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Advanced oxidation and a metrological strategy based on CLC-MS for the removal of pharmaceuticals from pore & surface water

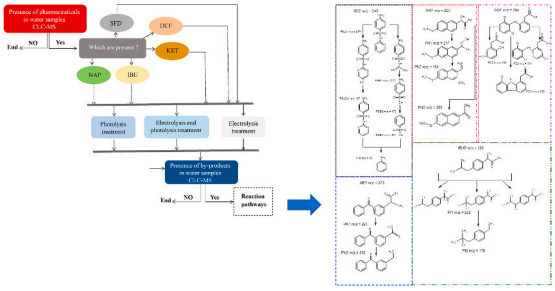
Jihène Ben Attig [a,b,c], Fernanda Lourdes Souza [d], Latifa Latrous [c], Pablo Cañizares [e], Cristina Sáez [e], Ángel Ríos [a,b], Mohammed Zougagh [b,f], Manuel Andrés Rodrigo [e,*]

[a] Department of Analytical Chemistry and Food Technology, Faculty of Chemical Sciences and Technologies, University of Castilla-La Mancha, Campus Universitario, 13071, Ciudad Real, Spain
[b] Regional Institute for Applied Scientific Research, IRICA, Camilo José Cela Avenue, E-13005, Ciudad Real, Spain
[c] Laboratoire de Chimie Minérale Appliquée, Department of Chemistry, Faculty of Sciences of Tunis, University of Tunis El Manar, University Campus of El Manar II, 2092, Tunis, Tunisia
[d] Department of Chemistry and Molecular Physics, Institute of Chemistry of São Carlos, Trabalhador São-Carlense Avenue, 400, CEP 13566-590, São Carlos, SP, Brazil
[e] Department of Chemical Engineering, Faculty of Chemical Sciences and Technologies, Universidad de Castilla - La Mancha, Campus Universitario S/n, 13071, Ciudad Real, Spain
[f] Department of Analytical Chemistry and Food Technology, Faculty of Pharmacy, University of Castilla-La Mancha, 02071, Albacete, Spain

HIGHLIGHTS

- CLC-MS screening of pharmaceuticals in waters and detection at concentrations lower than 10 ng mL^{-1}.
- Removal of a mixture of five drugs was evaluated using several EAOP.
- Ibuprofen more recalcitrant than sulfadiazine, naproxen, diclofenac and ketoprofen.
- Photo-electrolysis more efficient than photolysis and electrolysis.
- Important differences in reactions pathways proposed for each technology studied.

GRAPHICAL ABSTRACT



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ABSTRACT

In this work, it is studied the photolysis, electrolysis, and photo-electrolysis of a mixture of pharmaceutics (sulfadiazine, naproxen, diclofenac, ketoprofen and ibuprofen) contained in two very different types of real water matrices (obtained from surface and porewater reservoirs), trying to clarify the role of the matrix on the degradation of the pollutants. To do this, a new metrological approach was also developed for screening of pharmaceuticals in waters by capillary liquid chromatography mass spectrometry (CLC-MS). This allows the detection at concentrations lower than 10 ng mL^{-1}. Results obtained in the degradation tests demonstrate that inorganic composition of the water matrix directly influences on the efficiency of the drugs removal by the different EAOPs and better degradation results were obtained for experiments carried out with surface water. The most recalcitrant drug studied was ibuprofen for all processes evaluated, while diclofenac and ketoprofen were found to be the easiest drugs for being degraded. Photo-electrolysis was found to be more efficient than photolysis and electrolysis, and the increase in the current density was found to attain a slight improvement in

* Corresponding author.
E-mail address: manuel.rodrigo@uclm.es (M.A. Rodrigo).

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the removal although with an associated huge increase in the energy consumption. The main reaction pathways for each drug and technology were also proposed.

1. Introduction

In the last decades, with the development of more and more sensitive analytical techniques, scientist have realized that presence of micropollutants in natural sources of water has become a major environmental problem (Sires and Brillas, 2012b; Feng et al., 2013; Luo et al., 2014). Initially, the extremely low concentrations detected were considered irrelevant, but recent studies have suggested a major influence on human health and viability of ecosystems, existing a direct correlation between the occurrence of these pollutants and the significance of the problems associated (Radjenovic et al., 2009; Matamoros et al., 2012; Pais and Nascimento, 2018; Fonseca et al., 2020). Proliferation of antibiotic resistant bacteria, and the increasing seriousness of endocrine disruption related illnesses, are worth to be highlighted, although they are not the only problems arising (Wu et al., 2010; Pais and Nascimento, 2018). The key actions to prevent the spreading of these species in the environment should be taken in the effluent of the municipal wastewater treatment plants, because this is the point in which the pollutants are more concentrated and, hence, where the treatments can be more effective (Vieno et al., 2007; Klavarioti et al., 2009; Radjenovic et al., 2009; Rodrigo et al., 2010; Urtiaga et al., 2013). However, the more urgent actions are required in drinking water sources trying to prevent the negative effects of these micropollutants on human health (Wu et al., 2010; Martínez-Huitle et al., 2023; Pais and Nascimento, 2018).

Pharmaceuticals is one of most important group of pollutants from the viewpoint of impact on environment and health (Hirsch et al., 1999; Klavarioti et al., 2009; Pais and Nascimento, 2018; Patel et al., 2019). The increase in their consumption have led to a serious environmental problem (Kummerer, 2009). They can enter into the environment from factories, hospitals, disposal of unused or expired drugs, and municipal wastewater treatment plants (Sim et al., 2013; de Oliveira et al., 2020). Some pharmaceuticals have persistent and recalcitrant characteristics, which makes the task of their complete removal through wastewater treatment processes very difficult (Wellington et al., 2013; Samal et al., 2022). As a consequence, they have been found in sewage treatment plant effluents, surface and drinking waters in many countries as China (Bo et al., 2015; Waleng and Nomngongo, 2022), the Mexico (Brown et al., 2006), Switzerland (Soulet et al., 2002), United States (Subedi and Kannan, 2015), England (Jones et al., 2007), Italy (Castiglioni et al., 2004; Feo et al., 2020), Turkey (Üstün et al., 2020) and Spain (Fonseca et al., 2020) at concentrations ranging from ng L^{-1} level to μg L^{-1}. Antibiotics and nonsteroidal anti-inflammatory drugs (NSAIDs) are the most widely used drugs in Europe and the USA which explain their high occurrence in water bodies (Wellington et al., 2013; Yang et al., 2017). The continuous accumulation of pharmaceuticals into the environment may cause negative effects in the aquatic or terrestrial ecosystems (Wellington et al., 2013; Ebele et al., 2017). It can induce behavioral changes in fish, affecting fish aggression, reproduction, and feeding activity (Ebele et al., 2017; Yang et al., 2017). Moreover, occurrence of antibiotics in the aquatic environment may develop antibiotic-resistant bacteria (Wellington et al., 2013).

Due to the low concentrations of antibiotics and NSAIDs and the intrinsic complexity of the water samples, efficient sample screening and degradation is required in treatment procedures (Castiglioni et al., 2004; Pedrouzo et al., 2007; de Oliveira et al., 2020). The availability of rapid and reliable screening methods is an important prerequisite when a large number of samples must be treated, in order to meet the urgent need for decontamination. The screening methods are defined as methods that are used to detect the presence of an analyte, or analyte group, at the concentration level of interest. Screening methods typically feature a high sample throughput and are used to sift large numbers of samples for potential positives. These methods avoid or reduce the routine use of more expensive and sophisticated degradation procedures. In this work, we are aiming to combine the advantages of capillary liquid chromatography mass spectrometry (CLC-MS) for the screening of emerging pollutants waters and efficient treatments to their degradation.

Regarding treatment, the complexity of many active ingredients of these medicines makes that biological treatments are not very efficient in their degradation and push the research on advanced oxidation processes (Stackelberg et al., 2004). Among these processes, it is worth to remark electrochemical advanced oxidation processes (EAOPs), because of their robustness and high efficiencies in the mineralization of the bare compounds and their metabolites (Sires and Brillas, 2012a; Panizza et al., 2014; Sirés et al., 2014; Martínez-Huitle et al., 2023; Cotillas et al., 2018; Loos et al., 2018; Lacasa et al., 2019). This has been confirmed in low TRL (technology readiness level) studies in which synthetic wastewaters polluted with very high concentrations of this species has been evaluated (typically in the range of 10^2–10^3 ppm of the pharmaceutical) with selected salts as main component of the water matrix (typically sodium sulfate and chloride) (Cotillas et al., 2018). These studies were very useful to confirm the good prospects of these technologies for the removal of the organics and to propose the oxidative reaction pathways of the pharmaceuticals, but they lack significance for real applications, because in the environment the concentration of these species is several folds below and the components of the water matrix are completely different (Mamelkina et al., 2017). As well, the combination of different types of AOP have been studied at these low TRL of 4–5, demonstrating that the combined effect of light irradiation or ultrasound applications with the electrolytic processes is not always positive and shedding light on the ways to make these combinations synergistic. Now, the interest is focused on the increase of the TRL of these studies, trying to face more realistic treatment cases of study. Low concentration is a real challenge but also the interaction of the real ionic components of the water matrix with the pollutants during the treatment, which is a goal of TRL 5–6 studies. There are strong differences between porewater and surface water, related to their different ionic speciation, which may have an impact on the performance of the electrochemical treatment.

This work compares the photolysis, electrolysis, and photoelectrolysis of a mixture of five pharmaceuticals in real water samples took directly from surface and porewater reservoirs and characterized by a very different ionic real speciation, in order to give information about the degradation of each pollutant, trying to shed light on the performance of the evaluated technologies. The five pharmaceuticals are sulfadiazine, naproxen, diclofenac, ketoprofen and ibuprofen, selected because they were found to be among the most relevant in environment. A new metrological approach for screening of pharmaceuticals in waters by capillary liquid chromatography mass spectrometry (CLC-MS) was also developed and used and, in addition, for the pore water matrix, the by-products formed were monitored and the main reaction pathways for each drug and technology were proposed.

2. Experimental

Water samples. In this work, real samples of porewater and surface water are intensified with a mixture of pharmaceuticals. Porewater samples (Water Matrix 1, WM_1) correspond to a large groundwater reservoir (Aquifer 23) placed in the center of Spain and were collected in well placed in the proximity of the town of Daimiel (Spain). Surface water samples (Water Matrix 2, WM_2) were taken from Gasset dam, near the town of Malagón (Spain). Distance between both towns is lower than

25 km and mineralogy of the placements are quite similar. Main characteristics of the matrices before being intensified with the pharmaceuticals are shown in Table SM1. Regarding pharmaceuticals, sulfadiazine (SDZ), naproxen (NAP), diclofenac (DIC), and ketoprofen (KET) and ibuprofen (IBU), were analytical grade from Sigma-Aldrich (St. Louis, USA) and used as received. For the study, both matrices were doped with 1 μg mL^{-1} of each analyte (SDZ, NAP, DIC, KET and IBU).

Experimental set-up & characterization procedures. Photolysis, electrolysis, and photo-electrolysis tests were carried out in a single compartment electrochemical flow cell connected to a bulk reaction tank. A volume of 500 mL of real doped water was recirculated at a constant flow rate of 26.4 dm^3 h^{-1}. During photolysis and photo-electrolysis tests, and UV lamp of 11.0 W and wavelength of 254 nm was used. UV-light was irradiated directly to the tank. All experiments were conducted for 1.0 h and samples were taken at defined times along the experiments. Temperature of the system was kept constant (25 °C) by means of a thermostatic bath (JP Selecta, Digiterm S-150) and a heat exchanger.

Electrochemical cell was equipped with a boron-doped diamond electrode provided by Adamant Technologies (Neuchatel, Switzerland) as anode and a grid of stainless steel as cathode. Both electrodes were circular (100 mm diameter) covering a geometric area of 78 cm^2. The thickness of the BDD coating was 2–3 μm of the thickness, the boron concentration was 500 ppm, and the sp^3/sp^2 ratio was 176.

The monitored parameters were pH and conductivity of the solution, total oxidants concentration, pharmaceutics concentration evolution and intermediates generated. The evolution of the pH and conductivity were determined by a pH-meter Crison pH25+ and a conductivity-meter Crison CM35+ (Crison Instruments, Spain), respectively. Total oxidants were determined by iodometric titration method using a volumetric titration system Metrohm Titrino SM 702 coupled to Tiamo PC software by Metrohm©.

A capillary LC pump (Agilent series 1200, Waldbronn, Germany) was utilized for the chromatographic system. For the chromatographic separation of the analytes a ZORBAX SB-C18 (150mm × 0.5 mm, 5 μm particle size) analytical column from Agilent Technologies was used. Detection was carried out with a UV–Vis diode array detector (Agilent, 1260 infinity model) equipped with a 2 μL flow cell coupled in series to an Agilent 6110 series quadrupole MS detector (Waldbronn, Germany) equipped with an atmospheric pressure ionization source electrospray (API-ES). Spectroscopic properties were obtained on a Secoman spectrometer.

Analytical strategy to be followed for screening and degradation of pharmaceuticals. The whole procedure followed in this work is schematically shown in Figure SM1. For screening of pharmaceuticals by capillary liquid chromatography mass spectrometry (CLC-MS), water samples were spiked with 1 μg mL^{-1} of SDZ, NAP, DCF, KET and IBUP and directly analyzed without any further treatment. The chromatogram obtained must provide the binary (yes/no) response about the presence or the absence of the pharmaceuticals in samples. Once the analytes are identified and quantified by CLC-MS, photolysis, electrolysis, and photo-electrolysis tests were carried out for their simultaneous removal from real water samples. The by-products formed after the treatments were monitored and identified using CLC-MS. Subsequently, main reaction pathways for each drug and technology were proposed.

CLC-MS conditions. For DAD detection, the wavelengths were fixed at 221 (IBUP), 227 (NAP), 251 (SDZ), 258 (KET) and 275 nm (DCF) and 227 nm. The optimal operating parameters for the MS detector in negative ionization mode were drying gas flow 13.0 L min^{-1}, drying gas temperature 200 °C, nebulizer pressure 59.94 psi and capillary voltage 4500 V. Selected ion monitoring (SIM) was used to detect and quantify the target analytes using external calibration. Previously, the analytes were qualitatively determined at full scan mode and matching their retention time and mass spectra with standards. The maximum peaks in mass spectra ions were: 249 (SDZ), 229 (NAP), 294 (DCF), 253 (KET) and 205 (IBUP).

Chromatographic analyses were carried out using a gradient consisting of 0.1% acetic acid in water as solvent A and acetonitrile as solvent B. The flow rate was 10 μL min^{-1}. The gradient elution was started with 20% solvent B, then increasing up to 50% of B until 13min, 100% of B until 16 min and decreasing to 20% of B until 18 min and kept constant for the final 7 min. Injection volume was 5 μL and the column was maintained at a temperature of 25 °C. At the end of the day, the column was flushed with pure acetonitrile to remove impurities and all channels were purged with pure isopropyl alcohol on a weekly basis. All solvents were filtered through a 0.45 μm nylon membrane before their use.

3. Results and discussion

Optimization of separation and detection of pharmaceutics by CLC-MS. Variables involved in CLC-MS analyses were optimized, the most critical being mobile phase composition, gradient elution, injection volume, flow rate, drying gas flow, drying gas temperature, nebulizer pressure and capillary voltage. The optimal experimental conditions are summarized on Table SM2, including both variables assayed in certain ranges.

Mobile phase composition and gradient elution were tested as already described in literature [24] with some modifications. To optimize the MS detection of each analyte, the drying gas flow was investigated within the 5–13 L min^{-1} range and 13 L min^{-1} gave the best results in terms of the peaks area. The temperature of the drying gas was also studied in a range from 50 to 300 °C, more than 200 °C decreasing of signal intensity of all the analytes was observed. So, the best results were obtained when 200 °C was applied. Additionally, the nebulizer pressure, ranging from 38, 67 to 59, 94 psi, was investigated and the 59, 94 psi was selected. Capillary voltage was varied from 2500 to 4500 V. As the voltage was increased, better peak areas were observed and, consequently a 4500 V voltage was selected. Therefore, under these experimental conditions, pharmaceutics species were separated and quantified in 25 min with excellent resolution. Once all these conditions were fixed, the same procedure was followed in all cases with the aim to follow the degradation of pharmaceutics and the evolution of their by-products by means CLC-MS analyses and, eventually, conduct subsequent experiments to assess the analytical performance of this new methodology in water samples in terms of repeatability and both detection and quantification limits. To identify pharmaceuticals based on their retention time, standard solutions were initially analyzed by CLC with conventional UV detection, first one by one and then in a mixture of them all. Once the analytes were identified it was necessary to quantify them given that conventional UV detection is not sensitive enough for this purpose. Thus, the LC device was coupled to a single quadrupole MS. Firstly, several analyses of the mixture in scan mode were performed to gather the MS spectra of every single chemical and select the ions to be monitored in SIM mode. Sensitivity provided by SIM is higher than scan mode, therefore SIM was chosen. All spectra showed the molecular peak as the main one in all cases, and empirical molecular weight values confirmed this fact. Then target ions for all compounds were introduced as MS parameters for SIM mode operation. They were: 249 for SDZ, 229 for NAP, 294 for DCF, 253 for KET and 205 for IBUP. As NAP and KET have the same retention time ($t_r = 17$ min) and also DCF and IBUP ($t_r = 19$ min), two channel was necessary to monitor all ions. The analytes would be clearly identified by their characteristic ions after fixing their monitoring times in the SIM settings.

Analytical characteristics of the method and intended use for water sample. The performance of the whole method was evaluated under the optimized conditions using spiked water samples. External calibration curves using peak areas were obtained by injecting 6 mixture standard solutions of SDZ, NAP, DCF, KET and IBUP in the 10–1000 ng mL^{-1} range. At least three replicates were analyzed at each concentration level. Each solution contained the five pharmaceutical standards

used in this work. Linear range, calibration equation and other figures of merit are summarized in Table SM3. Repeatability values of peak areas were obtained by injecting a mixture of the 5 pharmaceuticals containing 1000 ng mL^{-1} of each standard (n = 11). Repeatability values ranging from 3.48% to 8.61% and from 0.12% to 0.31% were found for peak area and retention time, respectively.

The limit of detection (LOD) and quantification (LOQ) defined as the concentration of analyte that produces a signal equivalent to the blank signal plus three times the standard deviation ($Y_{LOD} = Y_b + 3\,S_b$) and ten times the standard deviation ($Y_{LOD} = Y_b + 10\,S_b$) respectively, for each individual pharmaceutical analyte. In this case, because of the coincidence of the background signal with the blank signal, intercept values and their corresponding standard deviation from the calibration equations were taken for LOD and LOQ calculations.

As observed in Table 1, the limits of detection and the limits of quantification ranged from 2.96 to 7.95 ng mL^{-1} and from 9.87 to 26.5 ng mL^{-1}, respectively, which were quite reasonable using MS with CLC.

The proposed CLC-MS method can be adapted to other specific cases depending on the particular pharmaceutic analyte added to water sample and the cut-off set. Thus, a 'worst scenario' can be established for sample screening by choosing the least sensitive studied analyte as the criterion for classifying samples as positive or negative. So-called "positive samples" can be further processed by photolysis, electrolysis, and photo-electrolysis for their simultaneous removal from real water samples.

Degradation of pharmaceuticals by photolysis, electrolysis, and photo-electrolysis. Fig. 1 shows the removal of the drugs during the photolytic process for both water matrices.

KET was quickly and completely degraded within 5 min of light irradiation, while IBUP was the most recalcitrant compound attaining less than 50% of removal after 1.0 h of treatment. DCF and SDZ are degraded faster in WM_1 and NAP in WM_2, pointing out the important influence of the components of the water matrices on the degradation of these species. These results agree with others found in the literature. Thus, the high efficiency of photolysis in the degradation of DCF was also demonstrated by Kovacic et al. (2016), which complete DCF conversion into by-products within 9 min of treatment in a batch photoreactor (0.8 L containing 29.62 mg L^{-1} at pH = 5.78 and T = 25 °C). The low degradation rates of IBUP were also demonstrated by Szabó et al. which showed that the photodecomposition rate of ketoprofen is almost forty times higher than that of ibuprofen in a tubular photoreactor with a UV lamp 15 W at 254 nm containing a mixture of the drugs at an initial concentration of 1.0×10^{-4} M. The refractory character of IBUP was also highlighted elsewhere (Rodriguez-Chueca et al., 2019), which demonstrate very low degradation rates when advanced photochemical processes were applied in the treatment of seven different micropollutants.

Fig. 2 shows the degradation of the drugs in the two water matrices during the electrolysis at the two current densities applied. Part a shows that the electrochemical process was very effective in the drug removal specially for DIC, NAP and SFD compounds, for which 100% of removal was attained within the first 15 min of electrolysis. Besides, the increase in the current density resulted in improved degradation rates for all compounds, mainly for NAP, with an improvement of 40%. Also, important increases for KET and IBUP, which obtained 30 and 10% of improvement in the removal percentage, respectively. On the other hand, Part b shows that the drugs removal was faster in WM_2 as compared to WM_1, being almost all drugs completely removed at the beginning of the treatment. In this case, the application of higher current densities does not result in the improvement of the drugs removal, because the process is extremely fast even at the low values.

The combination of photolysis and electrolysis can remove all drugs within 1.0 h of treatment as shown in Fig. 3. For WM_1 (Part a) the degradation rates decrease in the sequence DIC > KET > SFD > NAP > IBUP. Photo-electrolysis was found to be slightly more efficient at highest current density with an improvement around 10% for SFD and KET removal and 20% for NAP. This may be associated to a higher generation of oxidants in the medium responsible to quickly remove the drugs. Experiments carried with WM_2 (Part b) shows that all the drugs were completely removed within the first 15 min of electrolysis and this faster removal can be explained by the great radical species electrogeneration in this medium followed by their photoactivation.

The energy consumption (EC), calculated from the values of the cell voltage (E), current intensity (I), time (t) and reaction volume (Vr) as shown in eq. (1), is a very important parameter that should be considered for the comparison of technologies. In this work, the values were calculated within 1.0 h of treatment.

$$EC = (E \cdot I \cdot t)/V_r \quad (1)$$

The energy consumption during the electrolysis process were 21.37 at 10 mA cm^{-2} and 119.0 kW h m^{-3} at 30 mA cm^{-2} for WM_1 while for WM_2 the EC values were 18.56 and 114.6 $kWhm^{-3}$ at 10 mA cm^{-2} and 30 mA cm^{-2}, respectively. This means that for both water matrices the increase in current density is not worth it. In the photo-electrolysis treatment, the energy consumption considers the energy requirement of the electrolytic process plus those from UV-C lamp used in the photolytic treatment. In this way, the energy consumption for photo-electrolysis treatment during the experiment with WM_1 were 49.27 and 141.15 $kWhm^{-3}$ at 10 mA cm^{-2} and 30 mA cm^{-2}, respectively. The results for WM_2 were 47.0 and 141.3 $kWhm^{-3}$ at 10 mA cm^{-2} and 30 mA cm^{-2}, respectively. This corresponds to an increase in the energy consumption with respect to only electrolysis process of 2.3 and 1.1 times for experiments carried with WM_1 and 2.7 and 1.2 times for WM2 at 10 mA cm^{-2} and 30 mA cm^{-2}, respectively. However, comparing the water matrices, once the time necessary to total removal of the drugs decreased significantly (from 1 h at WM_1 down to 15 min at WM_2), the energy consumption drops equally and the photoelectrochemical process becomes attractive.

Figure SM2 shows the evolution of pH (a, b) and the conductivity (c, d) for both water matrices. No regulation was made during the tests. For WM_1 (Part a), a very different behavior is observed between the photolysis and electrolysis processes. Thus, a slight increase in the pH of the solution is observed during the photolysis and a decrease in the pH is observed for electrolysis at 10 mA cm^{-2} and for photo-electrolysis processes, while for electrolysis at 30 mA cm^{-2} the pH does not suffer significant changes. This can be related to higher formation of

Table 1
Calibration data and figures of merit for the LC-MS confirmation method.

Analyte	Linear range (ng mL^{-1})	$Y = (a \pm S_a)X + (b \pm S_b)$	R^2	Sy/x	Repeatability, RSD (%)		LoD (ng mL^{-1})	LoQ (ng mL^{-1})
					Peak area	t_r		
SDZ	30–1000	(474.8205 ± 2.5032)X +(-7846.8079 ± 1258.2811)	0.9999	2092.6951	3.48	0.13	7.9500	26.5001
NAP	20–1000	(1563.1993 ± 6.5818)X + (9281.8806 ± 3020.7145)	0.9999	5820.8517	4.52	0.23	5.7972	19.3239
DCF	30–1000	(444.1457 ± 2.1868)X + (−14.3728 ± 1099.2618)	0.9999	1828.2242	4.86	0.31	7.4250	24.7500
KET	10–1000	(1501.8246 ± 3.4887)X + (5896.4591 ± 1482.4203)	1	3209.1737	4.89	0.23	2.9612	9.8708
IBUP	20–1000	(566.4911 ± 2.4468)X + (3305.6858 ± 1122.9450)	0.9999	2163.8907	8.61	0.12	5.9468	19.8228

a: slope (mV ng mL-1); Sa: standard deviation of the solpe; b: intercept (nA); Sb: standard deviation of the intercept; R: regression coefficient; Sy/x: standard deviation of residuals; LoD: limit of detection; LoQ: limit of quantification, RSD: relative standard deviation (n = 11) for pharmaceuticals concentration of 1000 ng mL-1.

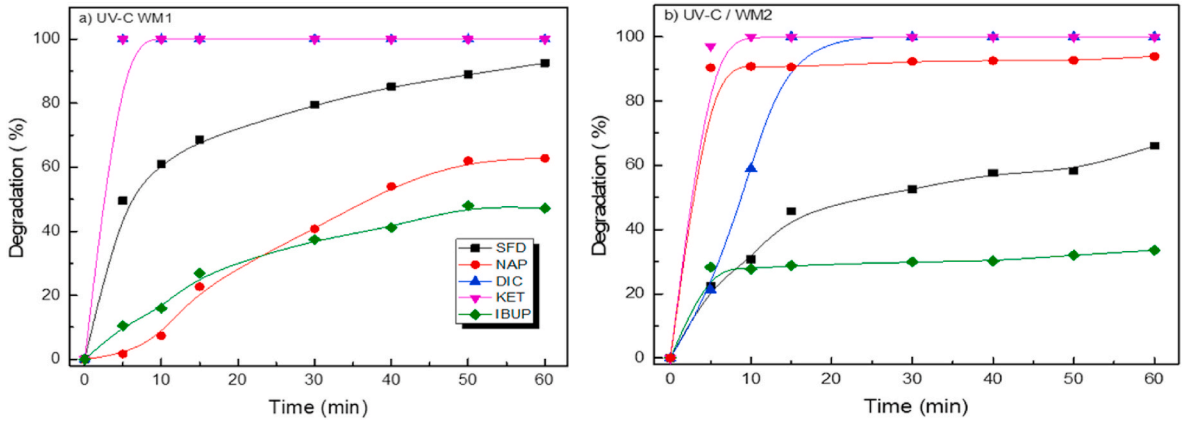

Fig. 1. Degradation of drugs during the photolysis treatment (■) SDZ, (●) NAP, (▲) DIC, (▼) KET, (◆) IBUP. Water Matrix: a) WM_1 and b) WM_2.

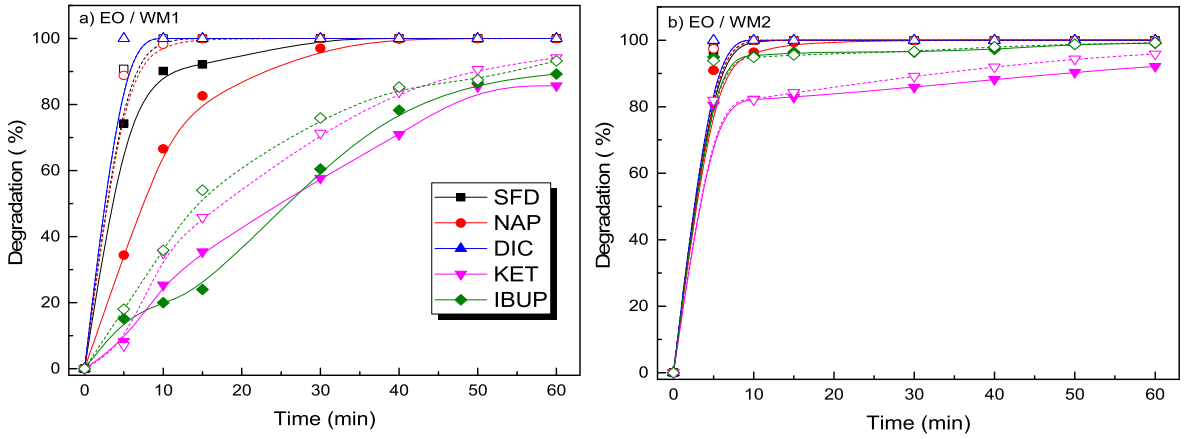

Fig. 2. Degradation of drugs during electrolysis treatment. Full points 10 mA cm^{-2} and empty points 30 mA cm^{-2} (■) SDZ, (●) NAP, (▲) DIC, (▼) KET, (◆) IBUP. Water Matrix: a) WM_1 and b) WM_2.

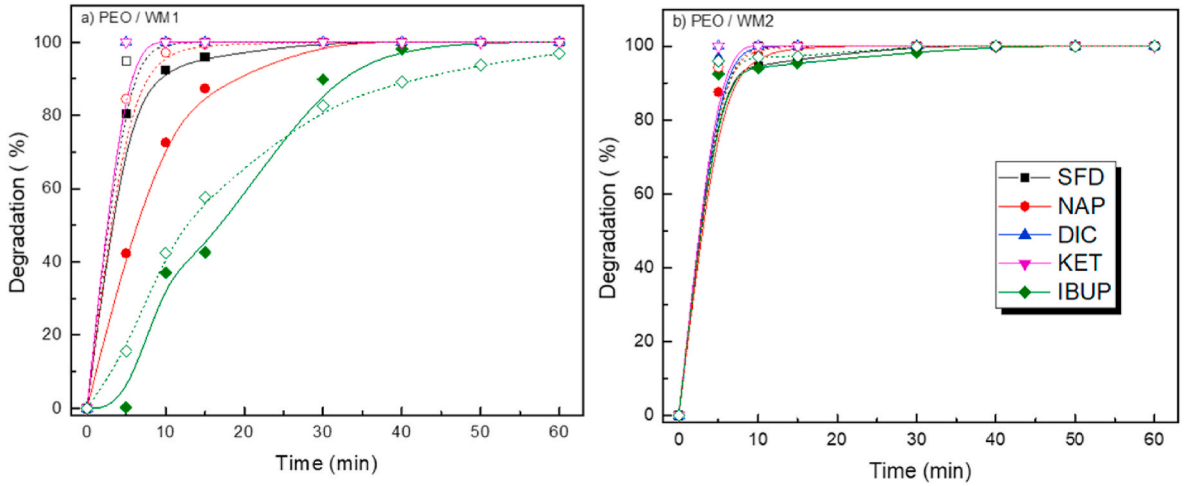

Fig. 3. Degradation of drugs during photo-electrolysis treatment. Full points 10 mA cm^{-2} and empty points 30 mA cm^{-2} (■) SDZ, (●) NAP, (▲) DIC, (▼) KET, (◆) IBUP. Water Matrix: a) WM_1 and b) WM_2.

carboxylic acids at the end of treatments. For WM_2 (part b) no significant pH changes were observed for all processes studied. Conductivity does not show any relevant changes with any of the technology, matrices or conditions applied.

Fig. 4 shows the evolution of total oxidants for all technologies evaluated. As clearly shown, lower oxidants concentrations were produced during the photolytic process. Similar oxidants concentrations were obtained at lower current density for both water matrices. However, at 30 mA cm^{-2} higher concentrations of oxidants remain in the water matrix 2 (part b). This can be explained in terms of the higher concentration of sulfate and chloride ions contained in this water matrix (as shown in Table 1). As it known, these species can be electrolytically

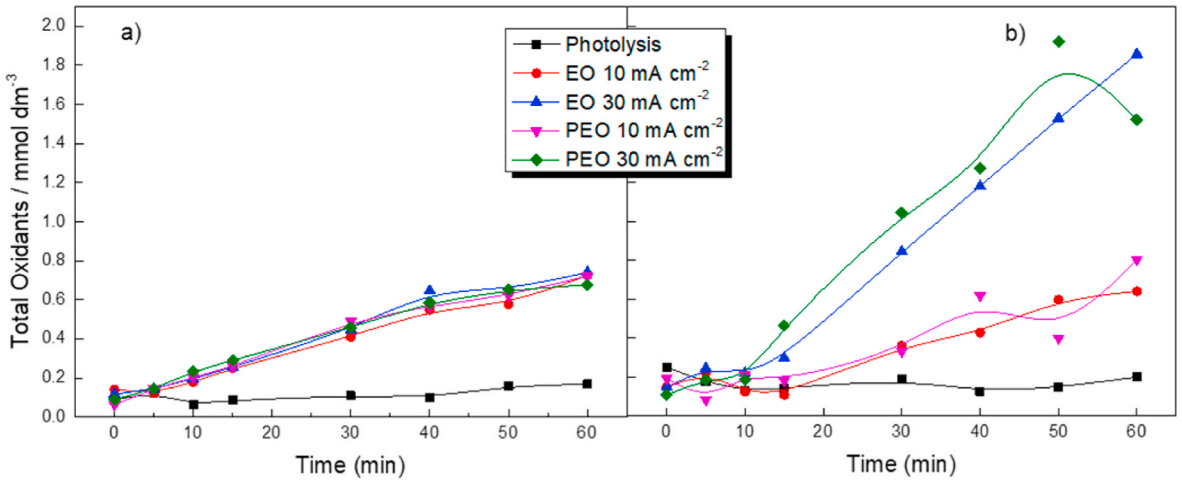

Fig. 4. Total oxidants obtained over time during the (■) photolysis, (●) electrolysis at 10 mA cm^{-2}, (▲) electrolysis at 30 mA cm^{-2}, (▼) photo-electrolysis at 10 mA cm^{-2}, (◆) photo-electrolysis at 30 mA cm^{-2}. Water Matrix: WM_1 (part a); WM_2 (part b).

and photolytically activated generating powerful radicals in the medium responsible to attack the pharmaceutical compounds (Lourdes Souza et al., 2014).

Identification of by-products and mechanism proposal. In the case of doped porewater, the by-products formed were monitored to shed light on the oxidation pathways of the three technologies. Thus, for each technology studied, samples collected at regular time intervals were injected into the MS. Table SM4 shows the identified products, as well their structure, *m/z* ratio, retention time and % of relative abundance for each technology tested. As can be seen, numerous by-products could be identified for three technologies studied (up to 21 aromatics intermediates). In terms of technology, photo-electrolysis was found to have more intermediates detected, which can be attributed to the higher rate of oxidation reactions. On the other hand, the photolytic process resulted in less degradation of compounds and consequently, fewer intermediates detected. As previously mentioned, out of the drugs added to the matrices, IBUP was the most resistant compound, and identifying its by-products was more challenging than the other drugs.

Based on the detected intermediates, and at the light of the current literature, possible degradation schemes for each compound were proposed for photolysis, electrolysis and photo-electrolysis treatments. Fig. 5 shows the proposal for the main photodegradation pathways. SFD suffers a cleavage in the pyridine ring forming the compound PS_1. Subsequently, radical hydroxyl attack *S*–N bond, which through hydroxylation generates the compound PS_2. Finally, the amine group (NH_2), was cleaved forming the compound PS_3. Similar degradation mechanism of SDF also was proposed by Yadav et al., 2018) (Yadav et al., 2018) during UV-C/TiO_2 treatment. Sulphaniclic acid also was identified as by-product of degradation of SDZ by gamma-ray irradiation which can be further oxidized forming 4-aminophenol and 4-nitrophenol as shown by Liu et al., 2014) (Liu et al., 2014). For NAP two main aromatics products were detected suggesting that the first stages of the photooxidation consists of its decarboxylation forming the 1-(6-methoxynaphthalen-2-yl)ethyl hydroperoxide (PN_1 m/z = 217). The latter is broken forming the olefin 2-ethenyl-6-methoxynaphthalene carboxylic acid (m/z = 184). The by-products detected at retention times of 4.9 min, 16.09 and 18.0 min with m/z 259 (PD_1), 311 (PD_2) and 255 (PD_3) respectively, were identified as by-products from photodegradation of DCF. The product PD_1 comes from the loss of one chlorine atom followed by cyclisation and formation of (8-chloro9H-carbazol-1-yl) acetic acid. The MS fragmentation process of the PD_1 yielded fragment ions at m/z = 214 and 179 helping to confirm its identification. Then, PD_1 may loss the second chlorine and, then, the molecule can attach 2 oxygen atoms through the double bonds (PD_3, m/z 255). PD_2 was identified as an epoxide based on its m/z 310, which is 14 units higher than parent compound suggesting the addition of oxygen and loss of 2 hydrogen atoms. This by-product also was identified by other authors after photolysis of DCF (Salgado et al., 2013; Kovacic et al., 2016). The products identified as 1-(3-benzoylphenyl) ethenone and (3-ethylphenyl) (phenyl) methanone were recognized as by-product of KET, as result of its decarboxylation (Musa et al., 2007; Szabo et al., 2011; Illes et al., 2014) and further photoionization of PK_1 m/z 224 forming the PK_2 m/z 210. Hydroxylation of the aromatic ring and dimeric products was not found after photolytic treatment, opposite to what it was observed in the literature for others treatment processes (Feng et al., 2014). Regarding IBUP, no by-products were identified during the photolysis tests, despite the findings of Szabó (Szabo et al., 2011), which showed that the main degradation route during the photolysis of IBUP consists of its decarboxylation.

Fig. 6 shows the main electrolytic reaction pathways. For SDZ only one product was identified. Contrary to photolytic process, which the main route happed by a cleavage of C–N bond in the heterocyclic ring of SFD, during the electrochemical process, the pathway occurs thought hydroxylation of SFD, suggesting an attack of hydroxyl radical (•OH) in the pyridine cycle of sulfadiazine, due to strong negative charge of the nitrogen atom bonded on aromatic ring, leading to formation of 5-OH-sulfadiazine. This important intermediate also was suggested by other authors all along the treatment by Fenton-process, photolytic, gamma-ray irradiation (Liu et al., 2014). For NAP electro-degradation, two pathways can occur, once three main products were detected. The first mechanism involves the oxidation of the deprotonated form of NPX molecule yielding 2-acetyl-6-methoxynaphtalene (PS_1 with m/z = 200) as reported by other authors (Boscá et al., 1990; Kanakaraju et al., 2015; Diaz et al., 2019). The other occurs by decarboxylation followed by oxidation yielding the 1-(6-methoxynaphthalen-2-yl) ethanone identified as PN_3 with m/z 200. The electrooxidation of DCF suggested that more than one pathway can develop, because of the harsh oxidation action of BDD (•OH). The first one consists of the dehydration of DCF through ring closure reaction forming (2,6-diclorophenyl)-indolin2-one (PD_1 m/z 279). Then, it may be attacked by HO• leading to cleavage of the drug to from 2,6-dichloroaniline (PD_2 m/z 163) and possibly the 2-hydroxyphenylacetic acid (no identified) which further suffer a hydroxylation yielding the product 2,5-dihydroxyphenylacetic acid (PD_3 m/z 180). Similar by-products of DCF electrooxidation were also found by others authors using electrooxidation with Pt and BDD electrodes (Brillas et al., 2010) and by Fenton reaction (Bae et al., 2013). Another alternative route occurs throughout the formation of hydroxylated intermediate at m/z = 310 (PD_4). These products differ from those obtained during the photolytic treatment, as also pointed out by other authors (Pérez-Estrada et al., 2005; Keen et al., 2013), and this

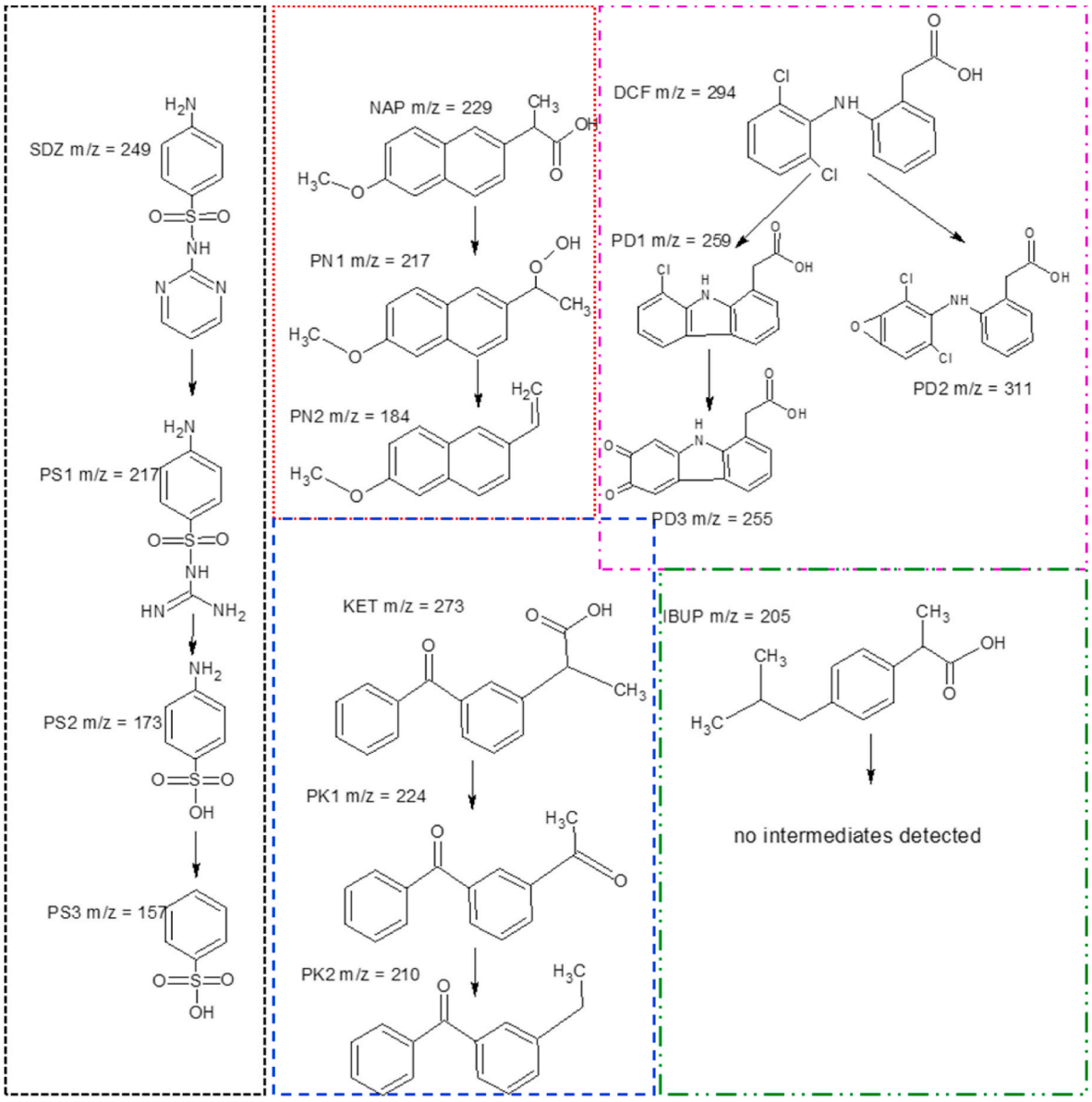

Fig. 5. Tentative pathways by photolysis for preferential pharmaceutics compounds degradation being SFD (black), NAP (red), DCF (magenta), KET (blue) and IBUP (green).

difference may be explained in terms of the higher presence of hydroxyl radicals during the electrolysis. Regarding KET, the two products identified as PK_1 and PK_2 are the same products observed throughout the photolytic treatment. It was expected the hydroxylation of the KET molecule as main reaction route as proposed by Feng et al., (2014) (Feng et al., 2014). However, this was not observed in this work. In the case of IBUP, radicals •OH could attack the carbon of its propionic group resulting in the formation of hydroxylated IBUP, PI_1 *m/z* 222 that, in turn, can undergo decarboxylation and lose of isopropanol to form PI_2 *m/z* 164 and PI_3 *m/z* 134. Similar route was observed by Wang et al., 2016 after electro-oxidation on metal-oxide-coated Ti (Wang et al., 2016). The hydroxylation of IBUP has been discussed by other authors proposing two routes, leading to formation of two isomers by attack of hydroxyl radical in its aromatic ring or in the side chains (Illes et al., 2013).

Fig. 7 shows that besides the by-products detected during the photolysis and electrolysis from SDZ degradation, two new intermediates could be identified for combined photoelectrochemical process. Both products are result of the degradation from PSA_1 that loses a hydroxyl radical and further a cleavage of sulphonamide bond forming aniline *m/z* = 93 as product, which can be further oxidized by hydroxyl radicals. This latter also can be a result from oxidation of PSA_3. Different mechanism for degradation of SFD was proposed by Amorim et al., 2014 (Amorim et al., 2014), with the identification of the fragments 203, 187 and 173 mass corresponding to the S–N bond breakdown of the SFD molecule and successive oxidations from the cleavage of the carbon located in the ring with two nitrogen atoms substituted and the subsequent N–C bond breakdown in the e-position of the SFD molecule. During the photoelectrochemical degradation of NAP any different by-product was detected different from those found in the electrochemical process. However, as discussed before, a decrease in the pH was observed, suggesting the formation of carboxylic acids from the opening of benzoic rings in the final stages of oxidation. Regarding DCF, similar by-products to the photolysis were identified in the photo-electrolysis. Thus, (8-chloro9H-carbazol-1-yl) acetic acid (PD3 *m/z* 259) was explained because of the dichlorination of DCF. From here, this compound may undergo an attack by hydroxyl radicals forming the PD_2 *m/z* 168. Besides, the hydroxylation of DFC produced

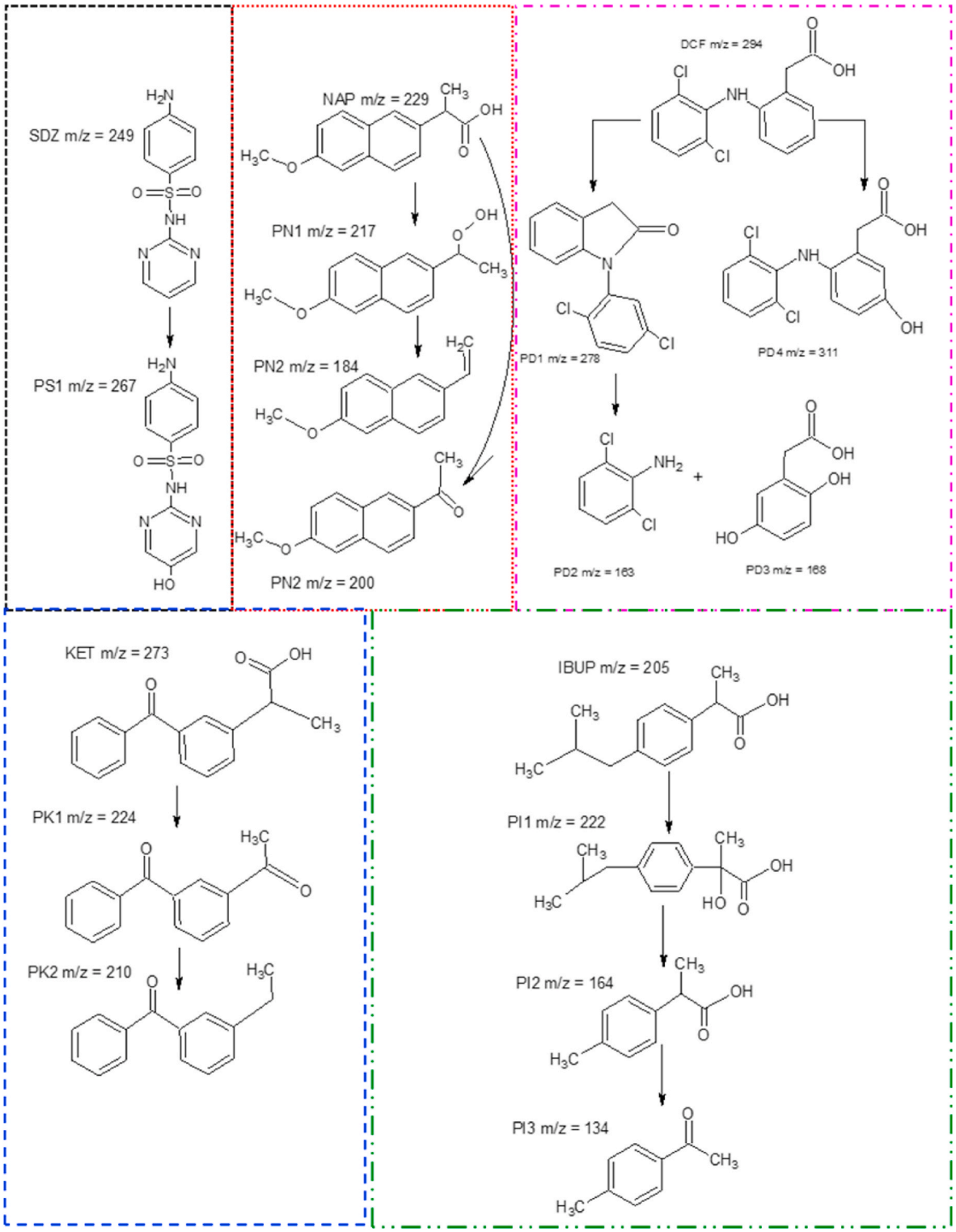

Fig. 6. Tentative pathways by electrolysis for preferential pharmaceutics compounds degradation being SFD (black), NAP (red), DCF (magenta), KET (blue) and IBUP (green).

the PD2 *m/z* 311, as discussed for the electrolysis treatment. Regarding to KET by-products, only two were identified. These compounds are the same observed for photolytic and electrochemical processes (PK_1 and PK_2) and are a result of decarboxylation of the target molecule (Feng et al., 2014). Finally, two products with *m/z* 222 and *m/z* 178 were identified because of IBUP photo-electrodegradation. The products with *m/z* 222 can be isomers from hydroxylation of IBUP (Mendez-Arriaga et al., 2010; Illes et al., 2013; Rodriguez-Chueca et al., 2019). Opposite to electrooxidation process, here the main reaction pathway occurs by decarboxylation of PI_1 hydroxylated in the isopropyl chain forming 1-(4-ethylphenyl)-2-methylpropan-2-ol PI_2 *m/z* 178. This reaction route also was demonstrated by Méndez-Arriaga during the degradation of IBUP by photo-Fenton process (Mendez-Arriaga et al., 2010). Final steps of reaction mechanism for electrolysis and photoelectrolysis processes

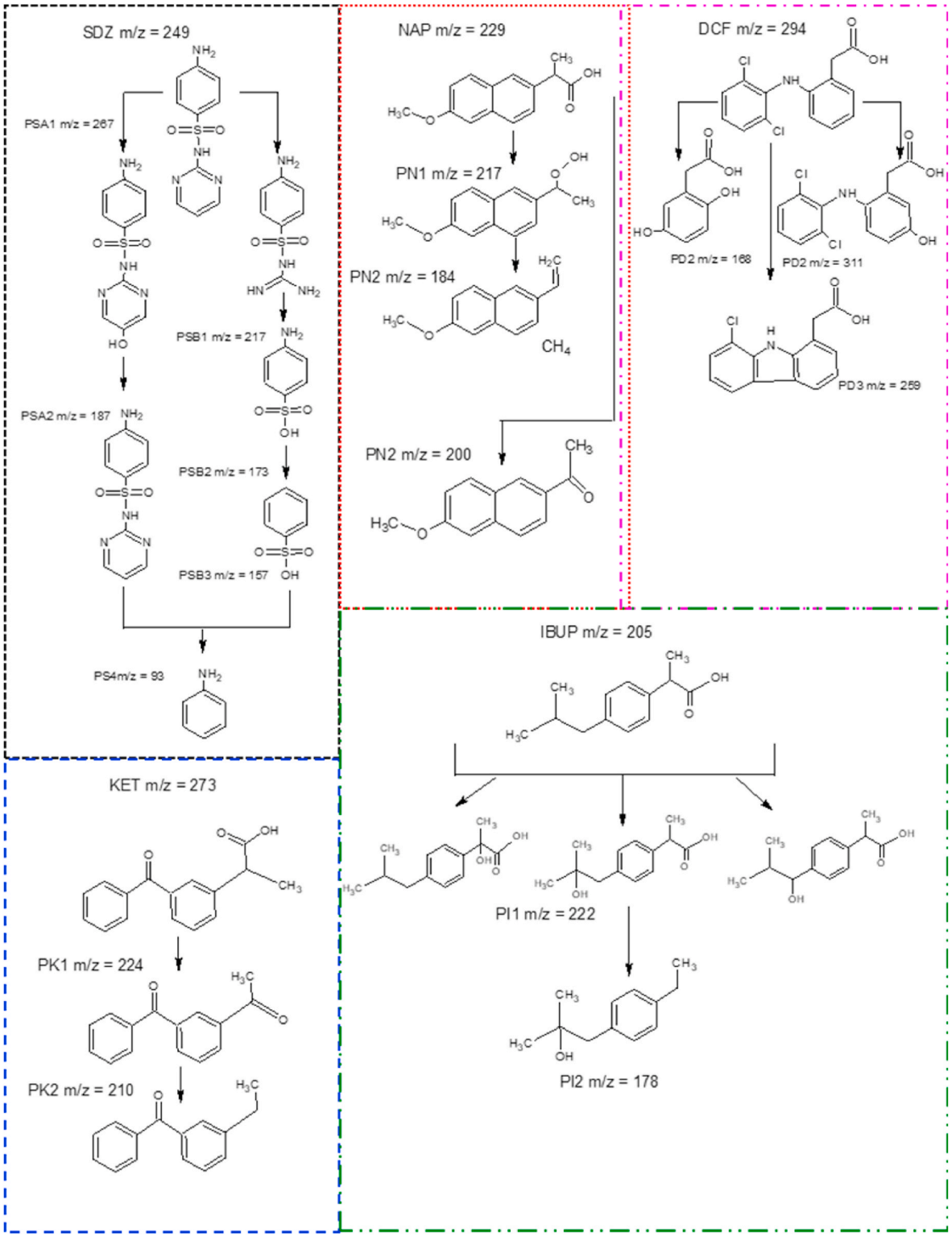

Fig. 7. Tentative pathways by photo-electrolysis for preferential pharmaceutics compounds degradation being SFD (black), NAP (red), DCF (magenta), KET (blue) and IBUP (green).

can led to cleavages of the benzene ring and further oxidation by OH producing linear carboxylic acids species. Then, these latter could be finally mineralized to CO_2 and H_2O via successive hydroxylation reactions.

4. Conclusions

From this work, the following conclusions can be drawn.

- A new metrological strategy was developed for screening and degradation of five pharmaceuticals (SDZ, NAP, DCF, KET and IBUP) from surface water and pore water.

- The origin of the water in which pharmaceuticals are contained and, hence, its different ionic speciation, may influence on the efficiency of removal of these pollutants by photolysis, electrolysis and photo-electrolysis. In the cases studies in this work, better performance in the drugs removal were observed in the removal of pharmaceuticals in surface water, because of the higher ionic content.
- Photolysis is not able to achieve the complete removal of all drugs contained in the mixture that doped the two water samples studied. KET and DIC were the most photoactive compounds attaining their complete removal at the end of treatment while IBUP was the most recalcitrant compound.
- Electrolysis performs much better than photolysis. SFD, NAP, DIC were completely removed at the end of treatment tests for both water matrices. The increase in the current density led to an improvement in the drugs removal over experiments with porewater for NAP, KET and IBUP with an improvement of 40, 30 and 10% in their removal. However, for surface water, no significant improvements were observed. In addition, the increase in the current density from 10 to 30 mA cm^{-2} leads to an increase in the energy consumption of 5.5 times for WM_1 and 6 times for WM_2.
- Photo-electrolysis can remove completely all drugs contained in the mixture within 1 h of treatment for both water matrices. IBUP was the most recalcitrant compound, mainly in the test carried out to WM_1. During the experiments with WM_2 all drugs were completely removed within 15 min of treatment.
- Up to 21 by-products are identified by LC-MS during the processes studied. Photo-electrolysis is the process that produces more intermediates. Based on by-products identified, distinct reaction pathways can be proposed for each technology studied.
- The photodegradation of SFD showed that the main reaction route was the cleavage in the pyridine ring followed by hydroxylation. For NAP and KET the first stage is their decarboxylation and no by-products of the IBUP oxidation are identified.
- During the electrolysis, a different route for SFD was observed and the main reaction pathway consists of the hydroxylation of SFD. Two routes were proposed to NAP and DCF. Similar mechanism of oxidation during the photolysis and electrolysis were proposed for KET. Three intermediates were identified for IBUP oxidation because of its hydroxylation and further decarboxylation.
- Highest number of products were identified during the photo-electrolysis. More the one possible reaction pathway was proposed for SDZ, NAP, DIC and IBUP. Besides, different by-products were identified compared to those found during the photolytic and electrochemical process.

Credit author statement

Jihène Ben Attig: Investigation, Data curation, Formal analysis, Writing – original draft. Fernanda de Lourdes Souza: Investigation, Data curation, Formal analysis, Writing – original draft. Latifa Latrous, Pablo Cañizares, Cristina Sáez, Ángel Ríos: Funding acquisition, Project administration, Supervision, Validation, Writing – review & editing. Manuel A. Rodrigo, Mohammed Zougagh: Conceptualization, Funding acquisition, Project administration, Supervision, Validation, Writing – review & editing.

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.

Data availability

Data will be made available on request.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.chemosphere.2023.138847.

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