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Leveraging insights into advanced oxidation processes for quaternary treatments

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ABSTRACT

This study assesses the efficiency of ozonation, photocatalysis, and electrooxidation to treat the effluent from an urban WWTP spiked with a mixture of 17 cytostatic compounds at 25 μg/L. This concentration allowed us to assess the efficiency of the different treatments, reaching good sensitivity for mass spectrometry detection avoiding sample treatments and study the kinetics when necessary. The presence of cytostatic drugs in urban wastewater poses significant environmental and health concerns due to their toxicity and persistence. Conventional wastewater treatment plants (WWTPs) only remove part of these contaminants, being necessary to add additional processes. Ozonation with 200 mg O_3/L achieved over 90 % removal for ten compounds, while the removal of seven compounds was below 60 %. Photocatalysis with TiO_2 (500 mg/L) degraded four compounds by over 90 %, but the removal of the other 13 compounds was below 75 %. Electroxidation was effective for removing 14 out of the 17 compounds with an average global removal of 75 % and 94 % for eight compounds. Results showed: i) single techniques do not achieve a high removal of all contaminants, ii) all compounds were removed by at least one of the treatments, and iii) there is a fragmentation of knowledge, and most lab studies do not predict the kinetic behavior of treatments of complex wastewater. The integration of multiple technologies (e.g. electrooxidation and ozonation would be needed to enhance the overall removal efficiency of WWTPs and accomplish stricter legislation. Further studies on potential challenges as by-product toxicity and energy consumption are necessary.

1. Introduction

Emerging contaminants (EC), including cytostatic drugs, are continuously discharged into the environment, impacting aquatic ecosystems. Even at trace levels (μg/L and ng/L), cytostatic drugs are persistent and, along with their mutagenic, teratogenic, and carcinogenic properties, raise significant concerns regarding long-term risks to both human health and aquatic organisms [1,2]. This requires flexible approaches to assess the ecological risk of ecosystem pollution and its implications, since risk assessors in different regions may encounter site-specific stressors [3].

Cytostatic drugs are designed to be highly stable, preventing premature breakdown in the human body. This stability makes them resistant to degradation in conventional treatments, such as biological processes and ultraviolet disinfection [4]. Therefore, urban wastewater is one of the main sources of cytostatic water pollution. The revised Directive EU 2024/3019 [5] aims further to improve water quality through the implementation of quaternary treatments.

A recent bibliometric study on EC and cytostatic compounds reveals that the cluster "treatment plants" is the most relevant in the last decade, based on the co-occurrence network analysis of keywords [6]. Most studies examine the efficacy of treatment methods, with results showing variable performance. Advanced treatments such as membrane treatment, adsorption, and advanced oxidation processes (AOP) are often explored [7,8]. Membrane treatments are effective, but suffer from fouling, are energy-intensive, and have high cost; therefore, they are primarily used for water reclamation when water is reused. Adsorption is cost-effective and efficient, but the effluent's complexity demands adsorbents tailored with specificity for target pollutants while maintaining broad-spectrum efficacy, which remains a limitation. On the other hand, pollutants are transferred from the aqueous to the solid phase; thus, additional treatments are required for both the regeneration

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of spent adsorbents and their final disposal. A remaining challenge is the adsorbent regeneration over numerous cycles, particularly for biosorbents [9,10].

AOP aim to mineralize the pollutants into non-toxic compounds, but the formation of by-products and degradation compounds may also happen [11]. Ozonation is commonly used in WWTPs for odour and refractory organic compounds removal [12] through (i) direct reactions with molecular ozone, and (ii) indirect oxidation via hydroxyl radicals (·OH). Ozone, with an oxidation potential of 2.07 V, is a highly reactive molecule that rapidly degrades contaminants with nucleophilic functional groups such as carbon double bonds, aromatic rings, and functional groups containing nitrogen, oxygen, sulphur, or phosphorus atoms. However, the short reaction time can potentially lead to the formation of harmful by-products. Ozone also generates non-selective ·OH radicals with a high oxidation potential (2.8 V), that degrade pollutants via hydrogen abstraction, radical-radical interactions, electrophilic addition, or electron transfer reactions at longer times [13]. The prediction of chemicals behavior when treating complex wastewaters is not possible as it is influenced by the specific water matrix, pH and DOC content [14]. Some transformation products may be more toxic than their precursors. Li et al. [54] found the inhibitory rate on *V. fischeri* increased from 9 % to 15 % due to the ozonation of the effluent of a WWTP. He et al. [15] predicted PRED TPs toxicity by using ECOSAR method, which indicated that some products had higher toxicity than parent compound. Blaney et al. [16] studied the fate of CIP and IFO during ozonation and their findings suggested that treated water may retain the ability to alkylate DNA and confer toxicity. However, TPs of CIP formed during the reactions under three UV-based processes (UV/Fe^{2+}/H_2O_2 and UV/TiO_2), as identified by Lutterbeck et al. [17], did not show toxicity against *V. fischeri*. Therefore, this issue must be tested case by case. A recent study from Zhang et al. [18] concluded that the combination of ozonation and adsorption with active carbon would be necessary to minimize the presence of transformation by-products.

Electroxidation has emerged as a promising AOP for the degradation of a wide range of EC, owing to its high oxidation potential, minimal chemical requirements, operational simplicity, versatility and modular design [19]. The process is based on the application of a current in an electrochemical cell with one or more electrode pairs, enhancing the oxidation of pollutants through (i) direct oxidation, where electrons are transferred directly to the anode surface; (ii) reactive oxygen species, formed from water oxidation, including ·OH; and (iii) weaker oxidants produced electrochemically from ions in solution [20]. The final degradation efficiency depends mainly on the cell design, mass transport, water matrix, electrode material, and applied current. Boron-doped diamond (BDD) anodes are particularly effective because they electrogenerated more reactive species and have a high corrosion stability [21–23]. A recent review remarks that most studies deal with spiked deionized water treatments and, therefore, there is a research gap on results using complex wastewater [24].

Ultraviolet (UV) lamps are commonly used for disinfection in WWTPs. Since there is a broad spectrum of photo-labile organic contaminants that can break down by photoxidation, the optimisation of this treatment could extend the removal of EC in current systems. Since photolysis alone is often insufficient for complete degradation of contaminants, the combination of UV with a catalyst is required to achieve higher degradation performances [25,26]. Photocatalysis is a process where light exposure triggers a semiconducting material to generate electron-hole (e^-/H^+) pairs and free radicals for the degradation of contaminants. Titanium dioxide (TiO_2), is an inert, non-toxic and cheap product and it is by far the most used photocatalyst, but the recovery of this nano-catalyst after usage may be a bottleneck at large scale if it is not supported [27–29]. The main drawbacks of these treatments are the high energy consumption, the limited penetration depth of UV light in water in the presence of turbidity, and the presence of radical scavengers (e.g., bicarbonates), which reduce efficiency.

The state of the art shows several recent reviews addressing the removal of pharmaceuticals, including antibiotics [30,31] and anti-inflammatory drugs [32]. Most of these reviews focus on a single AOP type or the removal of a specific pharmaceutical. A recent review from Hama Aziz et al. [33] highlights the need to assess EC degradation in real wastewater matrices and to evaluate the removal of diverse contaminants, since most studies are focused on removing single contaminants from pure water. There is also interest in the potential risks of transformation products during water treatment, as shown by the increasing relevance of keywords such as “transformation products”, “risk assessment” and “toxicity” in the last decade [6].

Furthermore, most studies on the degradation of cytostatic compounds consider high initial concentrations of the target compounds (mg/L), such as Lin et al. [34] and Blaney et al. [16], whereas real water concentrations are usually in the ng/L to μg/L range [35–37]. On the other hand, in many cases, the treatment is carried out with synthetic waters prepared with ultrapure water [16,38]. This facilitates the study of reaction kinetics, but these results do not mimic the behavior of the treatment with real wastewater matrices, containing organic matter and other compounds [39]. Therefore, there is a gap in knowledge on the efficiency of different treatments when treating real wastewater matrices.

In summary, despite the advances in wastewater technologies, the efficient removal of EC, particularly cytostatic compounds, remains a challenge. Each treatment presents inherent limitations, and comparisons across studies are hindered by methodological heterogeneity. Due to the fragmentation of knowledge, there is no consensus on the best treatment to degrade a wide range of EC to an efficiency higher than 80 %. These substances are characterized by low concentrations, diverse chemical structures, and persistence, which pose challenges to effective treatment. The implementation of quaternary treatment will significantly increase WWTP costs. A comparison study carried out by Bui et al. on tertiary treatments established a relative cost of 1 for ozone (10 g/m^3), 1.3 for UV (100 Wh/m^3), 2 for AC (140 mg/m^3), and 2.8 for RO [40]. When comparing different AOPs, ozonation is the most used. However, the viability of the process will depend on the required doses to efficiently remove a broad number of microcontaminants and the need of integrating complementary treatments.

Therefore, this study aims to generate new knowledge and insights on the efficiency of alternative AOP, such as ozonation, photocatalysis and electroxidation, to degrade complex mixtures of EC. The three methods are compared using the same real urban wastewater matrix spiked with a complex mixture of 17 pharmaceuticals, including cytostatic compounds. By understanding the different efficiencies for each contaminant under diverse operational conditions, this work will contribute to identifying effective standalone or combined treatment strategies for extending the limits of existing WWTPs.

2. Materials and methods

2.1. Wastewater sampling and characterisation

Water samples were collected from the final effluent of an urban WWTP in Madrid City, Spain. Grab samples were taken from the secondary treatment effluent. They were filtered through a 2.7 μm glass microfiber filter from Merck (Darmstadt, Germany) to remove suspended solids. Filtered samples were stored in the dark at −20 °C until they were used in the oxidation treatments. Six effluent samples were taken over one year. Water quality was characterized following standards methodology [41], including the determination of physicochemical properties such as pH (7.4–8.3), conductivity (346–1221 μS/cm), chemical oxygen demand (COD) (47–95 mg O_2/L), total organic carbon (TOC) (8–22 mg C/L) and dissolved solids (290–458 mg/L). The main differences are due to dilution when it rains.

TOC was determined to assess the mineralization of the samples. A TOC analyzer model Multiwin N/C 3100 (Analytik Jena, Germany) equipped with an AOX auto sampler was used.

2.2. Standards and chemicals

Cytostatic compounds were selected according to consumption rates, including 5-fluorouracil (5FLU), azathioprine (AZA), bicalutamide (BICA), capecitabine (CAP), cyclophosphamide (CP), cyproterone (CYP), doxorubicin (DOX), etoposide (ETO), flutamide (FLUT), gemcitabine (GEM), ifosfamide (IFO), megestrol (MEG), methotrexate (MET), mycophenolic acid (MPA), paclitaxel (PAC), prednisone (PRED) and tamoxifen (TAM). All these reference standards were purchased from Sigma-Aldrich (St. Louis, MO, USA) with a purity higher than 98 %. For standard solutions and mobile phases, acetonitrile (ACN), methanol (MeOH), formic acid (FA) and acetic acid from Supelco (LiChrosolv hypergrade) were used. Ultrapure water was obtained from a MilliQ water purification system from Merck Millipore (Mildford, MA, USA). TiO_2 AEROXIDE-powder (21 nm) from Sigma-Aldrich (St. Louis, MO, USA) was used as a catalyst in photoxidation experiments. During preliminary electroxidation studies, sodium sulphate anhydrous (Na_2SO_4) was needed as electrolyte (Labkem, Barcelona, Spain). Previous experiments were performed with NaCl (2 mg/L), and the removal results were better for Na_2SO_4. In addition, to the best knowledge, it is the most used salt in this process, probably to avoid chlorinated by-products.

Stock standard solutions were prepared individually at a concentration of 100 mg/L in MeOH and preserved at −20 °C for six months [42]. These stocks were used to prepare a mix of 17 cytostatics at 5 mg/L in ultrapure water for experimental purposes using wastewater effluents. For optimization studies of each treatment, the selected individual stocks were diluted to 20 mg/L in ultrapure water.

2.3. Advanced oxidation treatments

A preliminary study was conducted to select the operational conditions of each treatment. For these assays, four compounds were chosen: 5FLU, MET, MPA, and PRED. Using ultrapure water spiked with a standard solution of each targeted cytostatic at 20 mg/L, the three treatments were evaluated. During each experiment, a minimum of six samples were taken and analyzed by LC-DAD to study the evolution of the process.

Following the selection of the operational conditions, the evaluation of each treatment was conducted with real WWTP effluent spiked with 17 cytostatic compounds at 25 μg/L each. All experiments were performed in triplicate at the pH of the effluent (7.4–8.3). Oxidation treatments lasted 120 min (min).

2.3.1. Ozonation

Ozonation experiments were executed in a glass bubble column reactor (height = 400 mm, inner diameter = 6,5 cm) equipped with a porous plate at the bottom (porous diameter = 90–150 μm). The experiments were conducted in batch mode using 1000 mL of water per run. The ozone-enriched gas stream was fed into the reactor through a porous plate, promoting uniform bubble distribution. A gas stream outlet was located at the top of the reactor. Unconsumed O_3 was directed to a catalytic O_3 destructor model QD-2H (Quioz, Romeral, Chile). Treated effluent samples were collected with a syringe through a sealed sampling point located at the mid-height of the reactor.

O_3 gas was produced from air using different O_3 generators. For low-concentration experiments, ozone generators from ASP ASEPSIA S.L. (Madrid, Spain), models ZHI 10000 (22 W) and ZHI 500MG (40 W), providing 100 and 500 mg O_3/h, respectively, with a constant flow rate of 8 L/min, were used. For high-concentration experiments, an ozone generator Rilize model producing 1800 mg O_3/h at a flow rate of 4 L/min was used. The gas flow was regulated with a Bronkhorst® controller (Model F-201AV, Ruurlo, The Netherlands). In this setup, two online O_3 analyzers were connected (Model 964C, BMT Messtechnik GMBH, Berlin, Germany) to determine the in-flow and out-flow O_3 concentrations, so the actual O_3 consumption within the reactor. The concentration of dissolved O_3 in the aqueous phase was measured using a portable Hanna Checker HI 701 sensor (Eibar, Gipuzkoa). In the present study, the ozone dose (mg O_3/L) is considered as the amount (mg) of gaseous ozone injected into the system, calculated from the product of the ozone flow rate (mg/h) and the treatment time (h), and normalized by the reaction volume (O_{3dose} = mg O_3/h · treatment time (h)/ reaction volume (L)).

Treatment variables were evaluated using ultrapure water containing 5FLU, MET, MPA, and PRED at 20 mg/L, and then, the final conditions were applied to a real wastewater matrix.

2.3.2. Photocatalysis

Photodegradation experiments were conducted in LED photoreactors from APRIA Systems S.L. shown in Fig. S1 (Cantabria, Spain). First, three LED radiation sources: i) visible LED (λ = 400–700 nm; Irradiance = 315 lm); ii) UVA LED (λ = 365–370 nm; Irradiance = 1200 mW/LED); and iii) UVC LED (λ = 268–280 nm; Irradiance = 100 mW/LED) were applied in a collimator (Photolab LED275–0.1/365–1/450-1cb). In all cases, the water sample (50 mL) was placed in a 100 mL beaker, with a diameter of 5 cm and magnetic stirring. This study aimed to assess the photodegradation efficiency of four contaminants with different radiation lamps, treatment time (up to 120 min) and TiO_2 catalyst concentration (100–500-1000 mg/L). Data were validated with a 600 mL borosilicate column (Photolab LED365–16/450-16i) from Apria Systems S.L. (Cantabria, Spain), with a LED immersion lamp composed of 20 UV-A LEDs (λ = 365–370 nm; Irradiance = 1200 mW/LED; fluence rate = 78.5 mW/cm^2 at distance of 1.5 cm^2), temperature control and magnetic agitation.

The experiments with real wastewater were performed in a column with 1000 mL of sample, during 120 min, and a TiO_2 concentration of 500 mg/L, in batch mode with a recirculation stream between the column and a beaker, thanks to a peristaltic pump from Watson Marlow (SCI 323), purchased from Thermo Fisher Scientific (Sunnyvale, CA, USA).

2.3.3. Electroxidation

An electrolytic methacrylate cell of 1000 mL was designed with channels that allow the adjustment of the electrodes at different distances. Boron-doped diamond (BDD/Si NeoCoat) electrode was purchased with a surface concentration of 500 mg/L of boron. As cathodes, stainless steel (SS) electrodes were used. Both electrodes had the same shape and surface (200 cm^2). The power supply was obtained from Gety, a GLPS 3010 (0–30 V, 0–10 A) (Gety, Opava, Czech Republic). The optimization of treatment conditions was conducted with the addition of sodium sulphate (42 mM) in ultrapure water. Different variables such as electrode distance (0.5, 1, 2, and 4 cm); pH (3, 4, 5.5, 8, and 10); reaction time (60, 120 min and 24 h); and current density (2.5, 5, and 10 mA/cm^2) were evaluated. To develop the study with real wastewaters, the selected parameters were: 1 cm distance between electrodes, natural pH, and current density of 5 mA/cm^2. Magnetic stirring at 300 rpm was applied to ensure a homogeneous mixture.

2.4. Analysis of target compounds

Individual quantification of 5FLU, MET, MPA and PRED for the preliminary experiments was achieved with a liquid chromatograph (LC) (1290 series, Agilent Technologies, Santa Clara, CA, USA) coupled to a diode array detector (DAD) (1290 G4212A, Agilent Technologies). The chromatographic column was a Poroshell 120 EC-C18 (150 mm length, 4.6 mm diameter, 4 μm particle diameter) (Agilent Technologies), and the mobile phase composition included ultrapure water with 75 mM of acetic acid (A) and ACN (B), by applying different gradients to improve the detection of each compound. The instrumental parameters for these analytical methods, including gradient profile and absorption maximum wavelength, are shown in Table S1.

WWTP effluent samples were collected during the advanced oxidation treatments and analyzed using an Ultra Performance Liquid Chromatography (UPLC) (1290 Infinity II, Agilent Technologies) coupled to a triple quadrupole (MS/MS) mass spectrometer (6495C, Agilent Technologies), equipped with an electrospray ionization (ESI) interface in positive and negative mode. The chromatographic column was a Poroshell 120 EC-C18 (50 mm length, 3 mm diameter, 2.7 μm particle diameter) (Agilent Technologies). The mobile phase was composed of ultrapure water acidified with 0.1 % FA (A) and ACN with 0.1 % FA (B). The gradient was set from 5 % of solvent B to 100 % B within 18.5 min, maintained at 100 % B for 1.5 min, and decreased to 5 % B within 24 min at a flow rate of 0.6 mL/min. The injection volume was 20 μL, and the column was maintained at 40 °C. All samples injected were previously filtered through a 0.22 μm PTFE syringe filter (Agilent Technologies, Santa Clara, CA, USA) to reduce analytical interferences. Data was acquired in dynamic multiple reaction monitoring (dMRM) mode, where at least two transitions (Q, q) were selected for each targeted compound (Table S2) and processed using Agilent MassHunter Quantitative Analysis (version 10.1.67).

3. Results and discussion

3.1. Ozone treatment

3.1.1. Ozonation conditions for cytostatic removal

The results from the preliminary study, conducted with the four individual cytostatics (20 mg/L) in ultrapure water, are shown in Fig. 1. All compounds were sensitive to ozonation, with the removal efficiency following this order: MPA > MET>5FLU > PRED. At high ozone doses (1800 mg O_3/h), a complete removal of the targeted contaminants was achieved within 1 min. Despite the high removal efficiencies of the parent compounds, the TOC removal remained below 10 %, indicating very limited mineralization.

Fig. 1 shows the removal of the four cytostatic compounds and the total ozone concentrations (TC) required, calculated using ozone doses and reaction time (TC = level (mg O_3/L·min) × treatment time (min)). A dose of 100 mg O_3/L is necessary to achieve the complete removal of each compound, while a total ozone concentration of 50 mg O_3/L results in over 80 % removal in all cases. At lower O_3 concentrations, these contaminants would be only partially removed and a combination of treatments will be necessary [18,40].

Despite the extensive research on ozonation, comparing data across studies remains challenging due to fragmented knowledge concerning water matrices, contaminant types, ozone doses, study scales, and other variables. In agreement with Alvarez [43], typical O_3 dosages for wastewater treatments are: 2–15 mg O_3/L for micropollutants removal, 5–50 mg O_3/L for decolorization, and 20–75 mg O_3/L for desodoration. For COD removal, the required O_3 dosages vary widely, from 10 to over 1000 mg O_3/L. According to Mahmoodi and Pishbin [7], when using ozonation as advanced treatment in a municipal WWTP, O_3 is typically applied at 0.5 g O_3/g COD, which corresponds to approximately 25 mg O_3/L for an average COD level of 50 mg C/L. Therefore, regarding the data of the present study, degradation of the target contaminants is expected to range between 60 % and 100 %, in agreement with previously reported values [44–47].

In many studies, such as Garcia-Costa et al. [47], experiments are performed by pre-dissolving ozone in ultrapure water before adding the contaminants, thereby avoiding the mass-transfer step and focusing on the chemical reaction between ozone and the pollutants. While this approach allows for greater mechanistic clarity, it overlooks real-world factors. In contrast, the present study performs tests that consider the mass-transfer step and matrix effects, thus providing more realistic conditions. For instance, Garcia-Costa et al. [47] achieved complete removal of MPA in ultrapure water by pre-dissolving 1 mg O_3/L, whereas in the current study, an inlet dose of ~40 mg O_3/L was required. This highlights the role of the ozone mass-transfer step and the difficulty in comparing results from other studies.

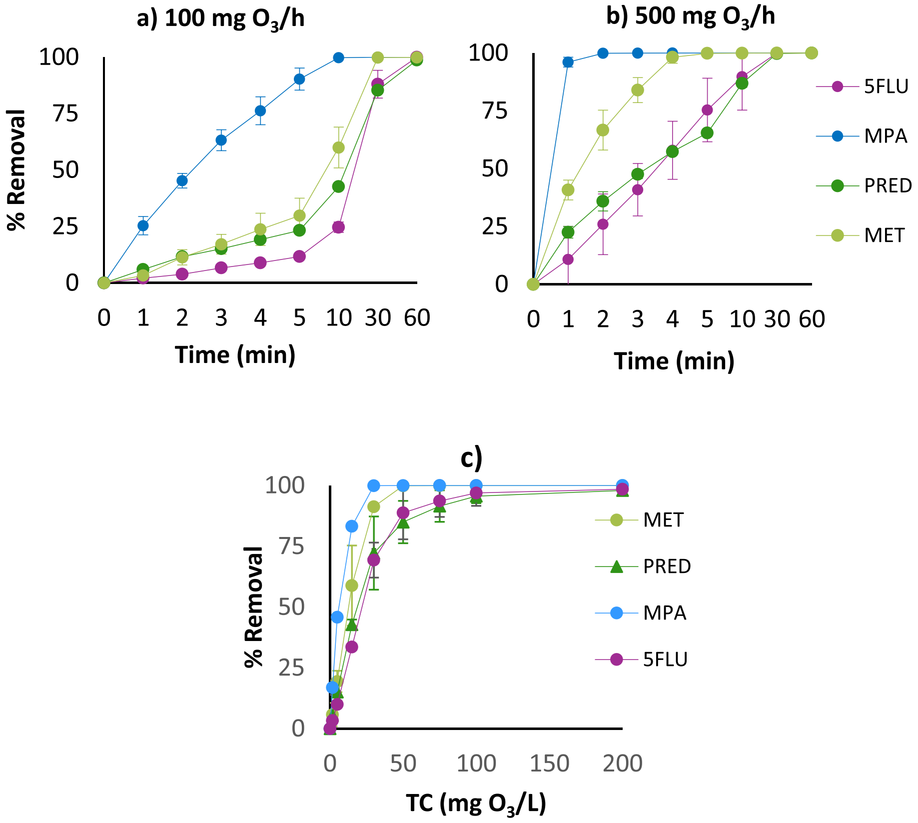

Fig. 1. Removal for the preliminary experiment with O_3, including four cytostatics dissolved in ultrapure water at 20 mg/L: a) Low-concentration, b) medium-concentration, and c) total O_3 concentration dose.

According to Garcia-Ac et al. [48], MET was completely degraded within 2 min using a pre-dissolved O_3 dose of 10 mg O_3/L. In another study, 5FLU was degraded with 52 mg O_3/L in a mixture with O_3/O_2, favoring the oxidizing conditions [45]; whereas in this study, it was degraded at 200 mg O_3/L in a mixture with air. He et al. [15] reached 90 % PRED removal with 7500 mg O_3/L (3 g O_3/h; 30 min; 200 mL). In contrast, the present study achieved the same result with a six-fold lower dose (~200 mg O_3/L). Most of the published studies were performed using ultrapure water, O_3-saturated matrices and high contaminant concentrations, which are not always representative of the degradation at low concentrations [15,16,38,45,49].

3.1.2. Cytostatic drugs removal in real effluent by ozonation

Based on the findings of this study, doses up to 200 mg O_3/L were selected for experiments involving the complex mixture of targeted pollutants at environmentally relevant concentrations (25 μg/L) in real wastewater effluents.

Fig. 2 presents the average removal rates of the cytostatic compounds significantly affected by ozonation. Notably, ten out of the 17 compounds showed substantial removal. A dose of 100 mg O_3/L achieved up to 75 % removal of these ten compounds, while 200 mg O_3/L was required to exceed 90 % removal. Nonetheless, seven compounds (GEM, AZA, CP, IFO, PRED, BICA, and FLUT) exhibited recalcitrant behavior, consistent with findings reported by Garcia-Ac et al. [48]; Cruz-Alcalde et al. [50]; and Garcia-Costa et al. [47].

Considering the influence of molecular structure on ozone reactivity, compounds containing double bonds, activated aromatic systems and non-protonated amines, such as those found in MET and CAP, undergo rapid ring breakdown via both direct and indirect ozonation pathways. Additionally, CAP also contains a halogenated group, which, may represent a site susceptible to ozone attack depending on the type of halogen and the position of the group [7,11,13]. However, other compounds containing halogen groups, such as FLUT or BICA, were less affected by the ozone treatment, due to the position of the trifluoromethyl group, that contributes to generation of more resistant structures to ozonolysis. The specific halogen and matrix composition modulates the behavior, for instance, chloride, carbonate, and phosphate ions inhibit non-catalytic ozonation by scavenging ·OH, whereas sulphate can enhance contaminant removal through sulphate radical formation [51]. However, AZA, which contains a sulphur atom, it did not show an optimal removal rate (26 %) due to the absence of C═C double bonds, and the position of its potentially oxidizable sites (sulphur and the aromatic ring) that make it relatively stable or not easily oxidise under selected ozonation conditions.

Preliminary experiments showed that PRED was completely degraded within 60 min (Fig. 1a), confirming its high ozonation reactivity. By contrast, only 38 % degradation was observed in the spiked effluent, underlining the scavenging effects of the complex water matrix composition. Gouveia et al. [52] concluded that PRED was efficiently degraded in effluents by predissolving 6.6 mg O_3/L for 10 min. Moreover, complete degradation of IFO, FLUT and BICA was only achieved when a high dose of hydrogen peroxide (55.5 mg H_2O_2/L) was added to the system. The improvement is attributed to enhanced ·OH generation, initiating fast and non-selective oxidation reactions [53].

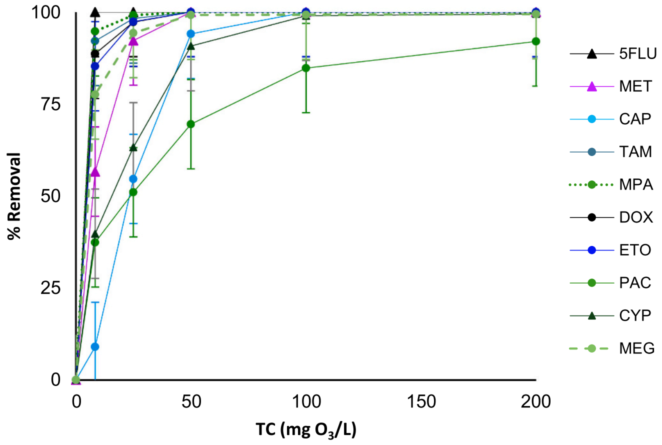

Fig. 2. Removal of ozone-sensitive cytostatic compounds with 200 mg O_3/h (reaction time of 120 min) in real wastewater.

Data show that significantly higher inlet doses (~at least ten times) are necessary in real wastewater treatments compared to experiments with predissolved ozone, as Antoniou et al. [44] reported that only 10 mg O_3/L was enough to remove over 90 % of most tested pharmaceuticals.

The concentration of dissolved O_3 remained below 0.1 mg O_3/L in all experiments, due to the rapid reaction of ozone in a complex matrix. Even at high doses (200 mg O_3/L), a pronounced matrix effect was observed, attributable to the organic matter's ability to partially quench O_3 molecules. Nevertheless, up to ten compounds exceed 90 % removal after 60 min of treatment. In the case of BICA and FLUT, average removals of 72 % and 58 %, respectively, were achieved, while GEM, AZA, IFO, CP and PRED removals were below 50 %, with the same ozone doses (100 mg O_3/L·h for 2 h).

In full-scale wastewater treatment studies conducted by Garcia-Costa et al. [47], IFO showed no measurable breakdown, whereas similar removal efficiencies for CP (56 %) and lower for BICA (38 %) were observed, by using 5 mg O_3/L. To better understand, these authors assessed the role of water matrix complexity during ozonation by comparing ultrapure water (50 mg O_3/L) with real water samples (river water and secondary effluent, 5 mg O_3/L), for both individual cytostatic compounds and with mixtures in solution. The authors obtained 99 % of CAP and MPA degradation in the three matrices. However, considering river water as a cleaner real matrix, they only achieved eliminations of around 30 % for BICA, CP and IFO. This has been attributed to the rapid reaction of ozone with inorganic and organic constituents naturally present in the water matrix, which significantly reduces its efficiency.

Regarding the results obtained by other authors, the complete removal of IFO and GEM was achieved in a hospital wastewater matrix [46]. However, very high O_3 doses were used (10 g/L), which may excessively increase the treatment cost. In another study performed by Li et al. [54], the complete elimination of FLUT in wastewater was achieved with 50 mg O_3/L. Most of the studies use high doses of O_3 gas or predissolved O_3 solutions to avoid gas-liquid mass-transfer issues and focus only on the oxidation step of the reaction. In the present study, 100 mg O_3/h was injected into the wastewater matrix. This O_3 flow rate allowed the obtention of removal curves to calculate the apparent kinetic constants (k') of each cytostatic compound and has demonstrated that optimisation of O_3 gas feed is possible. Seven compounds require improvement in the elimination ratio, which could be achieved by applying a higher dose of O_3 or by improving the dispersion method to achieve better dissolution of the O_3 gas input.

3.2. UVA treatments

3.2.1. Photodegradation conditions for cytostatic removal

The results of the removal efficiency by photocatalysis at different irradiances and TiO_2 concentrations are presented in Fig. 3.

The results confirm UVA light as the best source of radiation when using TiO_2 as a catalyst, as indicated by several studies [25,28,55]. Preliminary tests showed that PRED and MET were completely mineralized with 100 mg/L of TiO_2 and UVA (TOC removal ~98 %). To increase the removal efficiencies, 500 mg/L of catalyst is required, as also indicated by other authors [56]. Higher doses do not improve the results due to the light-shielding effect of excess solid particles in the aqueous matrix. The results achieved in this assay are similar to the ones reported in the literature, where removals of just 62.7 % and 60 % were obtained during the photocatalysis treatment of 5FLU and MET, respectively

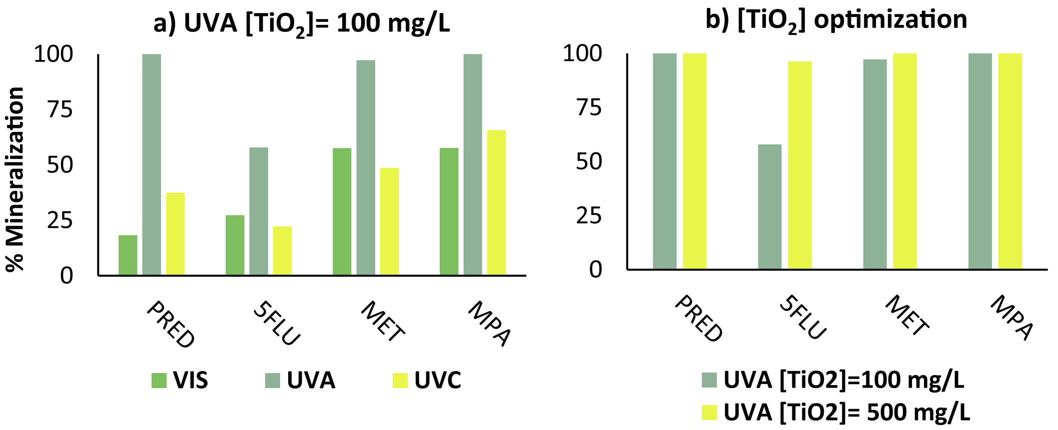

Fig. 3. a) Mineralization degree of PRED, 5FLU, MET and MPA at different radiation wavelengths with 100 mg/L of catalyst. b) Mineralization degree of PRED, 5FLU, MET and MPA with UVA light for 100 and 500 mg/L of catalyst.

[17,25,56,57]. Then, this pre-study was scaled up to 600 mL in the photocatalyst column, confirming the results from the collimator with almost no differences.

3.2.2. *Cytostatic drugs removal in real effluent by photodegradation*

The effect of photolysis on the spiked effluent is illustrated in Fig. 4 for the four UVA-sensitive compounds within the 17-mixture solution (DOX, TAM, MPA and ETO). This contrasts with research published by Calza et al. [25], DOX and MET in ultrapure water matrix were subjected to UVA photolysis (360 nm) for 60 min led to 10 % and 60 % removal rates, respectively. It is important to highlight that, they used higher contaminant concentrations (15 mg/L) for instrumental sensitivity and ultrapure water avoiding matrix effect. Another study, conducted by Franquet-Griell et al. [58], treated a mix of 16 cytostatic compounds at 50 μg/L each in ultrapure water with UV-C radiation (254 nm). Those authors achieved photolysis removal rates of 87 % for ETO (15 min), 85 % for MPA (90 min), and less than 1 % for IFO and CP (90 min), which is similar to the results presented here. In contrast, total elimination of PRED was achieved in 5 min, with more than 80 % removal for GEM, CAP, MEG and MPA. This demonstrates the clear influence of the type of light, the effect of the water matrix, and the necessity of a catalyst to achieve the removal of a broader number of contaminants via radical oxidants. Considering the results presented, it may be necessary to implement treatments requiring prolonged durations that seem unfeasible for full-scale WWTPs. Therefore, the current UV treatments used in WWTPs are not sufficient to degrade a large number of EC [59,60].

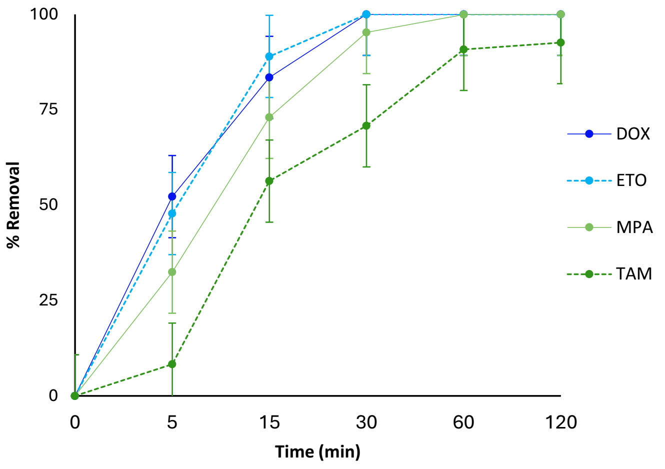

Fig. 4. Removal rates by photolysis of sensitive cytostatic compounds in effluent.

The photocatalysis tests conducted with 500 mg/L of TiO_2 are presented in Fig. 5. The catalyst enhanced the removal efficiency of nine out of the 17 compounds, while it did not show a remarkable effect for the photosensitive compounds. The catalysis also adsorbed the target pollutants as shown in Table S3. In the case of DOX and TAM a high removal efficiency is obtained by photolysis (99 and 91 % respectively) but also by TiO_2 adsorption (54–69 % respectively). However, when treating the real wastewater spiked with the target pollutants, while the removal efficiency of DOX remains high (97 %), it significantly decreases for TAM (75 %), as shown in Fig. 5.

Results are difficult to compare with published data because, in most cases, experiments have been performed with Ultrapure water [25,49,56,61], with a low number of contaminants. When they use spiked wastewater matrices [62], experiments at high concentrations were run due to the lack of accurate analytical methods for quantification at trace-level.

3.3. *Electroxidation treatment*

3.3.1. *Electrooxidation conditions for cytostatic removal*

Individual studies under different current densities (2.5, 5, and 10 mA/cm2) were tested in a previous electrooxidation assay with 5FLU, MET, MPA and PRED. An excessive temperature rise was observed at 10 mA/cm^2 (up 50 °C), which is likely to produce the evaporation of the sample. The treatment time was 120 min except for the PRED, which was extended to 24 h to determine the potential maximum efficiency.

The best removal of 5FLU was achieved at a current density of 5 mA/

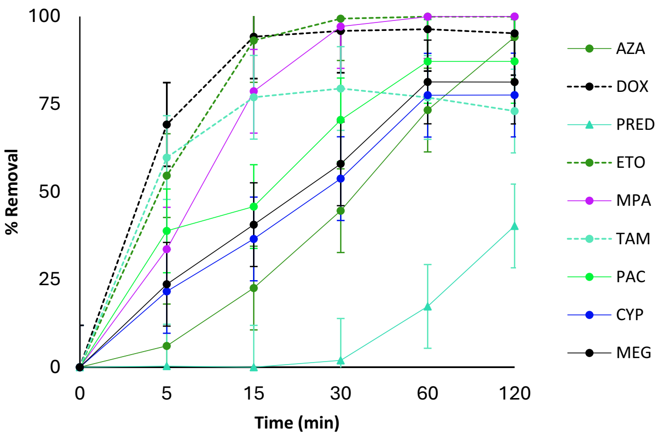

Fig. 5. Removal rates by photocatalysis (500 mg/L of TiO_2) of sensitive cytostatic compounds in effluent.

cm^2, where complete drug removal was reached in 75 min. At 2.5 mA/cm^2 and 10 mA/cm^2, the complete removal was achieved in 105 and 90 min, respectively. Despite these findings, current density does not appear to be a highly significant parameter for 5FLU removal. MET showed a marked difference at a current density of 10 mA/cm^2, as the compound was no longer detected in the solution after the second sampling. In contrast, at lower current densities of 5 mA/cm^2 and 2.5 mA/cm^2, removal efficiencies of 63 % and 34 % were obtained, respectively, without achieving a complete removal in 120 min. Finally, for MPA, a direct relationship between the percentage of removal and current density was observed, with higher current densities yielding greater removal rates. Despite the faster reaction rate at 10 mA/cm^2, complete removal of the compound was observed at 60 min under all tested conditions. The study of the electrode distance (from 0,5 to 4 cm) was not highly significant, and 1 cm was selected for the following experiments.

3.3.2. *Cytostatic drugs removal in real effluent by electroxidation*

Results from the electroxidation of the spiked effluent presented the widest range of affected compounds (Fig. 6), showing that this is one of the most effective techniques towards a broad variety of EC at trace level, as identified also by Fabiańska et al. [63] and Siedlecka et al. [64].

Although not all cytostatics achieved more than 90 % removal, all of them presented at least more than 54 % removal and 14 out of 17 more than 75 %. 5FLU, PRED, and CAP were the least affected compounds, exhibiting removal rates of 54 %, 63 %, and 67 %, respectively. This shares the tendency shown by Siedlecka et al. [64], where a 70 % of removal was obtained for 5FLU but using a higher initial concentration of 50 mg/L, 16 mA/cm^2, 6 g/L of Na_2SO_4 and BDD/SS as electrodes. These conditions enhance the electrical conductivity of the matrix since they used Ultrapure water, but do not reflect a real WWTP scenario. Initial concentration and current density are also higher than those used in the present study; hence, its removal rate is higher. Xu et al. [65] achieved a full removal of CAP in less than 30 min. In this case, they used a special anode (porous Ti/SnO_2-Sb/Ce-PbO_2), an ultrapure water matrix with Na_2SO_4 as electrolyte, which significantly enhanced the reaction. Fabiańska et al. [63] treated high concentrations (5–55 mg/L) of IFO and CP in simulated water during 240 min. At the optimal conditions, with a current density of 16 mA/cm^2 and in the presence of inorganic ions (Cl^- and PO_4^{3-}), full removal efficacies were achieved. In the present study, more than 75 % removal is achieved with just 5 mA/cm^2 without the addition of further inorganic ions.

Regarding the rest of the treated compounds, their removal rises above 82 %. It is important to highlight that the effectiveness of the treatment is significantly impacted by the type of anode material used [21] and the surface area used, since a large one is required to improve the removal rate [66].

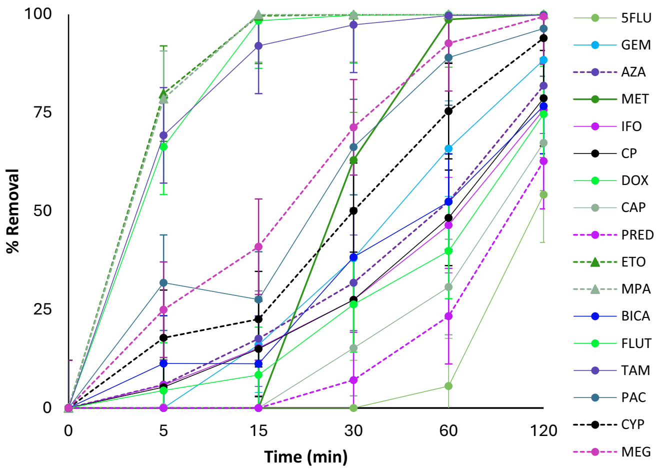

Fig. 6. Removal rates by electroxidation (BDD-SS) of sensitive cytostatic compounds in effluent (5 mA/cm^2).

3.4. *Overall assessment of the advanced oxidation processes*

The comparison of the three different AOP confirms the potential of the treatments and the need to extend their limits. None of them is capable of fully removing all 17 compounds in the spiked effluent.

Ozone doses of 200 mg O_3/L could reduce more than 90 % of ten compounds (5FLU, MET, DOX, CAP, ETO, MPA, TAM, PAC, CYP and MEG). However, FLUT and BICA showed a removal rate below 72 %. GEM, AZA, CP, IFO, and PRED were recalcitrant to ozonation. The gas-liquid mass transfer reaction is key to increasing these efficiencies, and further investigation is needed. The use of electroxidation as an additional treatment could improve the removal of GEM (88 %), AZA (82 %), CP (79 %), IFO, FLUT and BICA (75 %) and PRED (63 %). Photolysis is not viable to remove most of them, whereas photocatalysis improved the removal rates of AZA, PAC, CYP and MEG by 17 %, 50 %, 27 %, and 34 %, respectively.

The apparent kinetic degradation constants (k') of AOP during lab-scale trials treating the spiked effluent were calculated by using eq. (1) to evaluate the performance of the treatments (Table 1). This k' includes factors that were not quantified but effectively affected the processes, such as the mass transfer step of the reaction (especially for ozonation) or the punctual heterogeneity of the matrix, considering that not all the compounds present the same properties. The k' of the most degradable compounds follow a pseudo-first order equation, as also obtained in previous studies [47,58,64].

$$\frac{dC_i}{dt} = -k' \cdot C_i \tag{1}$$

This is an intermediate scenario between what researchers usually do in recent studies. On one hand, when kinetic studies are performed, pre-dissolving ozone in excess in ultrapure water with only the compounds to be studied is the main choice according to Beltran [13]. This configuration leads to the obtention of first-order reaction constants. On the other hand, when other factors are included such as stoichiometric oxidant concentrations or different water matrices, researchers obtain second-order reaction constants like Garcia-Ac et al. [48]. Nevertheless, due to the heterogeneous conditions of this study with different treatments and using lower doses of O_3, it has been selected the use of apparent pseudo-first order kinetic constants that allow the comparison between the different techniques and several other studies like {Citation} Garcia-Costa et al. [47]. Hence, this choice is aimed to gather heterogeneous information and put it into a common framework that allows a reasonable comparison for further studies.

Results in Table 1 demonstrate that ozonation was the most effective but also selective technique. For seven compounds (5FLU, MET, DOX, ETO, MPA, TAM and MEG) the k' values calculated were around 10^{-1} min^{-1}, for four compounds (CAP, BICA, CYP and PAC) present values of 10^{-2} min^{-1} and for six compounds (GEM, AZA, IFO, CP, PRED and FLUT) present values of 10^{-3} min^{-1}.

The k' values agree with the literature in magnitude order for similar photoxidation and electroxidation treatments, as shown in Table 2. Nevertheless, for ozone experiments, one order of magnitude lower was observed for most of the compounds. This is explained by the effect of the mass-transfer step and the complexity of the matrix.

In Table 2, there is a comparison between the calculated pseudo-first-order constants in this study and the ones obtained by other authors. Due to the limited availability of studies under comparable experimental conditions, most reported pseudo-first-order rate constants (k) refer to purified water matrices. Thus, comparisons are restricted and may not fully reflect real scenarios. This underscores the need for more studies in complex matrices, so contributing to this area remains essential forward the field.

The calculated k' were compared to those reported by Garcia-Costa

Table 1
Apparent kinetic constants of pseudo-first order of the AOP performed and the overall % removal after 120 min (green for % Removal >90 %, yellow for 50–90 %, light red for 25–50 % and dark red for <25 %).

Compounds	k' O_3 (min^{-1})	k' UVA (min^{-1})	k' UVA-TiO_2 (min^{-1})	k' EO* (min^{-1})	Removal O_3 (%)	Removal UVA (%)	Removal UVA-TiO_2 (%)	Removal EO* (%)
5FLU	0.249	Ø**	Ø	0.003	98	17	24	54
GEM	0.003	Ø	Ø	0.016	45	0	0	88
AZA	0.002	Ø	0.020	0.013	26	77	94	82
MET	0.175	Ø	Ø	0.182	100	19	35	100
IFO	0.001	Ø	Ø	0.011	18	0	11	76
CP	0.001	Ø	Ø	0.012	16	0	14	79
DOX	0.389	0.142	0.230	0.222	100	100	97	100
CAP	0.054	Ø	Ø	0.007	100	0	25	67
PRED	0.003	Ø	0.004	0.008	38	60	43	63
ETO	0.358	0.150	0.163	0.321	100	100	100	100
MPA	0.584	0.086	0.096	0.309	100	100	100	100
BICA	0.012	Ø	Ø	0.013	72	0	6	77
FLUT	0.006	Ø	Ø	0.010	58	11	20	75
TAM	0.249	0.090	0.131	0.226	100	93	75	100
PAC	0.050	Ø	0.043	0.034	92	16	66	96
CYP	0.078	Ø	0.023	0.023	99	34	61	94
MEG	0.290	Ø	0.028	0.041	99	32	66	99

[*] EO: electroxidation.

[**] Ø: Kinetic constant not evaluable.

Table 2
Comparison between kinetic apparent pseudo-first order constant values of the present study and literature.

Present study				Literature			
Compounds Code	Treatment	k' (min^{-1})	Matrix present study	k' (min^{-1})	Matrix literature	k' study / k' literature	Reference
5FLU	O_3	0.249	WW				
	O_3	0.088	UW				
	UV			0.03	UW		[17]
	UV/TiO_2			0.13			
	UV			0.045	UW		[67]
	EO	0.003	WW	0.0086			[64]
GEM	O_3	0.003	WW				
	UV	Ø		0.0869	UW		[58]
MET	O_3	0.175	WW				
	O_3	0.162	UW				
	TiO_2			0.230	UW		[57]
	EO	0.182	WW	0.0254		7.17	[64]
IFO	O_3	0.001	WW	0.015	UW	0.092	[47]
	EO	0.011	WW	0.0098		1.14	[64]
CP	O_3	0.001	WW	0.018	UW	0.062	[47]
	UV	0.0001	WW	0.0001	UW		
	TiO_2	0.01	WW	0.0103	UW		[17]
	EO	0.012	WW	0.0097		1.19	[64]
CAP	O_3	0.054	WW				
	UV			0.0532	UW		[58]
	UV			0.015			[67]
PRED	O_3	0.003	WW	0.055	UW	0.057	[15]
	O_3	0.116	UW				
	UV			1.622	UW		[58]
	TiO_2	0.004	WW				
ETO	O_3	0.358	WW				
	UV	0.150	WW	0.1262	UW	1.19	[58]
	TiO_2	0.163	WW				
MPA	O_3	0.584	WW				
	O_3	0.698	UW				
	UV	0.086	WW	0.0284	UW	3.03	[58]
	TiO_2	0.096	WW				
BICA	O_3	0.012	WW	0.021	UW	0.549	[47]
	UV			0.060	UW		[54]
FLUT	O_3	0.006	WW	0.015	NO ww	0.427	[68]
	UV			0.001	NO ww		[68]

UW: ultrapure water; WW: Wastewater.

et al. [47] for their ozonation experiments, which yielded higher values for a mixture containing BICA, CP and IFO. Specifically, they reported rate constants of $1.2 \cdot 10^{-2}$ min^{-1} for BICA, $1.8 \cdot 10^{-2}$ min^{-1}, and $3.4 \cdot 10^{-2}$ min^{-1} for CP and IFO, respectively. Notably, in their study, an ozone dose of 3 mg O_3/mg DOC was pre-dissolved in the water matrix, effectively eliminating gas–liquid mass transfer limitations and thus favoring the reaction kinetics. Additionally, they conducted experiments with individual compounds, resulting in rate constants of $2.1 \cdot 10^{-2}$, $1.8 \cdot 10^{-2}$ and $1.5 \cdot 10^{-2}$ min^{-1} for BICA, CP and IFO, respectively. These findings suggest a degree of selectivity when ozonation is applied to mixtures of contaminants, with IFO being more readily oxidized than BICA.

He et al. [15] calculated a k' for PRED of $5.49 \cdot 10^{-2}\ min^{-1}$ when using 7500 mg O_3/L of total dose, while in this study, it was obtained as $3 \cdot 10^{-3}\ min^{-1}$ with 200 mg/L. This difference is mainly due to the difference in the water matrix. He et al. [15] used ultrapure water without any further competitor contaminant able to reduce PRED' selectivity. This fact is also appreciated when comparing the preliminary experiments of this study with the final tests in wastewater with 17 compounds. Therefore, for scaling up the ozonation process these differences should be carefully considered.

UVA treatments showed a group of recalcitrant compounds, while others are rapidly degraded. DOX, ETO and TAM present values of $10^{-1}\ min^{-1}$ and AZA, MPA, PAC and MEG present values of $10^{-2}\ min^{-1}$. Franquet-Griell et al. [58] calculated k' (min^{-1}) of photolysis with UV-C for PRED (1.622), GEM ($8.7 \cdot 10^{-2}$), CAP ($5.3 \cdot 10^{-2}$), CP (10^{-4}), ETO (0.1262), MEG (0.0165), and MPA (0.0284). This behavior corresponds to the one presented in this study for those compounds prone to being affected by UV light.

Finally, electroxidation affected more compounds but the distribution of values regarding k' was wider: DOX, ETO, MPA and TAM present values of $10^{-1}\ min^{-1}$; GEM, AZA, IFO, CP, BICA, FLUT, PAC, CYP and MEG present values of $10^{-2}\ min^{-1}$; and CAP, PRED, 5FLU around $10^{-1}\ min^{-3}$. This information agrees with the previous bibliographic data. Siedlecka et al. [64] calculated k' (min^{-1}) values of $8.6 \cdot 10^{-3}$ for 5FLU, $9.8 \cdot 10^{-3}$ for IFO, $9.7 \cdot 10^{-3}$ for CP and $2.54 \cdot 10^{-2}$ for MET, although they used 16 mA/cm^2 and 6 g/L of Na_2SO_4 to enhance the reaction. Nevertheless, their reaction surface area was 12.5 $cm^{2,}$ whereas in the present study, electrodes of 200 cm^2 were used.

To conclude this comparative analysis, a summary of the advantages and limitations of each treatment is presented. Ozonation was the most effective and fastest technique overall, but only for ozone-sensitive compounds, due to its high selectivity. UVA-based treatments exhibited two distinct behaviors: a group of recalcitrant compounds showed minimal degradation (<25 %), while others were rapidly and effectively removed (>90 %), indicating a challenge in achieving broad-spectrum efficiency. Electrooxidation showed the broadest effectiveness, impacting a wider range of compounds, with removal percentages between 54 % and 100 %, making it the most consistently efficient method across different cytostatic pharmaceutical pollutants.

4. Conclusions

The removal of a complex mix of 17 cytostatic compounds, each at 25 μg/L, in real wastewater effluents was evaluated using ozonation, photodegradation and electroxidation. Ozonation with 200 mg O_3/L achieved over 90 % removal for ten of the cytostatics; photocatalysis, with 500 mg/L of TiO_2, reached similar removal levels for four compounds; and electroxidation, with BDD/SS electrodes, resulted in over 90 % removal of eight compounds. None of the individual technologies were able to eliminate all contaminants. However, combining several treatment processes (e.g ozone and electrooxidation) may extend the limitations of single approaches, as each compound exhibited susceptibility to at least one of the tested technologies. Ozone efficiency when treating complex wastewater should not be underestimated for the design of quaternary treatments. Results show that large-scale treatments cannot be based on studied carried out with UP waters since the doses required to remove micropollutants are 10–20 times higher and the kinetic constants when treating WWTP effluents are 2.5–18 times slower than the obtained when working with UP-W. However, in the case of photocatalysis the differences are much lower only 1.2 slower and, in the case of electrooxidation, the k' for real wastewater is 1,2 times faster than in UP-W.

Due to the need of severe treatments, further investigations should be conducted to broaden the current limits of the individual technologies, since their yield is affected by several operational factors that could be enhanced, such as gas-liquid mass transfer for ozonation, electrode surface in electroxidation, or catalyst performance in photocatalysis. Due to the high costs of the ozone treatment at high dosages, the adaptation of current ozonation processes will be limited. Research should focus on improving mass transfer in large-scale reactors to increase ozone efficiency and reduce the dose. In this sense nano-ozonation is a very promising alternative. Moreover, given that complete mineralization was not achieved, it is essential to conduct further toxicological assessments to ensure that degradation by-products do not pose greater risks than the parent compounds.

CRediT authorship contribution statement

Cristina Corpa: Writing – review & editing, Writing – original draft, Validation, Methodology, Investigation. **Guillermo Nieto:** Writing – review & editing, Writing – original draft, Investigation. **M. Concepción Monte:** Writing – review & editing, Supervision, Formal analysis. **Ana Balea:** Writing – review & editing, Supervision. **Isabel Lopez-Heras:** Writing – review & editing, Formal analysis. **Angeles Blanco:** Writing – review & editing, Writing – original draft, Supervision, Resources, Project administration, Funding acquisition, Formal analysis, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jwpe.2025.108711.

Data availability

Data will be made available on request.

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