indicate the need for the use of oxidizing auxiliaries; that is, studies aimed at the application of photoirradiated AOTs, such as H_2O_2/UV, TiO_2/UV and photo-Fenton, are necessary. However, it is important to remember that the results obtained in this research may help to understand the behavior of studied PhACs in different UV-driven photochemical degradation processes.

4. Conclusions

The results of this study showed that the photolytic degradation of five different PhACs (acetaminophen, ACT; atenolol, ATL; bezafibrate, BZF; diclofenac, DIC; and ibuprofen, IBU)

followed apparent first-order kinetics, with removals ranging from 32% to 99% after 60 min of UVC irradiation at 254 nm. DIC and BZF showed high degradation rates, in contrast with ATL, which has the lowest molar absorption coefficient at 254 nm. Moreover, the results suggest that ACT photolysis occurs with a very low quantum yield. All the compounds exhibited lower photolysis rates when mixed in the solution. Nonetheless, good PhAC removals for all the conditions studied—less than 13% mineralization—was achieved. Therefore, for ATL, BZF and IBU, the toxicity of treated solutions to *V. fischeri* remained the same or slightly decreased following UVC irradiation—solution toxicity increased for ACT, while it notably decreased for DIC—this behavior is associated with the particular recalcitrant degradation products that originated in each case. Nevertheless, the solution of mixed PhACs became very toxic following irradiation. Finally, it can be concluded that photoirradiated treatments can be a suitable option for degrading the PhACs investigated, while oxidant addition may be needed for removing residual toxicity.

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Conflicts of Interest: The authors declare no conflict of interest.

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