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## OXIDATIVE DEGRADATION BY FENTON'S METHOD FOR TEN PHARMACEUTICAL DRUGS LARGELY USED IN A BRAZILIAN CITY

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### Abstract

Medicines have been recently recognized as one of the emerging contaminants in the environment. These are discharged after therapeutic use through human excretion or irregular discharges. Effluent containing high concentrations of drugs discharged from production facilities is also a cause of concern to nearby aquatic bodies. There is an increased interest in their removal due to environmental and public health problems related. Some drugs are resistant to conventional methods of liquid effluent treatment, and there is a risk of negative impacts in humans and animals if exposed repeatedly to the same medicines for prolonged periods. To date, the potential human, animal, and ecological risks associated with the discharge of these compounds to the environment and the potential techniques for liquid effluent degradation demand to be well discussed. Fenton degradation process represents one possibility of pharmaceutical removal of liquid effluents, as presented by the scientific literature. Therefore, this study presents a brief summary on Fenton degradation studies of ten of the most used drugs in city of Belo Horizonte, the capital of the state of Minas Gerais, Brazil. The result of the literature search about the studies of oxidative degradation of the drugs resulted in 45 articles found, applied to 6 drugs among the 10 most frequently used in Belo Horizonte. The needs regarding removal, disposal, and treatment of drugs represent an important challenge in environmental management.

**Keywords:** liquid effluent, Fenton process, medicines degradation, Brazil.

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## Introduction

The use and disposal of chemicals used in medicine, industry, agriculture, and residences has led to the spread of organic pollutants in the environment (Rehrl *et al.* 2020; Sousa *et al.* 2018; Bernhardt *et al.* 2017). Among the pollutants, pharmaceuticals have become a focus on environmental research, because they are a diverse class of biologically active molecules with application to humans and veterinary. Their effects may have an impact on other species unduly exposed to them.

The great use of drugs by the population and in the health-care sector generates excretion of mixtures of substances in unchanged form and their metabolites. When they reach the environment, they can trigger direct harmful effects as the possibility of bioaccumulation in the different trophic levels exposed (Golovko *et al.* 2020; López-Pacheco *et al.* 2019; Minguez *et al.* 2016). The complexity of these compounds hinders the adoption of specific regulations in relation to drugs and metabolites in environmental compartments, with emphasis on the aquatic environment.

Conventional wastewater treatments have shown limited efficiency in removing or degrading these pollutants leading to contamination of surface water and, eventually, groundwater (Bottero-Coy *et al.* 2018; Biel-Maeso *et al.* 2018; Azima *et al.* 2019; Tete *et al.* 2020; Golovko *et al.* 2020). The most consumed drug classes in the world are antibiotics, analgesics, anti-inflammatories, lipid regulators, antidepressants, chemotherapeutic agents, and hormones stand out. The concentration of drugs found in aquatic environments can vary from  $\text{ng.L}^{-1}$  to  $\mu\text{g.L}^{-1}$  and is directly related to the population's drug consumption pattern. The persistence and concentration of drugs after treatment mainly depends on the wastewater treatment plant (WTP) removal rate, seasonality of the weather and socioeconomic conditions, which is associated with access to drugs (Sjerps *et al.* 2017; Azzouz and Ballesteros 2013; Melo *et al.* 2009). In Brazil, sewage treatment is still partial and analysis of the presence of drugs in effluents are not routinely implemented.

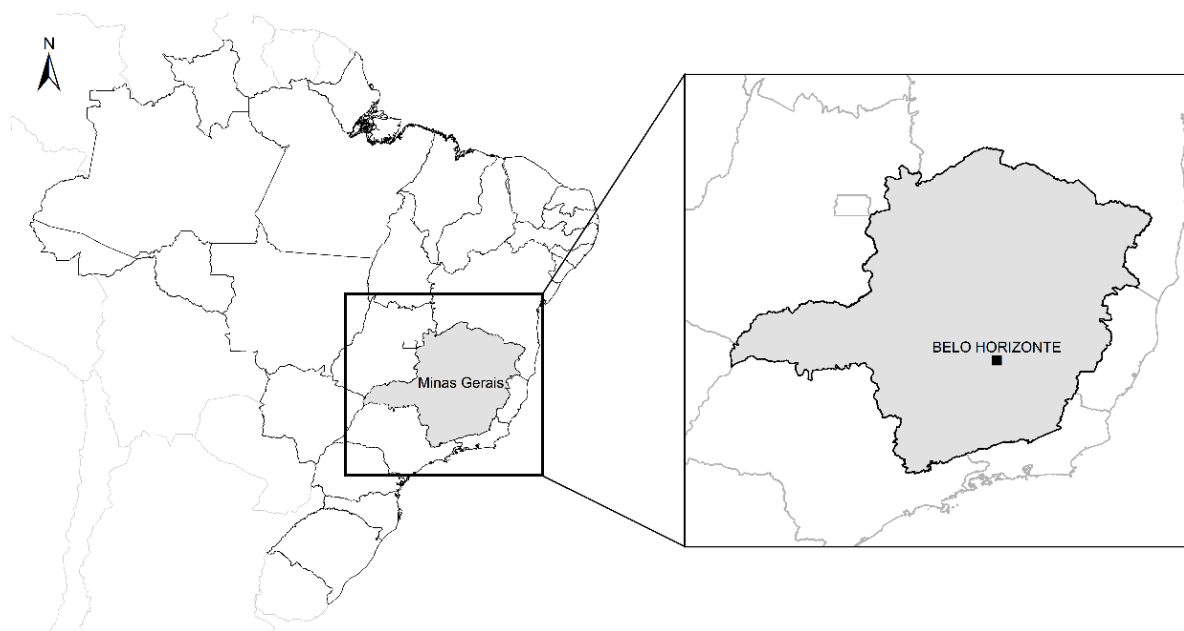
Conventional sewage treatments by biological and physical-chemical processes are the most used in Brazil. These processes have as advantages the high rates of organic matter removal and relative low costs (Melo *et al.* 2009; Queiroz *et al.* 2012; Brant *et al.* 2013). The drugs, focused in this study, have recalcitrant characteristics, and their removal rates are directly related to the structural characteristics and physicochemical properties of the molecule, as well as biodegradability, photo-stability, and lipophilicity (Picó and Barceló 2015; Minguez *et al.* 2016).

There are several studies indicating the detection of pharmaceutical residues in wastewater and water bodies in different Brazilian locations (Américo *et al.* 2017; Américo-Pinheiro *et al.* 2017; Becker *et al.* 2020; Beretta *et al.* 2014; Boger *et al.* 2021, Caldas *et al.* 2019, Campanha *et al.* 2015, Chaves *et al.* 2020, Da Silva *et al.* 2020; de Sousa *et al.* 2014; Ferreira *et al.* 2014; Gonçalves *et al.* 2017; Lopes *et al.* 2016, Machado *et al.* 2020, Machado *et al.* 2016; Montagner and Jardim 2011,

Monteiro *et al.* 2016). These studies showed that drug residues and their metabolites have been found in Brazilian water bodies as well as in drinking water, which may be associated with the limitations of sanitary conditions and the inefficiency of conventional WTP to eliminate these substances.

Drug residues were found in Minas Gerais, a Brazilian state (Figure 1), in the waters of the Doce River (Alvim *et al.* 2020; Foureaux *et al.* 2019), the Velhas River (Moreira *et al.* 2011), the Paraopeba River basin (Barros *et al.* 2018), drinking water supply reservoirs (Reis *et al.* 2019), and wastewater from WTPs (Brant *et al.* 2013; Moreira *et al.* 2011).

The presence of pharmaceuticals in water bodies that receive effluents from WTPs emphasizes the need for studies, in addition to conventional effluent treatments in order to increase the protection of the aquatic ecosystem, minimizing potential damage caused by organic pollutants (Campanha *et al.* 2015; Veras *et al.* 2019; Beretta *et al.* 2014; Moreira *et al.* 2011; Barros *et al.* 2018; Caldas *et al.* 2013; Ferreira 2013, Froehner *et al.* 2011; Monteiro *et al.* 2016; Pivetta and Gastaldini 2019).



**Figure 1.** Brazilian map showing Minas Gerais state and Belo Horizonte city, in detail.

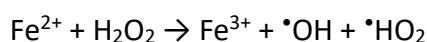
When discussing the environmental presence of pharmaceuticals, international organizations presented have introduced legislation and guidelines to ensure that drug levels in water bodies remain within acceptable limits. In Europe, for instance, the European Commission (EC) has implemented a method known as environmental risk assessment. This method is designed to comprehend potential impact of new drugs on the environment before commencing pharmaceutical production (Commission, 2020). It is a crucial strategy to incorporate information about the ecotoxicity of medicines in the environment and establish reduction goals for these substances (Khasawneh and Palaniandy, 2021). In Brazil, specific legislation regarding pharmaceutical compounds in wastewater is current lacking. However, some states are introducing an for an ecotoxicology parameter assessment before discharging into water body (Starling *et al* 2019). This can be considered an indirect strategy to monitor drugs and other recalcitrant substances in the environment.

Advanced oxidation processes (AOPs) have been used for degradation of various pollutants and the reduction of the total organic load (Seibert *et al.* 2020, Mackuľak *et al.* 2015, Napoleão *et al.* 2015). AOPs are defined as processes based on the formation of hydroxyl radical, highly oxidizing with high chemical reactivity. The interaction of hydroxyl radical (HO.) with organic matter promotes a chain reaction leading to degradation of a wide range of substances (Melo *et al.*, 2009).

Variations were introduced in the Fenton process, seeking to increase its efficiency. Ultraviolet (UV) radiation can be used to initiate the generation of hydroxyl radical, being called photo-Fenton. To degrade oxytetracycline Barbosa and Machion (2014) applied the method, which resulted in 82% removal of this antibiotic. By the same process Velasquez *et al* (2014) degraded, in 8 min, 90% sulfathiazole, and Monteiro *et al* (2018) managed to reduce nimesulide by 89.7% and 93.4% of ibuprofen using photo-Fenton. In the study with liquid effluents the degradation of the drugs was between 71.9% and 100% (Napoleon *et al.*, 2018).

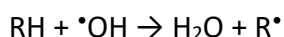
According to Giannakis *et al.* (2017) the application of AOP's to effluents leads to a gain in the final quality of the removal processes. The authors report that the application of Fenton and Photo-Fenton to raw effluents results in high removal of bacteria, with suppression of their growth, inactivation of viruses and yeasts. In addition, it promotes the breakdown of molecules of various contaminants, some of which are refractory to the biological process.

The use of Fenton's reagent allows the removal of recalcitrant compounds in water and effluents, and in soils. It is formed by hydrogen peroxide and iron(II) ions or others transition metals, and its catalytic and oxidative action generates highly reactive and non-selective hydroxyl radicals (Equation 1):



Equation 1

The ferrous ion ( $\text{Fe}^{2+}$ ) initiates and catalyzes the decomposition of  $\text{H}_2\text{O}_2$ , which leads to the formation of hydroxyl radicals ( $\cdot\text{OH}$ ). These radicals can oxidize organic compounds by abstraction of protons, forming organic radicals ( $\text{R}\cdot$ ) (Equation 2):



Equation 2

The Fenton reaction offers several advantages, notably the swift and non-selective destruction or degradation of contaminants. It is well-suited for the treatment of biological effluents, including those derived from both aerobic and anaerobic processes. On the other hand, the Fenton reaction comes with certain drawbacks. The associated costs and the safety considerations in handling hydrogen peroxide are noteworthy challenges. Additionally, the neutralization of effluents results in the formation of ferric sludge, necessitating careful planning for its final disposal. This aspect underscores the importance of addressing both economic and environmental considerations when contemplating the application of the Fenton reaction in wastewater treatment strategies. Therefore, this work aims to carry out a literature review about the application of Fenton's method and its variations for the removal of ten widely consumed drugs in a large Brazilian city.

### Metodology

The literature review was performed using the Google Scholar online database, Web of Science, Pubmed, and SciFinder platforms. The following keywords were used for the search: omeprazole, hydrochlorothiazide, captopril, acetylsalicylic acid, aspirin, losartan, furosemide, simvastatin, atenolol, enalapril and ibuprofen. All keywords were searched using the algorithm “drug name” AND (“Fenton Process” OR “Fenton Reagent”). The subject descriptors used to search for articles included: hydroxyl radicals, elimination in water matrices, degradation of emerging contaminants, combined in different ways with the keywords. The review was expanded by searching the bibliographic references of relevant studies and requesting studies not available to the authors.

The articles surveyed covered the period from 2008 to 2019. Specifically for the drug ibuprofen, the searches were directed to the years 2018 and 2019, since in the evaluated period a total of 1910 articles were published involving this drug. References cited in the articles selected in this review were also included, when relevant to the topic.

### Results and discussion

#### Most consumed drugs in Belo Horizonte/Brazil

The impact of pollutants on the aquatic ecosystem is related to the intrinsic toxicity of these contaminants, and their physical-chemical properties. These properties determine stability, persistence, and bioavailability for aquatic organisms. Thus, liposoluble substances tend to

accumulate more in sediments, while those that are more soluble in water tend to remain in the liquid phase as well as be leached, more easily, from slurry or sediments. Table 1 shows some properties of the most consumed drugs in Belo Horizonte.

The number of drugs listed in Table 1 refers to the distribution by the Unified Health System (SUS), which is the Brazilian public health system and serves more than 190 million people (MS, 2022). These drugs are also distributed by other government programs (Popular Pharmacy Program of Brazil, 2022) and can also be purchased directly from pharmacies. As used for the treatment of diseases of high prevalence in the population, this number of units consumed is certainly undersized. Among the most consumed drugs in Belo Horizonte, three are among the main generic drugs of continuous use in Brazil in 2018, according to ANVISA: captopril, atenolol, and losartan.

The toxicity classification for chemicals utilizes  $EC_{50}$  values:  $< 1 \text{ mg. L}^{-1}$ ,  $1 \text{ a } 10 \text{ mg. L}^{-1}$ ;  $10 \text{ a } 100 \text{ mg. L}^{-1}$ ; and  $> 100 \text{ mg. L}^{-1}$  to define as very toxic, toxic, harmful and non-harmful to aquatic organisms. In a study by Jacob *et al.* (2020), omeprazole exhibited a very toxic classification, while simvastatin was deemed harmful. Atenolol underwent testing with *D. magna* ( $EC_{50} - 48\text{H}$ ), *P. subcapitata* ( $EC_{50} - 72\text{H}$ ), and *A. salina* ( $EC_{50} - 48\text{H}$ ) and exhibited no toxicity, as reported by Minguez *et al.* (2016).

**Table 1.** Most consumed drugs in Belo Horizonte (reference year 2016)

Drug <sup>a</sup>	Quantity (10 <sup>6</sup> units)	Formula	Therapeutic class <sup>b</sup>	Solubility in water at 25 °C (mg.L <sup>-1</sup> ) <sup>c</sup>
Omeprazole	555	C <sub>17</sub> H <sub>19</sub> N <sub>3</sub> O <sub>3</sub> S	anti-ulcer	82.3
Hydrochlorothiazide	492	C <sub>7</sub> H <sub>8</sub> ClN <sub>3</sub> O <sub>4</sub> S <sub>2</sub>	diuretic, antihypertensive	722
Captopril	383	C <sub>9</sub> H <sub>15</sub> NO <sub>3</sub> S	antihypertensive	1.9 10 <sup>5</sup>
Acetylsalicylic acid	294	C <sub>9</sub> H <sub>8</sub> O <sub>4</sub>	analgesic	3.33
Losartan	222	C <sub>22</sub> H <sub>23</sub> ClN <sub>6</sub> O	antihypertensive	8.22
Furosemide	218	C <sub>12</sub> H <sub>10</sub> ClN <sub>2</sub> O <sub>5</sub> S	diuretic	73.1
Simvastatin	208	C <sub>25</sub> H <sub>38</sub> O <sub>5</sub>	antilipemic	7.17 10 <sup>-8</sup>
Atenolol	192	C <sub>14</sub> H <sub>22</sub> N <sub>2</sub> O <sub>3</sub>	antihypertensive	1.9 10 <sup>4</sup>
Enalapril maleate	168	C <sub>20</sub> H <sub>28</sub> N <sub>2</sub> O <sub>5</sub>	antihypertensive	1.64 10 <sup>8</sup>
Ibuprofen	163	C <sub>13</sub> H <sub>18</sub> O <sub>2</sub>	non-steroidal anti-inflammatory	21

<sup>(a)</sup>All drugs in tablet form; <sup>(b)</sup>Classification according to National Health Surveillance Agency electronic data sheet; <sup>(c)</sup>After being metabolized in the human body, the metabolite may present different solubilization.

Source: Belo Horizonte Municipal Health Department, 2016



The acute toxicity assay involving atenolol and three metabolites, conducted with three different organisms, demonstrated no toxic effect in the presence of atenolol and TP267 (atenolol acid). However, metabolites TP167 (1-amino-3-phenoxy-2-propanol) and TP117 (1-isopropylamino-2-propanol) caused harmful toxicity in daphnia and green algae, as demonstrated by Yi (2020). Toxicity tests for ibuprofen indicated toxicity to *V. fischeri* with  $EC_{50}$  of  $14.97 \text{ mg.L}^{-1}$  and *D. magna* with an  $EC_{50}$  of  $50.07 \text{ mg.L}^{-1}$ , as reported by Grabarczyk *et al.* (2020).

### Literature review results

The result of the literature search about the studies of oxidative degradation of the drugs presented in Table 1 resulted in 45 articles found, as shown in Figure 2.

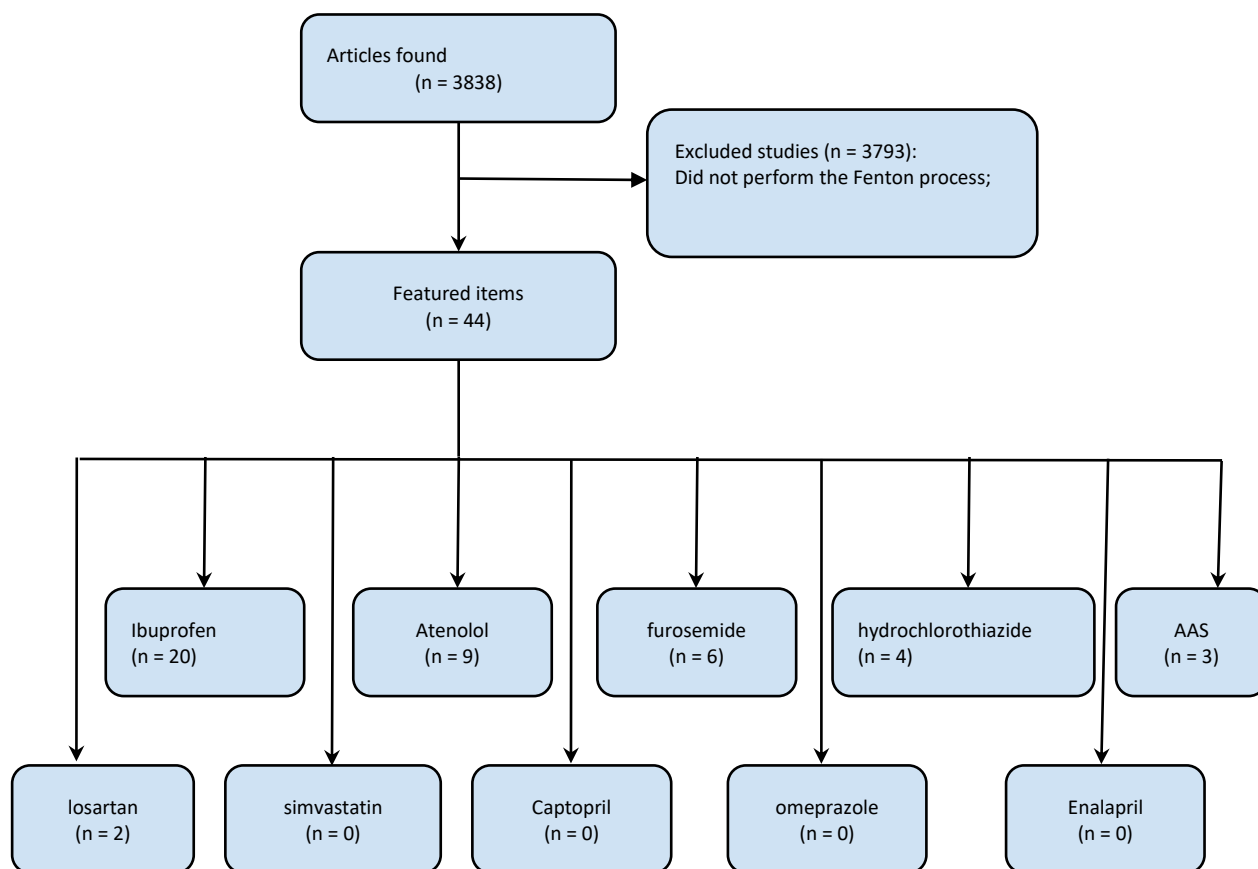


Figure 2. Flowchart of the article inclusion process.

Among the drugs selected in this study, atenolol (ATE) is an antihypertensive of the  $\beta$ -blocker class that has been detected in both WWTPs and rivers, often at higher concentrations than other antihypertensive drugs. ATE has low bioavailability in the human body, and 50% of the administered dose is not absorbed, being excreted unchanged. In the environment ATE has mobility and bioavailability (Maszkowska *et al.* 2014, Alder *et al.*, 2010). In a study conducted by Roberts *et al.* (2016) the presence of ATE was observed at different stages of the largest sewage treatment system in Australia and in receiving bodies of this WWTP, reaching a concentration of  $300 \mu\text{g.L}^{-1}$ . ATE contamination was also reported in river waters in Switzerland ( $83 \mu\text{g.L}^{-1}$ ) and in its effluents ( $2290 \mu\text{g.L}^{-1}$ ) (Alder *et al.*, 2010). In Brazil, in a study conducted by Sousa *et al.* (2014) in the Piraí and Jundiaí rivers (São Paulo state), ATE was detected in 43% and 100% of the samples collected, respectively (Sousa, *et al.*, 2014).

To improve absorption some drugs are administered as a prodrug, that is a biologically inactive compound which can be converted into the active substance in the gastrointestinal or intracellular tract. In these cases, these are in the environment in the active form, post metabolization. This is the case of omeprazole, which is administered as a prodrug, being converted into the active metabolite in the acidic pH of the stomach. In this way it is eliminated in the environment as an active metabolite, and not in the full form in which it is administered (Hernando *et al.*, 2007). Omeprazole is rarely found in sanitary effluents, while its metabolites have been identified both in urine and in sanitary effluents and surface waters. Boix *et al.* (2016) analyzed 30 samples of effluents from WWTP in 10 Italian cities, identifying 6 metabolites of omeprazole, four of them present in more than 70% in the samples.

The determination of losartan (LOS) in effluents has few studies in relation to water environments. In one study, conducted in the USA, the concentrations of LOS found were  $200 \mu\text{g.L}^{-1}$  in summer, and  $430 \mu\text{g.L}^{-1}$  in winter (Xing *et al.* 2018). Azima *et al.* (2019) observed that LOS and its carboxylate derivative showed refractory characteristics to the biological treatment of WWTPs, remaining in effluents and reaching surface waters. In Japan, hospital effluents, WWTP effluents and river waters downstream of the release were analyzed, and the maximum values found from LOS were 786, 171 and  $32 \mu\text{g.L}^{-1}$ , respectively; and the carboxylic metabolite were 686, 147 and  $18 \mu\text{g.L}^{-1}$ , respectively (Azima *et al.*, 2019).

Despite having a high medical prescription in Spain, simvastatin (SVT) excretion occurs by metabolites, and thus SVT was not found in the monitoring of the influents and effluents of the WWTP Castellon de la Plana, in Spain (Gracia-Lor *et al.*, 2012). Its Kow value of 4.68 shows the tendency of its adsorption in suspended solids, as well as in sediments (Grung *et al.*, 2007). Tete's (2020) research found SVT in the influents ( $11.7 \mu\text{g.L}^{-1}$ ) and effluents ( $2.65 \mu\text{g.L}^{-1}$ ) of Daspoort WWTP, which uses physical-chemical and biological treatment (Pretoria, South Africa), as well as in the waters of the Apies River ( $1.59 \mu\text{g.L}^{-1}$ ) downstream of WWTP (Tete *et al.*, 2020). In Sweden SVT



was quantified in samples of 15 influents, effluents, slurries of WWTPs, and in bodies of water, downstream and upstream of DWTPs. (Drinking water treatment plant) The results show a constant presence of SVT in WWTPs, with medians of  $84 \text{ ng.L}^{-1}$  in the influents and  $130 \text{ ng.L}^{-1}$  in effluents, and  $320 \text{ ng.g}^{-1}$  in dry sludge. These values found from the slurries can be due to the high value of the SVT logKow. In the bodies of water sample were found  $38.5 \text{ ng.L}^{-1}$  upstream and  $34 \text{ ng.L}^{-1}$  downstream (Golovko *et al.*, 2021).

The study by Marsik *et al.* (2017) indicated the presence of ibuprofen (IBU) in waters produced by 6 DWTPs in Japan. Its excretion was around 15%, with the other fractions such as the metabolites hydroxi-ibuprofen (1-OH IBU and 2-OH IBU) and carboxy-ibuprofen (CBX IBU) (Simazaki *et al.*, 2015). This drug and its metabolites were quantified in effluents of WWTPs and in the waters of the river that receives these effluents in Spain: IBU –  $1900$  and  $750 \text{ }\mu\text{g.L}^{-1}$ , 1-OH IBU -  $920$  and  $450 \text{ }\mu\text{g.L}^{-1}$ , 2-OH IBU -  $3150$  and  $3000 \text{ }\mu\text{g.L}^{-1}$  and CBX IBU -  $5370$  and  $3950 \text{ g.L}^{-1}$ , respectively (Ternes *et al.*, 2004; Ferrando-Climent *et al.*, 2012). In Portugal, Paiga *et al.* (2016) evaluated 5 points along the Lis River. IBU and its metabolites (HIBU and CBX IBU) were identified in all samples collected, both from the river and from the effluents of the WWTPs.

The presence of salicylic acetyl acid (AAS) and its main salicylic acid metabolite (AAS<sub>t</sub>) was monitored by Paiga *et al.* (2016), along the Lis River in Portugal. Only the metabolite was found, present in all the aliquots analyzed. In the effluents of the WWTPs, the values of AAS<sub>t</sub> varied between  $106$  and  $296 \text{ }\mu\text{g.L}^{-1}$ , and in the river waters this variation was from  $25$  to  $294 \text{ }\mu\text{g.L}^{-1}$ .

The prodrug enalapril (ENA) transforms into enalaprilat in the body, being thus eliminated, through the renal system (Stankiewicz *et al.* 2015, López-Serna, 2012). This drug and its metabolite have been reported both in effluents (Gurke *et al.*, 2015), as well as in surface waters (López-Serna *et al.*, 2013) and groundwater (López-Serna *et al.*, 2012). In the monitoring of the WWTP in Dresden, Germany, there was 60% removal of the ENA (Gurke *et al.*, 2015). In the Ebro River and its tributaries, both ENA and its metabolite ENAprilate were found, with frequency and average values of 100% and 87%, and  $7.23 \text{ ng.L}^{-1}$  and  $6.23 \text{ ng.L}^{-1}$  (López-Serna *et al.*, 2013). In three groundwaters, in the Barcelona area, with distinct geological characteristics and recharge sources, ENA and its metabolite were identified. The concentration range varied, with enalapril mean values significantly lower ( $0.02 \text{ ng.L}^{-1}$  to  $0.18 \text{ ng.L}^{-1}$  in three aquifers), and then those found for ENAprilate:  $2.42 \text{ ng.L}^{-1}$  to  $4.78 \text{ ng.L}^{-1}$  in the three aquifers (López-Serna *et al.*, 2012). Its detection may indicate that the focus should be on the metabolite and its degradation products to better evaluate their impacts on the various aquatic ecosystems.

Removal of the most prescribed drugs in the studied municipality by Fenton reaction and its derived techniques

The information found in the articles included in this paper is consolidated in Table 2, seeking to show the efficiency of the Fenton and Photo-Fenton process as an alternative or complement to conventional sewage treatment processes for drug removal. The removal rates (Table 2) found were high, with values above 90%, while the reductions of TOC (total oxygen organic) showed a high variability. These data indicate the heterogeneity of the degradation of drug molecules.

For the drugs Omeprazole, Captopril, Enalapril and simvastatin, no studies were found on the application of Fenton reaction for its degradation until the final date of the search.

The execution of the Fenton process and its variations depend on the control of some variables to obtain the best efficiency. These variables are in all types of Fenton, such as pH, iron, and hydrogen peroxide concentrations. However, the electric current, cathode and anode cells, and radiation are found in specific types of Fenton, such as in electro-Fenton for the first two and photo-Fenton for the latter. The analysis of the articles (Table 2) made it possible to extract and group them through similarities in the procedures. This allowed establishing 6 topics, relating to the efficiency obtained by each researcher and the drug studied. The topics were: use of the TOC parameter to evaluate efficiency, matrix change, hydraulic retention time versus operational optimization, electrode uses and application of electric current, association of distinct types of processes.

**Table 2.** Information about the Fenton process for studied drugs (*continues*)

Drug	Reference	Process Used	Matrix	Operational conditions	Removal (%), time (min)
Hydrochlorothiazide (HTZ)	Klamerth <i>et al.</i> (2012)	Photo-Fenton Solar EDDS pH neutral	Real effluent, after secondary biological treatment, with carbonate removal	[HTZ] 3783 $\mu\text{g.L}^{-1}$ , pH <sub>i</sub> = 3, [H <sub>2</sub> O <sub>2</sub> ] 50 $\text{mg.L}^{-1}$ , kept constant during test, [Fe] 5 $\text{mg.L}^{-1}$	[HTZ] = 131 $\mu\text{g.L}^{-1}$ 96% removal in 60 min
	Arzate <i>et al.</i> (2017)	Photo-Fenton solar	Real effluent, batch, and continuous photo-Fenton treatment.	[HTZ] 4718 $\mu\text{g.L}^{-1}$ , pH <sub>i</sub> = 5.8, pH <sub>end</sub> = 6.3, increase in hydraulic retention time = higher consumption of H <sub>2</sub> O <sub>2</sub>	[HTZ] <sub>20min</sub> = 93% [HTZ] <sub>40min</sub> = 96% [HTZ] <sub>80min</sub> = 98%
	Paiva <i>et al.</i> (2018)	Photo-Fenton	Distilled water	Catalyst: [Fe <sup>2+</sup> /Fe <sup>3+</sup> /FeO <sub>x</sub> ] 18 $\mu\text{mol.L}^{-1}$ , [H <sub>2</sub> O <sub>2</sub> ] 2.0 $\text{mg.L}^{-1}$ , pH 2.6, time 25 min	90% removal in 30 min

**Table 2.** Information about the Fenton process for studied drugs (*continues*)

Drug	Reference	Process Used	Matrix	Operational conditions	Removal (%), time (min)
	Paiva <i>et al.</i> (2018)	Photo-Fenton	Aqueous solution	Condition after optimizing process, FeO <sub>x</sub> ferrioxalate 1.0 mg.L <sup>-1</sup> , [H <sub>2</sub> O <sub>2</sub> ] 2.0 mg.L <sup>-1</sup> , pH = 5	Toxicity reduction after 60 min, with test organism <i>Vibrio fischeri</i> , [HTZ] 90%, pH = 6.0, no adjustments before disposal
Acetylsalicylic acid (ASA)	Ma <i>et al.</i> (2016)	Electro-Fenton	Aqueous solution	pH 3, [Fe] 0.3 mM, flow rate 3.5 mL/min, [H <sub>2</sub> O <sub>2</sub> ] electro generation, [ASA] 50 mg.L <sup>-1</sup>	Graphite Felt, 65% removal, N.I. time .
	Yang <i>et al.</i> (2018)	Electro-Fenton	Aqueous solution	pH = 3 [Fe] [H <sub>2</sub> O <sub>2</sub> ] = electro generation Reaction time: 10 min	TOC = 62% AAS = 100%
	Napoleão <i>et al.</i> (2018)	Photo-Fenton UV	Pharmaceutical industry effluent	[ASA] 0.65 mg.L <sup>-1</sup> 150 min reaction [H <sub>2</sub> O <sub>2</sub> ] = fractional addition of 2 ml every 30 min up to 120 min	ASA = 71 % TOC <sub>total</sub> = 67% Time N.I.
	Martínez-Pachón <i>et al.</i> (2019)	Photo-Electro-Fenton	Aqueous solution	pH = 3 [LOS] 4.7 x 10 <sup>-5</sup> mol.L <sup>-1</sup> [H <sub>2</sub> O <sub>2</sub> ] = electro generation	100% in 90 min of reaction
Losartan potassium	Martínez-Pachón <i>et al.</i> (2019)	Photo-Electro-Fenton with organic acids	Composite sample (24h), WTP effluent	Fe (III)- oxalate: presence of Fe <sup>+2</sup> /Fe <sup>+3</sup> : Higher production of •OH [H <sub>2</sub> O <sub>2</sub> ] = electro generation	pH ~neutral: 60% in 60 min  Fe(III)oxalate 70% removal 90 min
		Sono-Fenton		Ultrasound as a reactor: Frequency: 357 kHz UVA lamp 90min pH = 7.8 [LOS] = 2.19 µg.L <sup>-1</sup>	84,9% Time N.I.
	Serna-Galvis <i>et al.</i> (2019)	Sono-Photo-Fenton	Composite sample (24h), WTP effluent	Ultrasound as a reactor: Frequency: 357 kHz UVA lamp 90min pH = 7.8 [LOS] = 2.19 µg.L <sup>-1</sup>	78.5% Time N.I.
		Sono-Photo-Fenton in the presence of oxalic acid		90min pH = 7.8 [LOS] = 2.19 µg.L <sup>-1</sup>	74.9% Time N.I.
Furosemide (FUR)	Klamerth <i>et al.</i> (2012)	Photo-Fenton	actual effluent	[FUR] 1100 ng.L <sup>-1</sup> pH <sub>initial</sub> = 2.8 [H <sub>2</sub> O <sub>2</sub> ] 50 mg.L <sup>-1</sup> kept constant during test [Fe] 5 mg.L <sup>-1</sup>	100% in 60 min of reaction
	Olvera-Vargas <i>et al.</i> (2015)	Electro-Fenton with BDD e Pt	Aqueous solution	[H <sub>2</sub> O <sub>2</sub> ] = electrogeneration [Fe <sup>2+</sup> ] = 0.1 mM	TOC Removal 95% in 8 h
	Olvera-Vargas <i>et al.</i> (2016)	Electro-Fenton with BDD / carbon fiber electrode	Aqueous solution	pH = 3 [H <sub>2</sub> O <sub>2</sub> ] = electrogeneration [Fe <sup>2+</sup> ] = 0.1 mM	TOC removal: 1 h: 60% 2 h: 80% 8 h: 90%

**Table 2.** Information about the Fenton process for studied drugs (*continues*)

Drug	Reference	Process Used	Matrix	Operational conditions	Removal (%), time (min)
	Cuervo Lumbarque <i>et al.</i> (2018)	Fenton	Aqueous solution [DOC] 15 mg.L <sup>-1</sup>	[FUR] 500 µg.L <sup>-1</sup> pH = 5 [Fe] 12.5 mg.L <sup>-1</sup> [H <sub>2</sub> O <sub>2</sub> ]= 533 mg.L <sup>-1</sup>	97% after 1 min [DOC] 40% in 120 min:
			simulated effluent, [DOC] 60 mg.L <sup>-1</sup>	[FUR] 500 µg.L <sup>-1</sup> pH = 5 [Fe] 12.5 mg.L <sup>-1</sup>	97% after 1 min [DOC] 15% in 120 min
			Actual hospital effluent, [DOC] 73 mg.L <sup>-1</sup>	[FUR] 500 µg.L <sup>-1</sup> pH = 5 [Fe] 12.5 mg.L <sup>-1</sup>	90% in 1 min 98.9% after 120 min [DOC] 15% in 120 min
	Cuervo Lumbarque <i>et al.</i> (2019b)	Solar Homo/Heterogeneous Photo-Fenton Catalyst: Fe+ Alg: sodium alginate sphere + Fe immobilized [3g]	Aqueous solution, simulated effluent, real hospital effluent	[FUR] 500 µg.L <sup>-1</sup> pH = 5 [Fe] continuous release of spheres, by reaction demand [H <sub>2</sub> O <sub>2</sub> ]= 25 mg.L <sup>-1</sup>	Removal 99% N.I. time
Atenolol (ATE)	Isarain-Chávez <i>et al.</i> (2011)	Electro-Fenton e Electro-Fenton Solar	Aqueous solution	[ATE]100 mg.L <sup>-1</sup> pH = 3 [H <sub>2</sub> O <sub>2</sub> ]= electro generation [Fe <sup>2+</sup> ] = 0.5 mM T = 35°C	88% in COD (4 h), combined Pt electrode/air diffusion electrode 94% in COD (4 h), single Pt/boron-doped diamond electrode
	Li <i>et al.</i> (2012)	Fenton	Secondary effluent from WWTP	pH = 3 [H <sub>2</sub> O <sub>2</sub> ] = 2.5 [Fe] [Fe] 20 mg.L <sup>-1</sup> [ATE] <sub>spiked</sub> = 1µg.L <sup>-1</sup>	100% in 30 min
	Li <i>et al.</i> (2013)	Fenton and Fenton-Like	Secondary effluent from WWTP	pH = 3 [H <sub>2</sub> O <sub>2</sub> ] = 2.5 [Fe] [Fe] 20 mg.L <sup>-1</sup> [ATE] <sub>spiked</sub> = 1µg.L <sup>-1</sup>	[Fe] > 1.25 mg.L <sup>-1</sup> 75% after 30 min Fenton Like [Fe] > 5 mg.L <sup>-1</sup> 80% after 120 min
	Klamerth <i>et al.</i> (2013)	Photo-Fenton Solar EDDS pH neutral	Real effluent, after secondary biological treatment, with carbonate removal	[ATE] 1126 ng.L <sup>-1</sup> initial pH = 2.8 [H <sub>2</sub> O <sub>2</sub> ]50 mg.L <sup>-1</sup> kept constant during test [Fe] 5 mg.L <sup>-1</sup>	[ATE] = 35 ng.L <sup>-1</sup> 97% in 60 min
	Pietro-Rodríguez <i>et al.</i> (2013)	Solar Photo Fenton	Real	pH = 2.0 [Fe] 5 mg.L <sup>-1</sup>	84% in 20 min
	Neamtu <i>et al.</i> (2014)	Photo-Fenton with simulated solar irradiation	Aqueous solution	[ATE] = 2 µM [H <sub>2</sub> O <sub>2</sub> ]= 300 µM [Fe] = 30 µM	80% TOC in 30 min 10 min: 38% 30 me: 72% 60 min: 98%
	Neamtu <i>et al.</i> (2014)	Photo-Fenton with simulated solar irradiation Photo-Fenton	Lake Geneva	[ATE] = 2 µM [H <sub>2</sub> O <sub>2</sub> ]= 300 µM [Fe] = 30 µM TOC=2.98mg.L <sup>-1</sup>	60% in OCD 60 min.

**Table 2.** Information about the Fenton process for studied drugs (*continues*)

Drug	Reference	Process Used	Matrix	Operational conditions	Removal (%), time (min)
			WWTP effluent	[ATE] = 2 $\mu\text{M}$ [H <sub>2</sub> O <sub>2</sub> ] = 300 $\mu\text{M}$ [Fe] = 30 $\mu\text{M}$ TOC = 9.31 mg.L <sup>-1</sup>	35% in OCD 60 min.
			Aqueous solution	[ATE] 20 mg.L <sup>-1</sup> [Fe] = 20 mg.L <sup>-1</sup> [H <sub>2</sub> O <sub>2</sub> ] = 100 mg.L <sup>-1</sup>	70% IN TOC 60 min
	Veloutsou, Bizani & Fytianos (2014)	Photo-Fenton	Aksios river water	[DOC] 2.4 mg.L <sup>-1</sup> [ATE] 20 mg.L <sup>-1</sup> [Fe] = 20 mg.L <sup>-1</sup> [H <sub>2</sub> O <sub>2</sub> ] = 100 mg.L <sup>-1</sup>	90% in 180 min
			Volvi lake water	[DOC] 16 mg.L <sup>-1</sup> [ATE] 20 mg.L <sup>-1</sup> [Fe] = 20 mg.L <sup>-1</sup> [H <sub>2</sub> O <sub>2</sub> ] = 100 mg.L <sup>-1</sup>	85% in 180 min
	El-Hanafi <i>et al.</i> (2014)	Electro Fenton	Aqueous solution	[ATE] 0,17 mM pH = 3 [Fe] 5 mM [H <sub>2</sub> O <sub>2</sub> ] = electro generation	87% Time N.I.
Ibuprofen (IBU)	Skoumal <i>et al.</i> (2009)	Electro-Fenton, UVA Photo-Electro-Fenton, and Photo-Electro-Fenton Solar	Aqueous solution	pH = 3 [Fe] = 0.5 mM	Electro-Fenton 100% in 40 min  UVA Photo-Electro-Fenton 100% in 40 min  Photo-electro-Fenton Solar 100% in 20 min
	Klamerth <i>et al.</i> (2012)	Photo-Fenton solar EDDS pH neutral	WWTP tertiary effluent	pH = 6.7 [H <sub>2</sub> O <sub>2</sub> ] = 50 mg.L <sup>-1</sup> [Fe] = 5 mg.L <sup>-1</sup>	81% in 60 min
	Loaiza-Ambuludi <i>et al.</i> (2013)	Electro-Fenton graphite felt cathode	Aqueous solution	pH = 3 [Fe] = 0,2 mM [IBU] 0.2 mM	100% in 20 min Intermediate compounds identified
	Monteiro <i>et al.</i> (2018)	Photo-Fenton with UV lamp	Aqueous solution	[H <sub>2</sub> O <sub>2</sub> ] = 28.0 mg.L <sup>-1</sup> [Fe] = 4.4 mg.L <sup>-1</sup> t = 360 min	93,35% COD = 91% TOC = 90 %
	Zhou <i>et al.</i> (2018a)	Electro-Fenton	Aqueous solution	pH = 3 [Fe] = 40 mg.L <sup>-1</sup> [H <sub>2</sub> O <sub>2</sub> ] = electro generation	floating cathode 100% in 60 min  Conventional submerged cathode 100% in 120 min  pH = 3 [Fe] = 70 mg.L <sup>-1</sup> [H <sub>2</sub> O <sub>2</sub> ] = electro generation Alternating current 100% in 60 min  constant current 100% in 100 min

**Table 2.** Information about the Fenton process for studied drugs (*continues*)

Drug	Reference	Process Used	Matrix	Operational conditions	Removal (%), time (min)
	Nadais <i>et al.</i> (2018)	Bio-Electro-Fenton	Actual effluent after secondary biological treatment. Filtered and doped with drugs	pH = 3 [Fe] = 5 mM [H <sub>2</sub> O <sub>2</sub> ] = electro generation	86% in 11 hours Presence of different compounds in the effluent affect IBU oxidation
	Lui <i>et al.</i> (2018)	Heterogeneous Electro-Fenton	Aqueous solution	Homogeneous Electro-Fenton pH = 3 [H <sub>2</sub> O <sub>2</sub> ] = electro generation	Homogeneous Electro-Fenton 90% in 60 min
				Heterogeneous Electro-Fenton using Cit-Fe/ACFs pH = 6.8 [H <sub>2</sub> O <sub>2</sub> ] = electro generation	Heterogeneous Electro-Fenton using Cit-Fe/ACFs 97% in 120 min
	Darie & Carja (2018)	Photo-Fenton Heterogeneous with Fe impregnated in Zn (LDH)	Aqueous solution	pH = 8,5 [H <sub>2</sub> O <sub>2</sub> ] = 100 mg.L <sup>-1</sup>	82% (solar radiation) in 4.5 hours
	Guettaia <i>et al.</i> (2018)	Photo-Fenton heterogeneous iron in mesoporous silica	Aqueous solution	[IBU] 50 mg.L <sup>-1</sup> pH = 11 [H <sub>2</sub> O <sub>2</sub> ] = 3,85 mg.L <sup>-1</sup> [Fe] = 0.25 g.L <sup>-1</sup>	80% IN 210 min TOC = 10%
	Adityusulindro <i>et al.</i> (2018)	Fenton heterogeneous Fe-zeolite catalyst	Aqueous solution	pH = 3,3 [H <sub>2</sub> O <sub>2</sub> ] = 6,4 mm Catalyst: 4.8 g.L <sup>-1</sup> 3 hours of reaction pH = 3.3 to 3.4l	[IBU] 88% IN 180 min [TOC] 27%
	Chen <i>et al.</i> (2018)	Fenton, Photo-Fenton, Photo/TiO <sub>2</sub> /Fenton (PCF)	Aqueous solution	[IBU] 0.15 mmol.L <sup>-1</sup> pH = 7 [H <sub>2</sub> O <sub>2</sub> ] = 0.05 mmol.L <sup>-1</sup> [Fe <sup>2+</sup> ] = 0.05 mmol.L <sup>-1</sup>	30 min reaction: Fenton: 90% Photo-Fenton: 60% PCF: 97%
				[IBU] 0.15 mmol.L <sup>-1</sup> [Fe <sup>2+</sup> ] fixed [Fe <sup>2+</sup> ]: [H <sub>2</sub> O <sub>2</sub> ] mmol.L <sup>-1</sup> ⊗ = 350 ηm	[Fe <sup>2+</sup> ]: [H <sub>2</sub> O <sub>2</sub> ] 0.05:0.1- 90% 0.05:0.5 - 92% 0.05:2 - 98%
				[IBU] 0.15 mmol.L <sup>-1</sup> [H <sub>2</sub> O <sub>2</sub> ] fixed [Fe <sup>2+</sup> ]: [H <sub>2</sub> O <sub>2</sub> ] mmol.L <sup>-1</sup> ⊗ = 350 ηm	[Fe <sup>2+</sup> ]: [H <sub>2</sub> O <sub>2</sub> ] 0.05:0.50- 97% 0.20:0.5 - 97% 20.0:0.5 - 97%
	Ayoub <i>et al.</i> (2018)	Photo Fenton heterogeneous	Waters of the Meurthe River, France	pH = 5,5 [H <sub>2</sub> O <sub>2</sub> ] = 0.007 M [Fe] = 1000 mg.L <sup>-1</sup>	95% in 30 min and 6 hours
	Herghelegiu <i>et al.</i> (2018)	Homogeneous Fenton and Photo-Fenton	Aqueous solution	pH = 3 [Fe]/[H <sub>2</sub> O <sub>2</sub> ] = 1.25 v/v	homogeneous Fenton 85.98% in 30 min  photo-Fenton 88.52% in 30 min



**Table 2.** Information about the Fenton process for studied drugs (*continues*)

Drug	Reference	Process Used	Matrix	Operational conditions	Removal (%), time (min)
	Dekkiche <i>et al.</i> (2019)	Photo-Fenton	Aqueous solution	pH= 2.8 [H <sub>2</sub> O <sub>2</sub> ] = 1.0·10 <sup>-3</sup> M [Fe] = 0.3 mM	98% in 90 min Mineralization
	Zhou <i>et al.</i> (2019)	Electro-Fenton	Aqueous solution	pH= 7 [Fe] =10 mg.L <sup>-1</sup> [H <sub>2</sub> O <sub>2</sub> ]= electro Generation	Modified Felt Graphite 75.3% in 100 min graphite Felt unmodified 57.6% in 100 min
	Ayoub <i>et al.</i> (2019)	Photo-Fenton	River surface water, downstream of WWTP, Collections: Mar/2017, Oct/2016	pH= 4 [H <sub>2</sub> O <sub>2</sub> ]/[Fe] = 0.4  2016 TOC <sub>i</sub> = 4.36 mg.L <sup>-1</sup> pH = 7.32 2017 pH = 7.26	March/2017 6 h of reaction: 93 to 100%  October/2016 OCD 30 min: 2.65 mg.L <sup>-1</sup> 6h: 2.44 mg.L <sup>-1</sup> 6 h of reaction: 93 to 100%
	Dong <i>et al.</i> (2019)	Neutral Photo-Fenton, Catalyst: Ferric-nitilotriacetate complex FeIII-NTA	Real effluent after aerated biological filter, enriched, final concentration of 450-500 µg.L <sup>-1</sup> of each drug	pH 7, [H <sub>2</sub> O <sub>2</sub> ] 1 mM, [Fe] 0.05 mM, [IBU] 450-500 µg.L <sup>-1</sup>	Fenton: 50%, Photo-Fenton >92% in continuous mode. Residence time 2 hours

*Legend: TOC – total organic carbon; DOC – dissolved organic carbon; [HTZ] – hydrochlorothizide; EDDS – Ethylenediamine-N,N'-disuccinic acid; LD – Detection limit; ASS – acetylsalicylic acid; LOS – losartan potassium; WTP – wastewater treatment plants; ATE – atenolol; FUR – furosemda; IBU – ibuprofen; i – initial.*

The total mineralization of the studied compounds does not occur in most experiments, although the removal rate achieved in the evaluated studies is above 90% (Table 2). The total organic carbon (TOC) values make it possible to establish the degree of degradation of organic matter present in the studies, making it possible to evaluate the efficiency of the AOPs.

One of the factors that can affect the drugs rate degradation is the presence of other sources of organic matter. The drug is composed of the active ingredient and the excipients to obtain the final formulation. Thus, there is the possibility of a removal of 100% of the drug, but not obtaining the same percentage for the removal of total organic matter as excipients, metabolites and degradation products can remain in the solution. In the study of Yang (2018) there was a 100% removal of the ASA, however, the TOC reduced only to 62%. This indicates the presence of non-degradable organic substances in the reaction condition and/or the formation of intermediate ASA degradation products. In the study by Méndez-Arriaga (2010) the degradation of ibuprofen was evaluated by Fenton and photo-Fenton processes with UV. The Photo-Fenton process obtained a removal of 40% of TOC, while in the Fenton process only 10% of removal was achieved. Monteiro (2018) applied the photo-Fenton process to IBU, with removal of

93% of the drug and 90% of TOC, in addition to reducing the toxicity of the solutions evaluated by seed germination test. Using electro-Fenton with iron citrate, at pH 6.8, Lui (2018) obtained an IBU removal of 89% in 60 min and 96% in 120 min. The results of electro-Fenton with FeSO<sub>4</sub> or IBU iron citrate showed similar values, with the difference in the need for neutralization of the solution made with FeSO<sub>4</sub> for release, generating a precipitation of iron hydroxide sludge.

Another factor that affects drug degradation is the composition of the matrix. In simple matrices, formed by the active ingredient of the drug and deionized water, the interferences are lower in relation to the matrices containing the excipients. The real effluents have a higher organic load, which leads to the consumption of the reagents used in the reaction, reducing the efficiency of the process. When using the photo-Fenton process for the degradation of equal concentrations of eight drugs, after 60 minutes, the ibuprofen removal efficiency was 70, 58 and 40% for three types of samples: ultrapure water, water from Lake Geneva, Switzerland, and the effluent from the local water treatment plant, Lausanne, respectively. The lower degradation achieved in effluent samples (WTP) may be related to the competition of hydroxyl radicals by competing compounds such as carbonates, chlorides and humics substances present in the effluent. Furthermore, the absorption of UV light is decreased by the higher turbidity of these samples (Neamțu *et al.* 2014).

The evaluation of furosemide degradation (FUR) was associated with seven other drugs (gemfibrozil, nimesulide, paracetamol, propranolol, dipyron, fluoxetine, and diazepam), with the application of heterogeneous Fenton and heterogeneous photo-Fenton Solar and different matrices: ultrapure water, simulated hospital effluent and real hospital effluent (Porto Alegre/Brazil). The removal efficiency obtained for FRU in the three matrices was 95% after 1 minute of reaction. It was observed only FUR and diazepam had their molecules completely broken down, leaving 30% of integrated propranolol molecules. The other drugs ended up with 60 to 70% of their molecules intact at the end of the 120-minute treatment process. They also sought to evaluate the degradation products formed (Cuervo Lumbarque *et al.*, 2018).

Using the Solar Photo-Fenton Like method (Cuervo Lumbarque *et al.*, 2019b) and a modified catalyst, the Fe(III)/EDDS complex (EDTA structural isomer) became possible to perform the tests at pH 7. The assays were optimized with ultrapure water and drugs, and later these conditions were adopted for synthetic effluents. In distilled water FUR was degraded with 7.5 min, and in the synthetic effluent with 12.4 min (Cuervo Lumbarque *et al.*, 2019a).

The combination of the electrochemical process with the oxidation promoted by the Fenton reaction amplifies the oxidative potentials in the degradation processes. Five of the most used drugs in Belo Horizonte were treated using this technique, in several studies, as shown in Table 2 (Ma *et al.* 2016; Yang *et al.* 2018; Olvera-Vargas *et al.* 2016; Olvera-Vargas *et al.* 2018; Isarain-Chávez *et al.* 2011;

El-Hanafi *et al.* 2014; Loaiza-Ambuludi *et al.* 2013; Zhou *et al.* 2018a; Zhou *et al.* 2018b; Lui *et al.* 2018; Zhou *et al.* al. 2019).

According to Zhou (2018a), when performing the Electro-Fenton process comparing the use of a floating method and a conventionally submerged cathode, the floating cathode proved to be more efficient. To achieve 100% removal of the drug Ibuprofen, under the initial conditions of pH 3 and iron concentration equal to  $40 \text{ mg.L}^{-1}$ , it took 60 and 120 minutes, respectively, for the floating and submerged cathode. Furthermore, for 120 minutes the removal of TOC presented by the first was 78.3%, while by the second it was 25.4%. Removing TOC with floating cathode may indicate good applicability for this Fenton option.

In the ibuprofen degradation study, Zhou (2019) sought to establish the removal efficiency through an Electro-Fenton in aqueous solution using modified graphite fiber and unmodified graphite fiber (pH 3,  $[\text{Fe}^{2+}] 10 \text{ mg L}^{-1}$ ). The process with modified graphite fiber had 75.3% efficiency, and with unmodified fiber electrode had 57.6%, with continuous flow reaction, after 100 minutes. The modified process favors electron and mass transfer between electrodes and electrolytes leading to higher generation of  $\text{H}_2\text{O}_2$ , with increased process efficiency (Zhou *et al.* 2019).

In an Electro-Fenton process, the analysis of the effect of alternating or direct current on the efficiency of ibuprofen degradation was studied. When using alternating current, a significant increase in the generation of  $\text{H}_2\text{O}_2$  was observed in relation to that generated with direct current, with TOC removal at 120 minutes of 89.3% and 59.5%, respectively (Zhou *et al.* 2018b). By using the Electro-Fenton process peroxide generation is produced in the electrolyte cell and may be a treatment system with lower reagent consumption.

The association of techniques in the effluent treatment process has transformed into a search for options to improve the efficiency of the removal of emerging recalcitrant pollutants, as well as their degradation products formed during the processes used (Zhou *et al.*, 2019, Zhou *et al.*, 2018b, Cuervo Lumbarque *et al.*, 2019a, Dong *et al.*, 2019, Chen *et al.*, 2018, Adityosulindro *et al.*, 2018, Guettaia *et al.*, 2018, Klammerth *et al.*, 2013).

Antihypertensive drugs, inhibitors of the renin-angiotensin-aldosterone system, have been found in sanitary effluents, rivers, and lake water columns (Fonseca *et al.* 2020; Golovko *et al.* 2020; Kot-Wasik *et al.* 2016). For this purpose, tests were conducted using electro-Fenton and photo-electro-Fenton, seeking to degrade losartan and valsartan, at pH close to neutral. Light emitting diodes (LED) were used as light source. The degradation obtained with photo-electro-Fenton was more efficient for drugs and led to increased biodegradability after this treatment (Martínez-Pachón *et al.* 2019).

Klamerth (2012) conducted a pilot-scale study using the effluents from the ETE of Almería, Spain. Photo-Fenton and modified Photo-Fenton degradation tests were performed at neutral pH with two complexing reagents. Among the 60 drugs identified were atenolol and hydrochlorothiazide furosemide. Atenolol presented less than 5% residual concentration, using photo-Fenton at neutral pH, while furosemide and hydrochlorothiazide did not present residual concentrations. Degradation products and metabolites were not focuses of this research (Klamerth *et al.*, 2012).

When comparing Photo-Fenton and Fenton, the first presents, in some studies, a higher removal efficiency than conventional Fenton, this is a consequence of the generation of OH radicals through the photo-reduction of ferric ions, through the addition of ultraviolet light. In this study, the removal efficiency of ibuprofen was 66% by Photo-Fenton and 57% by traditional Fenton (Chen *et al.*, 2018). In Herghelegiu work (2018) the results were higher, with efficiency of 89% and 86% for Photo-Fenton and Fenton, respectively, for the same drug. The difference was not significant in this last study, making it necessary to evaluate the energy costs involved. These differences in the efficiency of ibuprofen degradation may be associated with the pH used by the studies: Chen *et al.* (2018) worked at acid pH, different from the alkaline pH adopted in Herghelegiu in his study (2018).

Li (2013) used traditional Fenton (with  $\text{Fe}^{2+}$ ) and Fenton-Like ( $\text{Fe}^{3+}$ ) to degrade Atenolol and 18 other substances present in WWTP (USA) samples, keeping the pH 3 and iron concentration at  $20 \text{ mg L}^{-1}$  and molar ratio of  $\text{H}_2\text{O}_2/\text{Fe}^{(2+/3+)}$  of 2.5. To achieve the same removal efficiency of 99%, the reaction time for Fenton-Like was four times longer. For a Fenton reaction, with the addition of half  $\text{Fe}^{2+}$ , the same removal occurred with 30 minutes, showing to be more efficient and economical (Li *et al.*, 2013).

#### Application of Fenton process and its derived techniques in effluent polishing

The implementation of a post-treatment system by AOP, in the secondary effluent of an WTP, Local, in Spain, Arzate *et al.* (2017) studied the gain in increasing the hydraulic retention time (HRT). A continuous Solar Photo-Fenton process was used, and for a 20, 40, and 80 minute HRT the hydrochlorothiazide drug removal rate was 93%, 96% and 98%, respectively.

This type of study can indicate ways to be implemented in the final polishing of sanitary effluents, aiming to obtain a reduction in the release of emerging contaminants into the environment.

WTPs use biological treatment processes for raw effluents, which remove simple organic matter. The secondary effluent produced in this first treatment has recalcitrant organic compounds, such as drugs.

Seeking a polishing of the WTP effluent in Spain, Arzate *et al.* (2017) assessed the implementation of a post-treatment system by AOP. Hydraulic retention times (HRT) were evaluated with the implementation of a continuous Photo-Fenton Solar process. The hydrochlorothiazide removal rate was 93%, 96% and 98%, respectively, for HRT of 20, 40 and 80 minutes.

The results obtained in this research are indicative that the implementation of AOP as a stage in the final polishing of sanitary effluents, can lead to a reduction in the release of emerging contaminants into the environment.

Among the evaluated processes, it was observed that the Photo-Fenton solar process at pH 3 exhibited superior efficiency. For instance, tests with real effluents demonstrated a removal rate of above 99% for HTZ (Arzate *et al.*, 2017) and close to 100% for FUR (Klamerth *et al.*, 2012), while exceeding 80% for ATE (Neamtu *et al.*, 2014, Veloutsou, Bizani & Fytianos, 2014), and achieving nearly 100% removal for IBU (Ayoub *et al.* 2019). However, it is worth noting that a drawback of these processes is the necessity to neutralize the solution for final disposal.

Other processes are conducted at pH close to neutral, using iron sources from organic complexes. HTZ, IBU, and FUR were degraded above 90% under these conditions (Klamerth *et al.*, 2012). Processes involving carbon fiber electrodes, catalytic processes with titanium, or zeolites exhibited remarkably high removal rates. It is essential to consider the investment costs for acquiring the system and its operational maintenance.

The analysis of process efficiencies should be directed towards implementing these treatments for real effluents under conditions that can be rapidly implemented, achieving significant removal at a lower operational cost.

## Conclusion

It was found in the literature that degradation processes using Fenton reaction were applied to 6 drugs among the 10 most frequently used in Belo Horizonte. Among the most studied drugs are ibuprofen, atenolol, and furosemide. The traditional Fenton reaction has been modified to speed up the process and make it more efficient and cleaner, reducing waste formation. Modified processes such as photo Fenton and electron-Fenton showed good results for drug degradation. In general, the studies showed higher efficiency in the removal of recalcitrant drugs than conventional treatments of sanitary and/or industrial effluents. The analysis of degradation products generated during the Fenton reaction has scarcely been done still, even less than the determination of total organic carbon. These two parameters increase the reliability in the degradation of emerging contaminants.

It's crucial to note that the majority of drug degradation studies highlighted in this review are conducted on a bench scale, typically within research laboratories and universities. These studies often use post-treatment effluents, where the organic load has been significantly reduced through filters or biological treatments. While these bench-scale studies are valuable for optimizing reaction conditions, it's essential to recognize their limitations.

To comprehensively evaluate real effluents from wastewater treatment plants, it becomes necessary to assess not only the drugs but also their metabolites and degradation by-products, as these substances may carry toxicities. Transitioning from isolated laboratory systems to real-world conditions is a critical step in understanding the broader environmental implications.

Therefore, while studies in research settings are indispensable for optimizing reaction conditions, they serve as a foundation for the eventual application and adaptation of these processes to more complex matrices, mirroring real-world conditions. This ensures a holistic understanding of the efficacy and potential environmental impacts of drug degradation processes.

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