I&EC research
Industrial & Engineering Chemistry Research

Article

Cite This: Ind. Eng. Chem. Res. 2020, 59, 647−653

pubs.acs.org/IECR

# Photocatalysis Using UV-A and UV-C Light Sources for Advanced Oxidation of Anti-Cancer Drugs Spiked in Laboratory-Grade Water and Synthetic Urine

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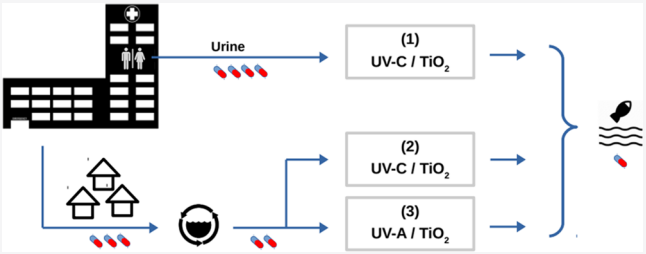
**ABSTRACT:** The presence of anti-cancer drugs in European surface waters appeals for the development of novel treatment processes. In this work, light emitting diodes (LEDs) that emit light at 255 nm (UV-C) and 365 nm (UV-A) wavelengths were compared in terms of their ability to degrade four anti-cancer drugs by UV and UV/$TiO_2$ processes. None of treatments tested was able to degrade cyclophosphamide and ifosfamide. Nevertheless, etoposide and paclitaxel were successfully eliminated by UV-C and UV-C/$TiO_2$. Moreover, higher energetic yields were obtained with UV-C light for the degradation of anti-cancer drugs by photocatalysis than with UV-A. The option of using this treatment to deal with pollution at the source by performing essays in synthetic urine was shown to be not adequate, as drug photocatalysis was totally inhibited by the presence of radical scavenger species present in the urine matrix.




## 1. INTRODUCTION

Anti-cancer drugs were widely detected in European wastewaters[1] at levels ranging from 100 ng/L to a maximum concentration reported for 5-fluorouracil of 124 $\mu g/L^2$. As drugs are not completely metabolized by human body, a fraction is excreted in sewage systems, which reaches wastewater treatment plants. However, biological treatments applied are not 100% efficient as some drugs are adsorbed on activated sludge,[3] and others are non-biodegraded.[4] Furthermore, pollution related to cancer treatment is expected to rise as annual new cancer cases are expected to grow to 22 million in 2032.[5]

The four anti-cancer drugs investigated in this work were selected based on different environmental risk assessment works:[1,6−9] etoposide, paclitaxel, cyclophosphamide, and ifosfamide. The genotoxic, mutagenic, cyanogenic, teratogenic, and fetotoxic characters of these cytostatic agents[10,11] motivate the scientific community to develop innovative water treatments. In a previous work, our research group has reviewed removal efficiencies of pharmaceutical compounds obtained by several advanced oxidation processes, photolysis (UV) with ozone ($O_3$) and hydrogen peroxide ($H_2O_2$) and titanium dioxide photocatalysis (UV/$TiO_2$),[12] evidencing that UV/$O_3$/$H_2O_2$ and UV/$TiO_2$ treatments have high potential for cytostatic drug removal. However, in regard to the environmental impact related to the production of oxidizing chemicals ($O_3$ or $H_2O_2$), photocatalytic processes have interesting sustainable advantages.[13]

Advanced oxidation processes are able to degrade persistent drugs thanks to the in situ production of highly reactive oxygen species. The photocatalytic process based on the activation of $TiO_2$ is able to degrade adsorbed micropollutants and form free active radicals.[14,15] Low- and medium-pressure mercury UV lamps are commonly used for its activation; however, over time, such lamps are replaced by light emitting diodes (LEDs) for several reasons: no mercury disposal issue, higher energy efficiency, longer lifetime, monochromatic spectrum emission, no warm-up time, and smaller dimensions.[16] Up to date, a promising literature material is available on photocatalytic degradation of persistent anti-cancer drugs.[17−22] However, no consensus exist on which UV spectrum is the most appropriate to degrade anti-cancer drugs by photocatalysis in aqueous media. The present work will thus investigate which of the UV-

Received: August 22, 2019
Revised: December 12, 2019
Accepted: December 18, 2019
Published: December 18, 2019






DOI: 10.1021/acs.iecr.9b04608
Ind. Eng. Chem. Res. 2020, 59, 647−653

$C/TiO_2$ or UV-A/$TiO_2$ process requires the lowest amount of energy to degrade the four anti-cancer drugs paclitaxel, etoposide, cyclophosphamide, and ifosfamide.

After investigating drug degradation in pure water, a second part of this work studies the possibility to degrade anti-cancer drugs from the pollution source, urine. Treatment of the specific concentrated pollution on-site at the hospital would significantly decrease operational costs.[23] However, in order for the treatment of urine to be effective, this strategy must act on different levels simultaneously: urine of patients taking certain medication should be collected in hospital thanks to No-Mix toilets,[24] and a specific training should be provided to request the safe return of an out-patient's urine to the hospital wastewater facility. Adverse effects of natural organic matter and various ions on the photocatalytic efficiency have already been reported at different extents by previous photocatalytic works.[25−29] However, to the best of the authors' knowledge, studies on suspended photocatalysis of anti-cancer drug in synthetic urine is a novel field of investigation.

## 2. MATERIALS AND METHODS

**2.1. Materials and Handling Precautions.** The four drugs presented in Figure 1 were purchased at the highest

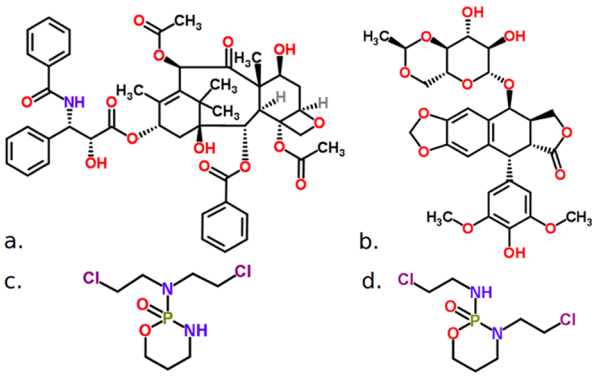



**Figure 1.** Molecular structure of (a) paclitaxel, (b) etoposide, (c) cyclophosphamide, and (d) ifosfamide drawn on ChemSpider (www.chemSpider.com).

purity grade available (>98%, Sigma-Aldrich, Germany): paclitaxel, etoposide, cyclophosphamide, and ifosfamide. Stock solutions were prepared following strict safety guidelines.[30] Once dissolved in methanol, stock solutions (1.2−9.4 mg/mL) were stored in the dark at −20 °C as recommended by Negreira et al.[31] *Para*-chlorobenzoic acid (pCBA) was also purchased at the highest purity grade available (>98%) from Sigma-Aldrich. It is a well-known molecular probe used to assess the presence of hydroxyl radicals.[32] Finally, photocatalytic experiments were performed using titanium dioxide P25 (70/30 wt % anatase/rutile) purchased from Evonik, Degussa, Germany.

**2.2. Water Matrix Characterization.** Two water matrices were investigated in this work: laboratory-grade water produced by a Milli-Q water system (Millipore, CA, USA; Resistivity:18.2 MΩ at 25 °C; TOC < 5 $\mu g.L^{-1}$; bacteria < 1 CFU $mL^{-1}$; particulates < 0.22 $\mu m$) and synthetic urine prepared by dissolving chemicals (ordered at a purity of >98% from Sigma-Aldrich, Germany) presented in Table 1 in laboratory-grade water.[33]

**Table 1. Synthetic Urine Composition (g/L)**

| KCl | NaCl | urea | citric acid | ascorbic acid |
|---|---|---|---|---|
| 3.8 | 8.5 | 24.5 | 1.03 | 0.34 |
| $KH_2PO_4$ | creatinine | NaOH | $NaHCO_3$ | $H_2SO_4$ |
| 1.18 | 1.4 | 0.64 | 0.47 | 0.28 mL/L |

**2.3. Photocatalytic Experiment.** Anti-cancer drugs were detected in European wastewaters at maximum concentrations of 124 $\mu g/L$ (5-fluouracil)[2] and 100 $\mu g/L$ (carboplatin).[34] In this work, experiments were conducted with each drug spiked individually at 500 $\mu g/L$ in laboratory-grade water. This ensured that the investigated concentrations tested ($C$) were the same order of magnitude as the concentrations reported in occurrence studies, and that the concentration of the analytes could be followed by direct injection in the LC−MS/MS and detected up to 5 $\mu g/L$. Degradation rates were defined as the slope of the linear regression of $\ln(C/C_0) = -k \times t$, with $k$ the pseudo-first order apparent rate constants and $t$ the light irradiation time.

Experiments were performed with a collimated beam reactor (see Figure 2) using two LEDs as light sources (Aquisense,

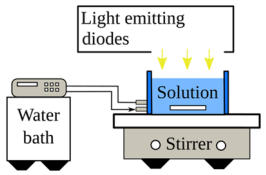



**Figure 2.** Reactor scheme.

PearlBeam). The distance between the light source and the surface of the investigated solution was 20 mm. The technical specifications of the diodes are presented in Table 2. During

**Table 2. Technical Specifications of LEDs (Supplier Data)**

| LED type | UV-C | UV-A |
|---|---|---|
| peak wavelength (nm) | 254.2 | 367.3 |
| full width half maximum (nm) | 11.6 | 8.1 |
| fluence rate[a] ($\mu W/cm^2$) | 21.43 | 739.50 |

[a]at a distance of 20 mm from the source

the tests, a magnetic stirrer was used to ensure homogeneous mixing of the 50 mL solution while a cooling bath (Lauda, Microcool, Germany), connected to the double jacket reactor, permitted to maintain the temperature at 25 ± 1 °C. Photocatalytic experiments were conducted using a titanium dioxide catalyst (P25, Evonik, Degussa, Gremany).

**2.4. Analytical Methods.** For pCBA analysis, a solvent mixture of water/acetonitrile 50/50% (v/v) was used as the mobile phase in isocratic mode with a flow rate of 0.8 mL/min in the Luna C18 separation column (5 $\mu m$, 150 × 2.0 mm) maintained at 35 °C. Detection was then performed using an ultraviolet absorbance detector set at 240 nm (Waters Chromatography, Milford).

In the case of anti-cancer drug analysis, a gradient of solvents was used to separate compounds as shown in Table 3. The gradient was adapted from the work of Negreira et al.[35] A tandem mass spectrometry detector (LC−MS/MS Waters 2695 separation module, Ireland) was connected to the column in order to detect and quantify the drugs. These


DOI: 10.1021/acs.iecr.9b04608
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**Table 3. Solvent Gradient for HPLC-MS/MS**

| time (min) | 0 | 7 | 10 | 12 | 15 |
|---|---|---|---|---|---|
| Solvent B/A ratio[a] | 5% | 100% | 100% | 5% | 5% |

[a]A: 0.5% formic acid in Milli-Q B: HPLC grade acetonitrile

methods were described in more details in a previous publication.[36]

## 3. RESULTS AND DISCUSSION

**3.1. Catalyst Load Optimization.** Oxidation potential of photocatalytic processes has been studied in the past using the hydroxyl molecular probe *para*-chlorobenzoic acid (pCBA).[32,37−39] In this work, pCBA was used to determine the optimal catalyst concentration leading to a maximal production of free OH radicals. As it can be seen in Figure 3, this probe is only degraded when the $TiO_2$ catalyst is present

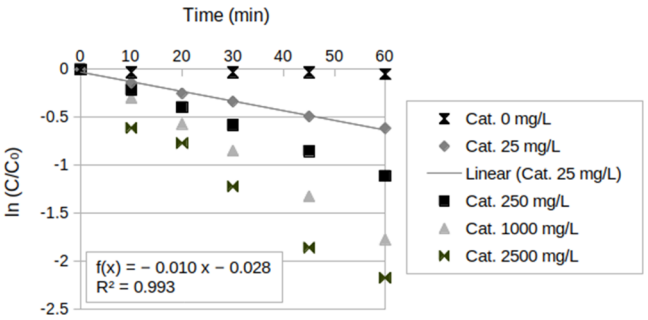


**Figure 3.** Pseudo-first-order kinetics of pCBA (0.5 $\mu$M) degradation obtained in laboratory-grade water under UV-C light using different concentrations of the titanium dioxide catalyst.

in the solution. Moreover, pCBA follows a pseudo-first-order degradation kinetic, as high linearity coefficients ($R^2 > 0.91$) are obtained when plotting the linear regression of $\ln(C/C_0) = k \times t$ in Figure 3, where $k$ is the time-based degradation rate constant and $t$ is the time of UV exposure in min.

Each of the time-based degradation rate constants obtained for the UV-C LED on Figure 3 was reported in Figure 4 (see

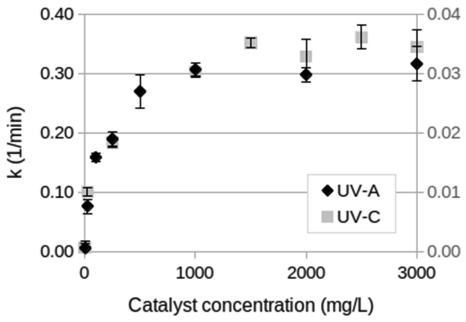


**Figure 4.** Time-based degradation rate constants of pCBA in laboratory-grade water in function of catalyst loads obtained with UV-A (diamonds) and UV-C (squares) light sources.

squares) together with additional tests carried out with the UV-A LED. pCBA concentrations were adapted to the intensity of the LED investigated: 0.5 $\mu$M for UV-C and 5 $\mu$M for UV-A LED. This ensured complete pCBA degradation over experimental time and thus improvement of result accuracy. A proportional increase of removal rates to the catalyst load was observed below a catalyst concentration of 1.5 g/L. However above this threshold, a phenomenon defined in the literature as light screening occurs: the high amount of catalyst particles reduces photon penetration length in the solution.[40] Therefore, this threshold was selected as the optimal catalyst concentration (1500 mg/L) for further tests performed with the LED emitting at 255 and 365 nm wavelengths (see Figure 4). Previous degradation studies performed in laboratory-grade water corroborate this result.[12] In section 3.2.2 the efficiency at which each LED converts photon energy into free OH radicals will be discussed taking into account the intensity of light emitted.

**3.2. Light Source Comparison.** *3.2.1. Apparent Degradation Rate.* Figure 5 shows the influence of the catalyst

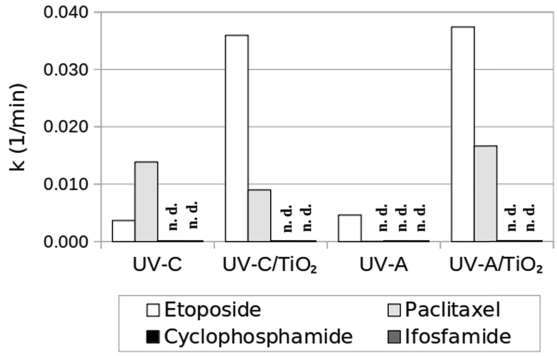


**Figure 5.** Time-based degradation rate constants obtained by direct photolysis (UV) and photocatalysis (UV/$TiO_2$, 1.5 g/L) of four anticancer drugs spiked in laboratory-grade water at 500 $\mu$g/L using the UV-C and UV-A LEDs (n.d. means non degraded drugs).

presence and LED type on drug degradation. The four anticancer drugs were spiked at 500 $\mu$g/L in laboratory-grade water. None of the applied treatment was able to degrade cyclophosphamide and ifosfamide, which are known for their chemical stability.[10,41] A study published by Kim and Tanaka on direct UV photolysis concluded that cyclophosphamide was the second most stable compound out of 30 pharmaceuticals and personal care products.[42] The high stabilities of these two drugs are probably related to the resonance stabilization uttered by the presence of amine groups, as it can be seen in Figure 1. Besides direct photolysis tests presented in Figure 5, photocatalysis experiments were also performed with no improvement of degradation. However, the literature reports cases of effective degradation operating at similar $TiO_2$ (P25) concentrations.[21,43] Unsuccessful degradations observed are probably related to the significantly lower power of the investigated LEDs in comparison to the solar simulator and the medium mercury lamps used in these literature studies.

Unlike cyclophosphamide and ifosfamide, etoposide degradation was detected in all tests and improved by catalyst presence as presented in Figure 5. This is not a novel result as UVs[44] and UV/$TiO_2$[45] are reported to be efficient processes in the literature for the removal of etoposide. The number of conjugated double-bond systems ($\pi$ bonds) present in the etoposide and paclitaxel molecules (see Figure 1) can explain why UV-C photons are able to directly excite bonds, which breaks during relaxation, inducing drug degradation. Contrary to etoposide, paclitaxel was only degraded directly by the UV-C source at a pseudo-first order apparent rate constant of 13.9 $\times 10^{-3}$/min but not by UV-A photons. This can be explained by the fact that photons with 365 nm wavelengths (UV-A)



DOI: 10.1021/acs.iecr.9b04608
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have lower energy than the ones emitted in the UV-C range and thus did not have enough energy to overtake the potential barrier required for exciting paclitaxel chemical bonds. In the mixture exposed to UV-C, the addition of the catalyst did not increase the paclitaxel degradation rate constant, but decreased from $13.9 \times 10^{-3}$ to $9.0 \times 10^{-3}$/min. In other words, the negative effect related to catalyst light screening overcame the positive ones of photocatalytic oxidation. In the opposite way, photons in the UV-A spectrum range were not able to degrade paclitaxel, but were able to activate photocatalytic oxidation resulting in a degradation rate constant of $16.6 \times 10^{-3}$/min. To summarize results of Figure 5, UV-C processes were able to efficiently remove etoposide and paclitaxel by direct photolysis and photocatalysis, while the UV-A LED required the presence of $TiO_2$ to degrade these two drugs.

In order to assess the evolution of total organic carbon and the formation of by-products during etoposide and paclitaxel degradation, further tests could be conducted at higher concentrations of anti-cancer drugs.

*3.2.2. Electrical Energy per Order.* Electrical energy per order (EEO) values were calculated as the amount of energy required to treat a volume of 1 L and decrease its drug concentration by one order of magnitude:[46,47]

$$\mathrm{EEO} = \frac{I}{V \times k} \quad (1)$$

with the lamp intensity ($I$), the reactor volume ($V$ = 0.05 L), and the time-based degradation rate constant ($k$). $I$ was calculated as the LED fluence rate (given in $\mu W/cm^2$, see section 2.3) multiplied by the surface area irradiated by UVs (38 $cm^2$).

The degradation rates presented in Figure 5 were transformed into electrical energy per order thanks to eq 1 and plotted in Figure 6. However, cyclophosphamide and

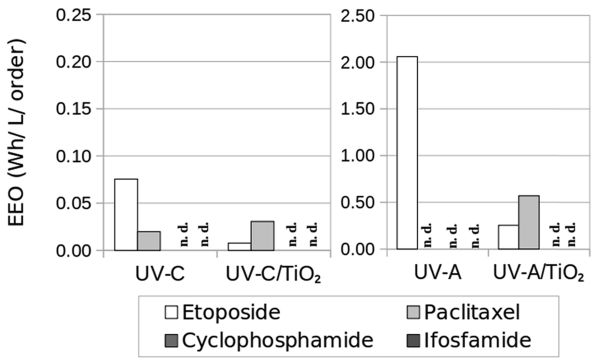


**Figure 6.** Electrical energy per order (EEO) obtained by direct photolysis (UV) and photocatalysis (UV/$TiO_2$, 1.5 g/L) of four anti-cancer drugs spiked in laboratory-grade water at 500 $\mu$g/L using the UV-C and UV-A LEDs (n.d. means non degraded drugs)

ifosfamide were not reported in Figure 6, as they were non degraded (n.d.) by the investigated processes. Results evidenced that the UV-C LED consumes less energy to remove drugs than the UV-A LED. Indeed, the highest relevant EEO value obtained with the 255 nm-wavelength photons was 0.075 Wh/L/order (UV-C of etoposide), while the lowest figure of the UV-A LED was 0.254 Wh/L/order (UV-A/$TiO_2$ of paclitaxel). It was concluded that for an equal amount of energy (mW) irradiated by the LED, UV-C rays were more efficient to break chemical bonds of etoposide and paclitaxel than UV-A photons. Xiao et al. made similar conclusions from their work on bromate degradation.[48] Furthermore, 255 nm rays were more efficient to degrade drugs by UV/$TiO_2$ than 365 nm-wavelength photons. In brief, higher energetic yields were obtained with UV-C light for the degradation of anti-cancer drugs by photocatalysis than with UV-A.

**3.3. Photocatalysis of Drugs in Synthetic Urine.**

*3.3.1. Anticancer Drugs Degradation.* Experiments were also performed in synthetic urine to investigate the possibility of treating pollution at source (e.g., hospital setting with urine separation toilets). Results of photocatalysis are presented in Table 4 with drugs spiked individually at 500 $\mu$g/L in a $TiO_2$

**Table 4. Degradation Percentages of Four Anti-Cancer Drugs Spiked in Synthetic Urine at an Individual Concentration of 500 $\mu$g/L ([$TiO_2$] = 1.5 g/L)**

| | UV-C/$TiO_2$ | | | | UV-A/$TiO_2$ | | | |
|---|---|---|---|---|---|---|---|---|
| % | ETP | PAC | CP | IF | ETP | PAC | CP | IF |
| 1-$C_{120}/C_0$ | 7.1 | 15.2 | 0.3 | 1.8 | −13.8 | 0.9 | 1.4 | 3.0 |
| 1-$C_{120,c}/C_0$ | 4.1 | 18.6 | 4.4 | 6.7 | 8.7 | 1.3 | 2.6 | 0.1 |

slurry of 1.5 g/L. As presented in Table 4, drug concentrations of samples exposed for 120 min to light were equal to the dark control. Unlike effective degradations observed in laboratory grade water for etoposide and paclitaxel (see Figure 5), the drop of removals in synthetic urine must be related to the presence of scavenging species in urine (see synthetic urine composition in Table 1). These scavengers (e.g., ions) could react with OH radicals produced by the photocatalytic process and form toxic products being more toxic than the parent drug compound.[49,50] Therefore, the possibility to form toxic by-products (e.g., halogenated organic by-products) in such matrices should be assessed in future investigations using gas chromatography analysis. In the next section, inhibition mechanisms occurring in the urine matrix are further investigated using the pCBA hydroxyl radical probe.

*3.3.2. Molecular Probe.* In order to have a better understanding of the urine species responsible for hindering the photocatalytic reactions, the effect of different solutions on pCBA degradation were investigated. Unless expressed otherwise, solutions were prepared by adding 1.5 g/L of catalyst in laboratory-grade water together with each component of the synthetic urine spiked individually to understand its effect. Time-based degradation rates obtained in these different matrices are reported in Figure 7. It can be seen

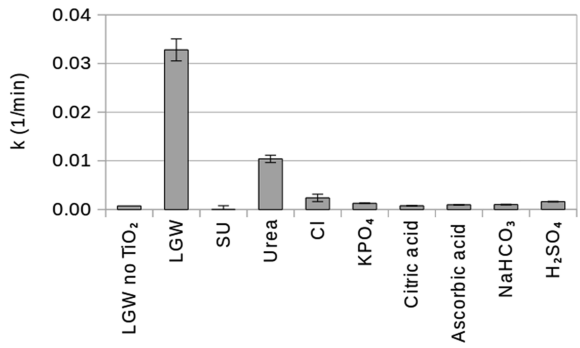


**Figure 7.** Time-based degradation rate constants of pCBA spiked at 0.5 $\mu$M in various aqueous matrices obtained by UV-C/$TiO_2$ with 1.5 g/L of the catalyst.



DOI: 10.1021/acs.iecr.9b04608
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that synthetic urine had the same inhibition effect on pCBA removal than on anti-cancer drug degradation. Moreover, results indicated that individual aqueous solutions of urea (24.5 g/L), sodium chloride (8.5 g/L), potassium phosphate (1.18 g/L), citric acid (1.03 g/L), ascorbic acid (0.34 g/L), sodium carbonate (0.47 g/L), and sulfuric acid (0.28 mL/L) impeded pCBA removal at a similar concentration than present in urine (see Table 1). As the probe is not degraded by direct photolysis (validated in Figure 3), inhibition of degradation in urine must be related to the photocatalytic activity. In fact, deterioration of photocatalytic efficiency by inorganic anions is a well-documented effect, even at low ion concentrations (10−100 mg/L),[25,26,28,29,51] and literature data reports two main deactivation routes:[29] one is related to the adsorption of anions on catalyst surface leading to deactivation of active sites. Bonding of $SO_4^-$ and $H_2PO_4^-$ on a catalyst was observed by Yap and Lim using XPS analysis.[28] A second route is linked to the affinity of ions to scavenge OH radicals leading to the formation of less-reactive radicals ($Cl^{\cdot}$, $NO_3^{\cdot}$, $SO_4^{\cdot-}$, $H_2PO_4^{\cdot}$, and $HCO_3^{\cdot}$).[28] This second mechanism, usually referenced as competition for free radicals, is also occurring in the presence of natural organic matters as creatinine, ascorbic acid, and citric acid. In addition, it is worth noting that ascorbic acid is a well-known antioxidant present in fruits and vegetables.[52] Therefore, it was concluded that urine components inhibit photocatalytic reactions by two different ways: active site deactivation by ion adsorption on the catalyst surface and radical scavenging. Alternative oxidation processes, not subjected to active site deactivation and catalyst screening effects, should be applied to remove drugs from urine matrices such as chemical oxidation ($UV/O_3$, $UV/H_2O_2$) or electro-oxidation. This latter process could take advantage of the high ion content present in urine matrices as effective charge carriers.

## 4. CONCLUSIONS

Photons emitted at two different ranges of wavelengths (UV-C and UV-A) were compared for their ability to degrade four anti-cancer drugs spiked in laboratory grade water at 500 $\mu$g/L: etoposide, paclitaxel, cyclophosphamide, and ifosfamide. First, the optimal catalyst amount for photocatalysis was selected thanks to a molecular probe degraded in the presence of hydroxyl radicals (pCBA). Degradation rates of pCBA increased proportionally with the catalyst load up to a catalyst concentration of 1.5 g/L above which screening effects limited the UV-C/$TiO_2$ and UV-A/$TiO_2$ processes. Therefore, 1.5 g/L was set as the optimal concentration for UV-C and UV-A photocatalysis essays. None of the performed essays was able to deliver enough oxidizing power to degrade cyclophosphamide and ifosfamide. However, etoposide and paclitaxel were successfully eliminated by UV-C (time-based apparent degradation rate constants of $3.6 \times 10^{-3}$ and $13.9 \times 10^{-3}$/min, respectively), UV-C/$TiO_2$ (time-based apparent degradation rate constants of $35.9 \times 10^{-3}$ and $9.0 \times 10^{-3}$/min, respectively), and UV-A/$TiO_2$ tests (time-based apparent degradation rate constants of $37.3 \times 10^{-3}$ and $16.6 \times 10^{-3}$/min, respectively). In order to determine energy yields of the two light sources, apparent degradation rates were transformed into electrical energy per order values (EEO). As for equivalent oxidation processes, EEO values obtained with UV-C were lower than the ones obtained with UV-A light, it was concluded that higher energetic yields were obtained with UV-C light for the degradation of anti-cancer drugs by photocatalysis than with UV-A. Finally, the efficiency of treating pollution at source by photocatalysis was assessed without success of degradation. In fact, pCBA degradation tests evidenced that most components present in synthetic urine inhibit photocatalytic reactions. Therefore, alternative oxidation processes should be applied to remove drugs from urine matrices such as chemical oxidation ($UV/O_3$ or $UV/H_2O_2$) or electro-oxidation.

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The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.


### Funding

This work was supported by the European Commission through the project ERA-NET Inno Indigo 2014 [grant number Inn-INDIGO/0002/2014] and Fundação para a Ciência e Tecnologia/Ministério da Educação e Ciência [grant number iNOVA4Health−UID/Multi/04462/2013] and Laboratory for Green Chemistry LAQV−Requimte [grant number UID/QUI/50006/2013], both financed through national funds and co-funded by FEDER under the PT2020 Partnership Agreement [grant number POCI-01-0145-FEDER-007265].


### Notes

The authors declare no competing financial interest.

## ACKNOWLEDGMENTS


The authors thank João Ferreira, Pedro Bastos, and Joana Quintela for the implementation of the analytical method described in this study.


## LIST OF ABBREVIATIONS

| | |
|---|---|
| ETP | etoposide |
| CAP | capecitabine |
| CP | cyclophosphamide |
| IF | ifosfamide |
| LGW | laboratory-grade water |
| LED | light emitting diode |
| pCBA | *para*-chlorobenzoic acid |
| EEO | electrical energy per order |
| UV-A | ultraviolet light (315−400 nm) |
| UV-C | ultraviolet light (100−280 nm) |

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DOI: 10.1021/acs.iecr.9b04608
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