



Review

Advanced oxidation process-mediated removal of pharmaceuticals from water: A review

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ABSTRACT

Pharmaceuticals, which are frequently detected in natural and wastewater bodies as well as drinking water have attracted considerable attention, because they do not readily biodegrade and may persist and remain toxic. As a result, pharmaceutical residues pose on-going and potential health and environmental risks. To tackle these emerging contaminants, advanced oxidation processes (AOPs) such as photo-Fenton, sonolysis, electrochemical oxidation, radiation and ozonation etc. have been applied to remove pharmaceuticals. These processes utilize the high reactivity of hydroxyl radicals to progressively oxidize organic compounds to innocuous products. This review provides an overview of the findings from recent studies, which have applied AOPs to degrade pharmaceutical compounds. Included is a discussion that links various factors of TiO₂-mediated photocatalytic treatment to its effectiveness in degrading pharmaceutical residues. This review furthermore highlights the success of AOPs in the removal of pharmaceuticals from different water matrices and recommendations for future studies are outlined.

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1. Introduction

Pharmaceuticals (drug products) containing active pharmaceutical ingredients (APIs), despite being designed to treat a variety

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of ailments in humans and animals, have shown a negative impact on the environment due to their continuous presence in surface water, groundwater, urban wastewater and also drinking water. The past two decades have witnessed extensive research directed towards the presence of pharmaceuticals in the environment and as a result, these organic compounds are now classified as emerging contaminants. This interest from the scientific community has stemmed from advancement in analytical methods for their detection in environmental samples down to parts per trillion (ng/L) (Richardson and Ternes, 2011; Sangion and Gramatica, 2016). Such advancements have allowed for the detection of a variety of pharmaceuticals in the environment, originating from both human and veterinary use. Recognizing the presence of pharmaceuticals in the environment, concerns have been raised to investigate their behaviour, fate, effects and toxicity as well as potential methods for their efficient removal from these water sources.

Environmentally concerning groups of pharmaceuticals include non-steroidal anti-inflammatory drugs (NSAIDs), antibiotics, beta-blockers (β -blockers), antiepileptic drugs, blood lipid-lowering agents, antidepressants, hormones, antihistamines (Khetan and Collins, 2007) and X-ray contrast media (Jiang et al., 2013), respectively. Wastewater treatment plants (WWTPs) have been identified as the main source for these pharmaceuticals as they collect discharges from hospitals, veterinaries, households, industries and pharmacies (Destrieux et al., 2017; Lee et al., 2017). Due to the differences in the physicochemical properties of APIs, the configuration of WWTP facilities and the sewage composition, the efficiency of treatments can vary significantly requiring a broad range of removal protocols (Fatta-Kassinos et al., 2011a; Luo et al., 2014; Mompelat et al., 2009; Tarpani and Azapagic, 2018). Several recent studies have confirmed the presence of pharmaceuticals in the influents and effluents of WWTPs (Causanilles et al., 2017; Lin et al., 2018).

The non-biodegradable nature and “pseudo persistence” of many APIs render conventional biological and chemical treatments ineffective, thus leading to an increased presence of the parent drugs and their metabolites in both, aquatic and terrestrial environments (Mirzaei et al., 2018; Xiang et al., 2018). For example, antibiotics are known to be not effectively removed by conventional methods. In addition, Phase-II metabolites of parent APIs are commonly undone, leading to higher concentrations in WWTPs' effluents than their influents (Mirzaei et al., 2018). When these incompletely treated effluents are released into the aquatic environment and utilized by end users for soil irrigation or amendment, the reclaimed water may impose risks to humans, soil, crops and biota (Biel-Maeso et al., 2018). Hence, pharmaceuticals have been recognized as important environmental pollutants, necessitating the search for effective and advanced technologies to remove them from wastewater streams and consequently the environment.

Among the water treatment technologies employed thus far, advanced oxidation processes (AOPs) present great potential for treating a wide range of emerging contaminants. AOPs involve the *in-situ* generation of highly reactive oxygen species (ROS) with low selectivity such as hydroxyl radicals (HO^\bullet), H_2O_2 , O_3 and superoxide anion radicals (O_2^\bullet), providing pathways of complete mineralization to CO_2 , H_2O and inorganic ions or acids (Dalrymple et al., 2007). AOPs are commonly classified into 2 major groups depending on their mode of activation, photochemical and thermal (non-photochemical) methods. Examples include ozonation, Fenton, photo-Fenton, photocatalysis, radiation, sonolysis and electrochemical oxidation. A search on SCOPUS displayed a marked increase in the number of studies on AOP applications in tackling the removal of pharmaceuticals, signifying an increase in knowledge in this field of study (Fig. 1).

This review initially focuses on the pollution status of

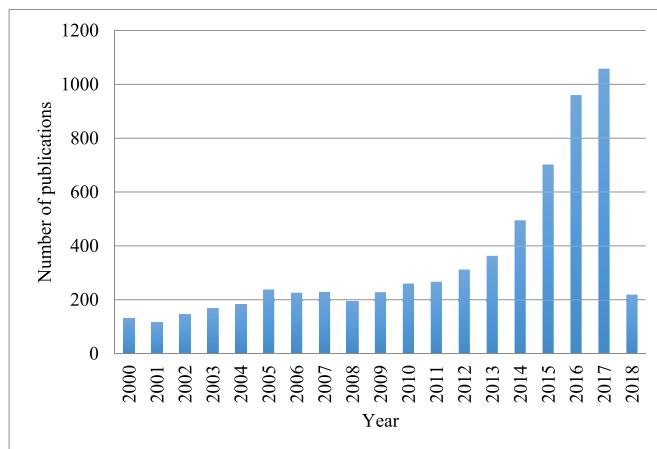


Fig. 1. Statistics of publications (2000–2018) on applications of AOPs for pharmaceutical degradation (Scopus database for search “AOPs AND pharmaceuticals” in all subject areas).

pharmaceuticals followed by an overview of various photochemical and non-photochemical degradation technologies for pharmaceuticals in (waste)water streams, with important and recent outcomes summarized. Additionally, special attention was given to TiO_2 photocatalysis, which has received considerable attention in pharmaceutical abatement.

2. Status of pharmaceutical pollution

Pharmaceuticals with endocrine disrupting properties (EDCs) are emerging as environmental pollutants, which is notable from legislative actions undertaken by environmental agencies in several countries. The United States Environmental Protection Agency (USEPA) has included three pharmaceuticals in their recent contaminant candidate list (CCL-3) together with eight synthetic hormones and other disinfection by-products and pesticides (Richardson and Ternes, 2011). Most APIs and EDCs have however remained unregulated, although the European Union (EU) and the United States of America (USA) in particular have shown great interest in combating the presence of pharmaceuticals in the environment (Esplugas et al., 2007; Metcalfe, 2013; Tarpani and Azapagic, 2018). This has resulted in several directives and frameworks such as the community program of research on endocrine disruptors and environmental hormones (COMPREHEND), ecotoxicological assessments and removal technologies for pharmaceuticals in wastewater (REMPHARMAWATER), environmental risk assessment of veterinary medicines in a slurry (ERAVMIS) and European Directives such as 2013/39/EU and EU 2015/495 and an endocrine disruptor screening program (EDSP) by the USEPA (Esplugas et al., 2007; Lofrano et al., 2018; Tarpani and Azapagic, 2018). In addition, the Food and Drug Administration (FDA) requires an environmental assessment report for APIs that are expected to be released into the environment with concentrations $\geq 1 \mu\text{g/L}$ (Nikolaou et al., 2007). These efforts clearly indicate that pharmaceuticals are considered an environmental threat for the future and therefore methods for their removal from the environment require immediate attention.

Important sources associated with the presence of pharmaceuticals in water bodies include inappropriate disposal of medications by households, pharmaceutical manufacturers, hospitals and pharmacies (Ziylan and Ince, 2011). These sources of pharmaceuticals in the environment have been extensively reviewed (Kanakaraju et al., 2014a; Kaur et al., 2016). In addition, animal

farming releases veterinary pharmaceuticals to the environment directly through aquaculture, agricultural runoff and leaching (Khetan and Collins, 2007). APIs from human consumption are mainly excreted in urine and faeces into receiving waters, with levels depending on the dose and individual physiology (Bound and Voulvoulis, 2005). Elimination from the human body occurs after the APIs have been partially or completely converted to water-soluble metabolites or, in some cases, without being metabolized. Through sewage systems, pharmaceutical residues eventually reach WWTPs. A review article reported the excretion rate of human and veterinary pharmaceuticals and their metabolites based on therapeutic use (Mompelat et al., 2009). Several metabolites such as clofibrilic acid, a major metabolite of lipid regulators and two major metabolites of carbamazepine, 10, 11-dihydro-10,11-dihydroxycarbamazepine and 10,11-dihydro-10,11-epoxycarbamazepine, have already been detected in the environment, raising considerable concern. Human or veterinary APIs with resistance to biological degradation may consequently translate into their persistence when released into water bodies (Ferrari et al., 2003).

The current knowledge considers treated municipal wastewater as contributing significantly to the presence of pharmaceuticals as well as other emerging contaminants (e.g. personal care products, hormones etc.) since WWTPs are not designed to combat the resilient and persistent nature of many APIs (Afonso-Olivares et al., 2017; Carmona et al., 2014; Schröder et al., 2016; Suárez et al., 2008). For example, the recent inclusions of diclofenac and the hormones 17 β -estradiol and 17 α -ethinyl estradiol into the EU watch list (known as Decision 2915/495) is a result of the inadequacy of WWTPs to remove these pharmaceuticals (Schröder et al., 2016). Studies performed on sewage treatment plants in different countries have supported this decision. For example, a sewage treatment plant in Japan was reported as the main source of six anti-cancer agents detected in the effluent (Azuma et al., 2015). Another study conducted in one of the largest WWTPs in Southern China revealed that twenty-four pharmaceuticals were detected in the influent with mean concentrations ranging from 2.3 to 890 ng/L, with sulphonamides, sulfamethoxazole, sulfadiazine, sulfamethazine, and trimethoprim being the most commonly detected compounds (Lin et al., 2018). Furthermore, the removal efficiencies of pharmaceuticals among WWTPs in different countries varied due to the nature of the organic compounds, geography, climate (Carballa et al., 2004) and operating conditions (Ziylan and Ince, 2011). In some cases, discrepancies occurred within WWTPs in the same country mainly due to the sampling methods (Tran et al., 2018).

When pharmaceuticals enter WWTPs that commonly consist of primary and secondary (and infrequently tertiary) treatment stages, they can be degraded or adsorbed onto the sewage sludge, depending on their physicochemical properties and the operating conditions of the treatment facility (Guerra et al., 2014; Kaur et al., 2016; Verlicchi et al., 2012). The presence of living organisms such as bacteria and fungi contribute to the degradation of pharmaceuticals in WWTPs (MacLeod and Wong, 2010), particularly in the secondary treatment stage (e.g. aerobic or anaerobic systems) where biological processes are involved. Nevertheless, biological degradation has been argued to have a minimal effect on the degradation of pharmaceuticals and this failure has been named as a key factor for their biological persistence (Klavarioti et al., 2009) and subsequent discharge into the aquatic environment. Contradictory evidence is however available on this aspect in the literature. For example, Heberer et al. (2002) reported that biodegradation contributed 99% to the removal of caffeine, but only 8% and 17% for carbamazepine and diclofenac, respectively, from sewage treatment plants in Berlin, while Yamamoto et al. (2009)

reported that all tested pharmaceuticals were resistant to biodegradation in river water under laboratory conditions. In another example, carbamazepine has been reported to be resistant to biodegradation and thus, its removal from surface water is assumed to occur via photodegradation (Donner et al., 2013). The discrepancies in the fate of APIs based on the above studies is due to their differing chemical characteristics and other factors such as water flows, season, natural environmental conditions and simulated conditions in the laboratory.

In general, the extent of pharmaceutical removal by biological process in WWTPs varies greatly between studies, depending on the treatment process, physicochemical properties of these organic compounds, microbial populations, operational parameters such as pH, temperature, sludge retention time, biomass concentration and hydraulic retention time, respectively (Baena-Nogueras et al., 2017; Martínez-Alcalá et al., 2017). A study reported that the biological degradation from a conventional activated sludge WWTP was crucial for the removal of diclofenac, naproxen and ibuprofen from water, with more than 80% removal while ketoprofen showed only 51.4% degradation (Martínez-Alcalá et al., 2017). In contrast to this, the removal of carbamazepine was attributed to the adsorption onto activated sludge (Martínez-Alcalá et al., 2017). Nitrification, a microbial-assisted oxidation in biological wastewater treatment was indicated to enhance lowering the concentrations of pharmaceuticals (Guerra et al., 2014). A recent study, which compared the aerobic biodegradation of 33 pharmaceuticals (and other personal care products) between two laboratory settings using freshwater and seawater, revealed that marine microorganisms enhanced biodegradation (90%) compared to freshwater (57%) after 28 days of incubation (Baena-Nogueras et al., 2017). The study highlighted that biodegradation was dependent on sample origin and water salinity. Another fact concerning biological degradation is that APIs belonging to the same therapeutic group may demonstrate differing biological degradation rates and adsorption onto sludge. For example, the biological degradation rate of ibuprofen and ketoprofen was much higher (>75%) than that of diclofenac (<25%) (Salgado et al., 2012).

In contrast to many studies performed on the assessment of biological processes applied in domestic or municipal WWTPs for pharmaceuticals' removal, there are limited studies on industrial pharmaceutical WWTPs (PWWTPs), which are known to apply a variety of treatment methods to their biological units. Biological units (e.g. membrane biological reactor, expanded granular sludge bed or biological contact oxidation) in two PWWTPs in northern China were reported to be effective in removing 62.0–78.3% of oxytetracycline, chlortetracycline, and tetracycline in their effluents compared to the concentration in their influents, although tetracyclines were still detected in their effluents (Hou et al., 2016).

As a consequence of incomplete removal from WWTPs, unrecovered or residual APIs and their metabolites are released into surface waters, groundwater and eventually into the aquatic environment (Xiang et al., 2018). A wide range of pharmaceuticals, including anti-inflammatories, analgesics, antibiotics, β -blockers, lipid regulators, antiepileptic and antidepressant drugs and hormones have been frequently detected in environmental waters (Lee et al., 2017). Typically, the existence of APIs in surface water, groundwater and drinking water occurs at trace levels ranging from ppt to ppb (ng/L to μ g/L) (Kümmerer, 2009b). Numerous investigations are available on the occurrence of APIs in surface waters (Moldovan, 2006; Paíga et al., 2016; Ternes, 1998), groundwater (Drewes et al., 2002; Koroša et al., 2016; Lopez-Serna et al., 2013) and sewage influents and effluents (Andreozzi et al., 2003; Arlos et al., 2015; Carballa et al., 2004; Gros et al., 2017; Heberer, 2002; Lindqvist et al., 2005). Detection of metabolites or conjugated metabolites in natural waters have also been reported

in various studies, signifying the potential impact and risks on human health and ecosystems (Azuma et al., 2015; Borgatta et al., 2015). In contrast, studies on the potential impacts of active metabolites have been rather limited.

Concentrations of pharmaceuticals are generally higher in sewage effluents compared to freshwater bodies or receiving waters. This is attributed to natural dilution effects and other natural elimination pathways such as hydrolysis, sorption (or adsorption) and photolysis by natural sunlight (Pal et al., 2010). Dilution effects, which determine the concentration of pharmaceuticals in the receiving waters, are governed by the wastewater flow from the WWTPs coupled with water flow in the receiving water (Caliman and Gavrilescu, 2009). The removal of pharmaceuticals via hydrolysis appears to be minimal (Ziylan and Ince, 2011), as they are commonly designed for oral administration (Andreozzi et al., 2003). In contrast, adsorption of pharmaceuticals onto suspended solids, sediments and sludge is an important physical process, which subsequently favours their removal in the presence of such materials. However, various factors contribute to the adsorption capacity of soils or sediments such as soil type, organic matter content, clay content and ion-exchange capacity (Drillia et al., 2005). Physicochemical properties of the API such as water solubility, octanol-water partition coefficient ($\log K_{ow}$) and soil-water distribution coefficient ($\log K_d$) are important factors in determining the degree of adsorption (Drillia et al., 2005). Typical characteristics of pharmaceuticals such as their low polarity, high hydrophilicity and a low $\log K_{ow}$ suggest a low binding capacity to soils, sludge or sediments (Caliman and Gavrilescu, 2009).

The presence of pharmaceuticals in trace quantities has subsequently resulted in adverse effects in aquatic and terrestrial organisms (Kümmerer et al., 2000; Oaks et al., 2004; Sebestyén et al., 2018) as well as potential toxicity on non-target organisms or aquatic environments (Ferrari et al., 2003; Santos et al., 2010). Concerns arising from mixtures of pharmaceuticals are also increasing, despite the focus of most studies on biological effects of single API compounds. A study by Brodin et al. (2013) revealed that the concentration of the psychotherapeutic drug oxazepam was significantly higher in the muscle tissue of the European perch (*Perca fluviatilis*) from the river Fyris (Sweden) than in the river water itself as a consequence of bioaccumulation. Their subsequent study also reported that oxazepam induced behavioural changes in fish at environmentally relevant concentrations (Brodin et al., 2014). Grabicova et al. (2017) investigated the bioaccumulation of selected psychoactive pharmaceuticals in different tissues of brown trout found in a stream affected by the effluents of a WWTP. The results revealed that the liver and kidney were the most affected organs. In addition, the emergence of antibiotic resistant genes and bacteria due to high usages of antibiotics has also been reported (Guo et al., 2018; Kümmerer, 2009a; Michael et al., 2013). Another worrying aspect of these resistant genes is that they can reach humans via the food chain, as shown in the case of lincomycin (Wang et al., 2018). Contraceptive pills containing ethinyl estradiol have been reported to induce feminization in the male fish and reduced sperm production in downstream of WWTPs (Sebestyén et al., 2018).

The presence of APIs in drinking water (Heberer et al., 2002; Jones et al., 2005; Rosa Boleda et al., 2011; Ternes et al., 2002) and groundwater (Lapworth et al., 2012; Yang et al., 2017) as a source of potable water represents an urgent concern although there is currently a lack of evidence for a direct link to human health impacts. Recycling of potable water has also raised human health concerns. For example, in California and Florida with such recycling programs, humans may consume water potentially containing active metabolites and degradants of pharmaceuticals (Carbonaro et al., 2013). Carmona et al. (2014) reported the

presence of diclofenac, propylparaben and ibuprofen in concentrations ranging from 1 to 39 ng/L, while naproxen and salicylic acid were detected more frequently in 8 sampled tap waters.

As water and wastewater containing pharmaceutical residues are becoming a potential threat to the ecosystem and show potential toxic effects to humans, destructive methods based on AOPs have been proposed for their elimination.

3. Advanced oxidation processes (AOPs) as a tool for the degradation of pharmaceuticals

Reactive oxygen or free radical species represent strong oxidants that can initiate AOPs in order to degrade pollutants to simple and nontoxic molecules. Free radical species are atoms or molecules containing at least one unpaired electron such as the hydroxyl radical (HO^\bullet), superoxide anion radical (O_2^\bullet), hydroperoxyl radical (HO_2^\bullet) or alkoxyl radical (RO^\bullet), with the HO^\bullet radical having attracted the most attention in this area. The characteristic features of HO^\bullet radicals are their non-selective nature, high reactivity and powerful oxidizing capabilities ($E^\circ = +2.80 \text{ V}$) (Andreozzi et al., 1999). They are ranked second to fluorine ($+3.03 \text{ V}$) and are able to attack a wide range of organic contaminants, with rate constants normally in the order of $10^6\text{--}10^9 \text{ M}^{-1} \text{ s}^{-1}$ (Andreozzi et al., 1999; Legrini et al., 1993). Reactions of HO^\bullet radicals with organic compounds can be either by hydrogen abstraction (Eq. (1)) from C-H, N-H, or O-H groups, or radical-radical interactions, e.g. the addition of molecular O_2 leading to the formation of the peroxy radical (Eq. (2)), or through direct electron transfer (Eq. (3)) yielding oxidized intermediates or, in the case of complete mineralization, the production of CO_2 , H_2O and inorganic acids (Legrini et al., 1993). Despite the high oxidation potential, kinetic rates of interactions between HO^\bullet radicals and organic compounds depend on the affinity of these compounds for the oxidant.



A considerable amount of work has been published relating to the application of AOPs for the abatement of pharmaceuticals in water. Application of AOPs to wastewater treatment in general has been extensively reviewed (Deegan et al., 2011; Gogate and Pandit, 2004; Klavarioti et al., 2009; Wang and Wang, 2016; Wang and Xu, 2012) including specific types of AOPs to pharmaceutical degradation such as photocatalysis (Dalrymple et al., 2007), non-thermal plasma treatment (Magureanu et al., 2015) and iron-based catalytic ozonation (Wang and Bai, 2017). A recent review by Ahmed et al. (2017) has provided an insight into the impact of various biological, chemical and hybrid techniques on emerging contaminants including pharmaceuticals. Recent representative studies on the degradation of pharmaceuticals are presented in Table 1. In this section, major findings of the chosen AOPs, namely ozonation, Fenton, photo-Fenton, sonolysis, UV and UV/peroxide oxidation, electrochemical oxidation and radiation are presented, while TiO_2 photocatalysis is discussed in the following section. According to Table 1, AOPs commonly applied for pharmaceutical wastewater treatment include three types: photochemical processes, non-photochemical processes and hybrid or combined processes (Fig. 2).

3.1. Ozonation

Chemical oxidation processes, ozonation and combinations of

Table 1

Overview on selected recent publications on the application of different types of AOPs to the degradation of pharmaceuticals.

AOPs applied	Pharmaceuticals	Water matrix	Significant findings	Reference
Single AOP				
Ozonation	Antibiotics, steroid hormone, lipid regulator, antineoplastic, non-steroidal anti-inflammatory drug, and psychostimulant	Synthetic wastewater, surface water, and effluents of municipal wastewater treatment plant	Specific ozone doses ranging from 0.82 to 2.55 mg O ₃ /mg DOC resulted in >99.9% removal for most of the studied pharmaceuticals. The increased toxicity for aqueous solutions of acidic pharmaceuticals at a specific ozone dose of 2.24 mg O ₃ /mg DOC was due to formation of more toxic by-products.	Almomani et al., 2016
	Indomethacin	Ultrapure water	Ozone doses of 2, 10, 20 and 35 mg/L resulted in complete indomethacin (25 µM) degradation within 7 min in contrast to poor mineralization (TOC), despite extending the reaction time to 30 min.	Zhao et al., 2017
	Propranolol	Milli-Q water	Complete removal of propranolol was achieved in 8 min. Total organic carbon (TOC) removal did not increase above 5%, despite increased contact time of 60 min. Low dose ozone was inefficient to improve biodegradability of ozonated samples.	Dantas et al., 2011
	Tetracycline	Deionized water	Direct ozonation showed complete degradation of tetracycline with H ₂ O ₂ concentrations with <i>tert</i> butyl alcohol (HO [•] radical scavenger) showing no effect on the degradation rate. Only 35% of COD removal was attained after 90 min ozonation.	Wang et al., 2011
	Carbamazepine, diclofenac, sulfamethoxazole, and trimethoprim	Milli-Q water	Carbamazepine, diclofenac and trimethoprim degraded completely when a lower dose of ozone was applied, 1.6 mg/L, 2.3 mg/L and 2.8 mg/L, respectively. However, sulfamethoxazole consumed a higher dose, 4.5 mg/L and longer time to achieve complete degradation due to the formation of highly reactive by-products.	Alharbi et al., 2016
	Amoxicillin	Distilled water and ultrapure water	The pseudo-first order reaction rates for amoxicillin by ozonation at pH 3, pH 7 and pH 10 were 0.064 min ⁻¹ , 0.321 min ⁻¹ and 1.970 min ⁻¹ , respectively, with pH 10 being the optimum one.	Kidak and Doğan, 2018
	Salicylic acid	Deionized water	Salicylic acid removal was observed to be more significant and rapid at pH 4 compared to pH 8 and pH 10. At pH 4 and in the presence of 1 mg/L of ozone, about 95% of salicylic acid was removed.	Hu et al., 2016
Fenton and photo-Fenton	Ibuprofen, acetyl sulfamethoxazole and metoprolol	Secondary effluent from wastewater treatment plant	Effect of pHs (6.5, 7.0 and 7.5) at a constant temperature, 20°C in the presence of organic matter on the ozonation treatment with an initial concentration of 1.5 mg/L showed that metoprolol degraded at the fastest rate followed by acetyl sulfamethoxazole and ibuprofen at all pHs.	Cai and Lin, 2016
	Amoxicillin	Distilled water	Complete and rapid oxidation was attained for amoxicillin in the presence potassium ferrioxalate complex within 5 min, while for FeSO ₄ 15 min was required in experiments using a solar simulator.	Trovó et al., 2011
	Ofloxacin and trimethoprim	Ultrapure water	Comparison of solar photo-Fenton between acidic pH (pH 2.8–2.9) and neutral (unadjusted pH 7) showed that complete degradation of ofloxacin and trimethoprim was attained likewise at the acidic pH but at a slower rate. Poor DOC removal was observed for both conditions.	Michael et al., 2012
	Nalidixic acid	Demineralized water, saline water, synthetic industrial effluent, real industrial effluent	Although complete degradation was obtained for nalidixic acid, degradation and mineralization was slower in saline water and synthetic industrial effluent with a compound parabolic collector.	Sirtori et al., 2011
	5-Fluorouracil	Ultrapure water	Solar simulated Fenton-like treatment (Fe ³⁺ /S ₂ O ₈ ²⁻) resulted in a higher degradation rate and dissolved organic carbon (DOC) removal than Fe ³⁺ /H ₂ O ₂ for the degradation of 5-fluorouracil. The degradation rate and DOC removal under Fe ³⁺ /S ₂ O ₈ ²⁻ was 0.04 min ⁻¹ and 40%, respectively while for Fe ³⁺ /H ₂ O ₂ system the values were 0.024 min ⁻¹ and 25%.	Koltsakidou et al., 2017
	Antipyrine	Aqueous solution	Ferrioxalate induced photo-Fenton reaction with UVA-LED was effective to degrade antipyrine as a result of the production of more HO [•] radicals in the system. The complete degradation of antipyrine was obtained after 2.5 min, while 93% of TOC removal was recorded after 60 min ([H ₂ O ₂] ₀ = 100 mg/L, [Fe] ₀ = 2 mg/L and [H ₂ C ₂ O ₄] ₀ = 100 mg/L, pH = 2.8).	Davididou et al., 2017
	Oxacillin	Deionized water	Based on the applied factorial design, removal of oxacillin (203 µmol/L) was found to be optimum when the concentration of Fe ²⁺ , H ₂ O ₂ and applied light power were 90 µmol/L, 10 mmol/L and 30 W, respectively.	Giraldo-Aguirre et al., 2017
	15 pharmaceuticals (in combination with other micro pollutants)	Municipal wastewater treatment plant	The highest percentage of micro pollutant degradation at 83% was achieved in the presence of UV (254 nm) using 30 mg/L H ₂ O ₂ and 2 mg/L Fe(III) at natural pH.	De la Cruz et al., 2013b
	Mixtures of 15 emerging contaminants (ECs)	Synthetic water, simulated effluent wastewater, real effluent wastewater	Mild solar photo-Fenton (Fe = 5 mg/L, H ₂ O ₂ = 50 mg/L) was efficient to degrade mixtures of 15 ECs (pharmaceuticals, personal care products, pesticides) without any pH adjustments. But, toxicity level increased, with the degradation products formed in real effluent wastewater.	Klamerth et al., 2010b
	Carbamazepine, ibuprofen, ofloxacin, flumequine, sulfamethoxazole	Municipal wastewater treatment plant effluent	Solar photo-Fenton using Fe: ethylenediamine-disuccinic acid (1:2) resulted in >96% removal of pharmaceuticals within 45 min while Fe: citrate (1:5) produced 94% removal after 96 min at neutral pH using nanofiltration concentrated sample.	Miralles-Cuevas et al., 2014
Photo-Fenton	Ciprofloxacin	Milli-Q water	Photo-Fenton degradation of low and high concentrations of ciprofloxacin in the presence of different iron sources (iron citrate, iron oxalate and iron nitrate) and pH (2.5, 4.5 and 6.5) gave different results. For a high	de Lima Perini et al., 2013

(continued on next page)

Table 1 (continued)

AOPs applied	Pharmaceuticals	Water matrix	Significant findings	Reference
			concentration of ciprofloxacin (25 mg/L) at pH 4.5, both the iron complexes iron citrate and iron oxalate produced total conversion within 10 min. Higher ciprofloxacin conversion was obtained using iron citrate for low concentration (1 mg/L) of this compound at pH 2.5 after 10 min.	
UV and UV/peroxide processes				
UV and UV/H ₂ O ₂	41 APIs (10 analgesics, 4 antiarrhythmic agents and 12 antibiotics and 15 others)	Municipal treatment plant	The removal efficiencies by UV and UV/H ₂ O ₂ were highly dependent on the type of pharmaceutical, while H ₂ O ₂ addition during the treatment enhanced the API removal up to 90% as well as DOC removal.	Kim et al., 2009
UV/H ₂ O ₂ and UV	Sulfamethoxazole, sulfamethazine, sulfadiazine, trimethoprim, bisphenol A, and diclofenac	Milli-Q water, lake water and wastewater treatment plant effluent	Photolysis rate of all the bioactive compounds using low pressure UV photolysis (254 nm) differed at pHs tested, while efficiency of UV/H ₂ O ₂ on the tested bioactive compounds was as follows: diclofenac > sulfamethoxazole > sulfamethazine > sulfadiazine > bisphenol A ≈ trimethoprim.	Baeza and Knappe, 2011
UV	Sulfasalazine, sulfapyridine and 5-aminosalicylic acid	Milli-Q water	Sulfasalazine was resistant to direct UV (254 nm) photolysis while sulfapyridine demonstrated the fastest degradation due to its high molar absorption coefficient, 15241 M ⁻¹ cm ⁻¹ .	Ji et al., 2018
UV/H ₂ O ₂ and UVC	Amoxicillin	Distilled deionized water	Degradation of amoxicillin by direct UV and UV/H ₂ O ₂ with a low pressure Hg lamp (254 nm) showed that the degradation of 100 μM of amoxicillin (pH 7, 20 °C) followed first-order kinetics and the degradation rate increased with the H ₂ O ₂ concentration. An addition of 10 mM H ₂ O ₂ improved the degradation rate up to six-fold when compared to direct UV.	Jung et al., 2012
UV	Ketoprofen, carprofen and diclofenac acid	Ultrapure water and methanol	The photolysis kinetics of ketoprofen, carprofen and diclofenac acid followed pseudo-first order kinetics. Degradation of diclofenac acid was much slower compared to carprofen and ketoprofen. The predicted toxicity revealed that the transformation products of ketoprofen were more toxic than the parent API.	Li et al., 2017
UVC/H ₂ O ₂ and UVC/S ₂ O ₈ ²⁻	17α-ethinyl estradiol, 17β-estradiol, azithromycin, carbamazepine, dexamethasone, erythromycin and oxytetracycline	Ultrapure water	In the presence of natural organic matter in the UVC/H ₂ O ₂ system, the degradation rates (k _{app}) of azithromycin, carbamazepine, dexamethasone and 17α-ethinyl estradiol were enhanced between 3% and 11%, while an inhibitory effect resulted in the case of 17β-estradiol, erythromycin and oxytetracycline.	Markic et al., 2018
UVC/H ₂ O ₂	Diclofenac	Ultra-pure water	Diclofenac completely degraded in solution within 2 min under UVC/H ₂ O ₂ compared to UVA/TiO ₂ , which took 156 min to achieve similar degradation. A much higher mineralization (TOC) rate constant, 3.92 × 10 ⁻⁴ s ⁻¹ was obtained from the UVC/H ₂ O ₂ treatment.	Perisic et al., 2016
UV	Sulfamethoxazole and ibuprofen	Deionized water	The direct photolysis (UV 254 nm) of sulfamethoxazole and ibuprofen at pH 3 and pH 7.55 followed pseudo-first order kinetics. The initial reaction rate of the neutral sulfamethoxazole at pH 3 was 0.9149 min ⁻¹ higher than anionic sulfamethoxazole at pH 7.55, 0.3558 min ⁻¹ in contrast to ibuprofen, where the initial reaction rate was higher for its anionic form at pH 7.55 (0.0263 min ⁻¹) than its neutral form at pH 3 (0.0043 min ⁻¹).	Luo et al., 2018
Sonolysis				
	Ciprofloxacin	Deionized water	Degradation of ciprofloxacin at frequency 544 kHz (pH 7, 25 °C) fitted pseudo-first-order degradation with a half-life of 102 min. Addition of <i>t</i> -butanol (0.45, 4.5 and 45 mM) slowed down the degradation of ciprofloxacin confirming that <i>t</i> -butanol acts as a radical scavenger and the degradation of ciprofloxacin occurred due to the HO [•] radical.	De Bel et al., 2011
	Diclofenac and carbamazepine	Milli-Q water and urban wastewater treatment plant	Degradation of diclofenac and carbamazepine followed first-order kinetics. The reaction rates were observed to increase with increasing power density from 100 to 400 W/L.	Naddeo et al., 2013
	Piroxicam	Ultrapure water, bottled water and surface water	The reaction rates of piroxicam (640 μg/L) at power density of 20, 36 and 60 W/L were 0.1157 min ⁻¹ , 0.1695 min ⁻¹ and 0.1967 min ⁻¹ , respectively.	Lianou et al., 2018
	Ibuprofen	Ultrapure water	Application of single ultrasonic frequencies, 20 kHz, 40 kHz, 200 kHz, 572 kHz and 1130 kHz to ibuprofen (50 μM) resulted in 0.033 min ⁻¹ , 0.035 min ⁻¹ , 0.038 min ⁻¹ , 0.234 min ⁻¹ and 0.090 min ⁻¹ , respectively, indicating increasing degradation with frequency. Addition of zero-valent iron markedly increased ibuprofen degradation even at low single frequencies, 20, 40 and 200 kHz.	Ziylan-Yavas and Ince, 2018
	Oxacillin	Distilled water	Sonochemical process (275 KHz) efficiently degraded oxacillin (47.23 μmol/L) and eliminated antimicrobial activity in the presence and absence of additives (calcium carbonate and mannitol).	Serna-Galvis et al., 2016
	Diclofenac	Milli-Q water	The optimum conditions, initial concentration, pH and frequency ultrasound for DCF degradation was found to be 30 μM, 3.0 and 861 kHz, respectively. Addition of Fe-containing additives improved diclofenac elimination in particular with paramagnetic iron oxide nanoparticles. Mineralization occurred after 60 min of sonolysis in all cases.	Guyer and Ince, 2011
Electrochemical oxidation				
	Diclofenac, sulfamethoxazole, iopromide and 17-α-ethinyl estradiol	Deionized water and hospital wastewater treatment plant	When the degradation rates of the four APIs in synthetic wastewater and real wastewater was compared, higher rates were obtained for the latter when current conditions I = 0.9 A, initial concentration, C ₀ = 0.5 mg/L and flow rate = 500 L/h were used. This was attributed to the consumption of less oxidative species by organic matter present in real wastewater compared to those present in synthetic wastewater.	Loos et al., 2018

Table 1 (continued)

AOPs applied	Pharmaceuticals	Water matrix	Significant findings	Reference
Radiation	Carbamazepine	Demineralized water, tap water and treated wastewater	Comparison of carbamazepine degradation in tap water, demineralized water and treated municipal wastewater using Nb/BDD anode and 14 mM of NaCl showed that electrolysis resulted better performance in demineralized water (for pH 2 > pH7 > pH 10) followed by tap water and treated municipal wastewater.	García-Espinoza et al., 2018
	Not stated	Wastewater samples from a pharmaceutical manufacturing plant	BDD-electro oxidation resulted in constant COD decrease in samples numbered as 55 to 61 with COD ranging from 5000 to 60,000 mgO ₂ /dm ³ when the applied electric charge was increased from 5 to 50 A h/dm ³ at a constant temperature (25 °C).	Pérez et al., 2017
	Carbamazepine	Deionized water	The increase of peroxymonosulfate concentration (mole ratio of peroxymonosulfate to carbamazepine from 10:1 to 30:1) increased the degradation of carbamazepine from 80% to 100% within 10 min of treatment time.	Wang and Wang, 2018
	Carbamazepine	Ultrapure water	TOC reduction in carbamazepine solution decreased with increasing H ₂ O ₂ concentrations (0–200 mM) at varying irradiation doses. Carbamazepine solution containing 50 mM H ₂ O ₂ produced highest TOC removal at 41% when the irradiation dose was 20 kGy.	Liu et al., 2016
	Carbamazepine	River water and ultrapure water	Addition of sulfite ion (SO ₃ ²⁻) prior to the electron beam radiation led to 85.4% of carbamazepine (75 mg/L) degradation in pure water. Sulfite radical ([•] SO ₃ ⁻), e _{aq} ⁻ and O ⁻ were concluded to be a contributing active species for carbamazepine degradation in the presence of Na ₂ SO ₃ .	Zheng et al., 2014
	Nineteen pharmaceutical compounds	Wastewater sample from WWTP	A 5 kGy radiation dose effectively decomposed low initial levels of pharmaceutical compounds (<50 ng/L). The extent of the degradation of the pharmaceuticals was found to be dependent on the type and concentration of the compound.	Reinholds et al., 2017
	Fluoxetine	Ultrapure water	Electron beam irradiation yielded 90% degradation of fluoxetine at radiation dose of 0.5 kGy whereas doses above 2.5 kGy led to a below detection limit.	Silva et al., 2016
	Piperacillin	Distilled water, synthetic wastewater	The initial value of the calculated radiation chemical yield for the degradation of piperacillin was 0.26 μmol/J. Comparison of electron-beam mediated antimicrobial inactivation in aqueous solution and synthetic wastewater revealed that the adsorbed dose and degradation products affected the findings.	Szabó et al., 2018
Combined AOPs Ozone/TiO ₂ solar photocatalysis	Mixtures of four pharmaceuticals (atenolol, hydrochlorothiazide, ofloxacin and trimethoprim)	Distilled water and simulated synthetic secondary effluent solution	Four APIs, atenolol, hydrochlorothiazide, ofloxacin and trimethoprim sequentially treated, by ozonation and solar photocatalytic oxidation revealed that initial ozonation step led to poor removal of TOC (10%), while subsequent solar TiO ₂ photocatalysis improved the TOC removal to 80% and 60% in distilled water and secondary effluent, respectively.	Márquez et al., 2014
Ultrasound/Fenton oxidation (sono-Fenton)	Ibuprofen	Distilled water and effluent from municipal wastewater treatment plant	Coupling of Fenton with ultrasound (20 kHz) enhanced the degradation of ibuprofen in the presence of 6.4 mM whereby 95% removal was achieved within 60 min and mineralization was also improved under the same conditions.	Adityosulindro et al., 2017
Ultrasound and ozonation	Diclofenac, sulfamethoxazole and carbamazepine	Distilled water	The combined ultrasound/ozonation process positively enhanced the degradation of three APIs in single and mixed solutions at an ozone flow of 3.3 g/h after 20 min of treatment time when compared to ozonation alone at the same flow.	Naddeo et al., 2015
Sonolysis and photolysis (UV/H ₂ O ₂)	Diclofenac, paracetamol, salicylic acid, chloramphenicol etc.	Synthetic pharmaceutical wastewater	Sonophotolysis resulted in the highest TOC removal of 91% in the presence of 900 mg/L H ₂ O ₂ , 80 W ultrasonic power and UV (253.7 nm). Two factors, ultrasound power and initial concentration of H ₂ O ₂ were concluded as having the most effect based on the three-level Box–Behnken experimental design performed.	Ghafoori et al., 2015
Sono-photocatalysis with TiO ₂ , sono-photoFenton and sono-biphotocatalysis with TiO ₂ and Fe ²⁺	Ibuprofen	Milli-Q water	Sono-biphotocatalysis produced the highest mineralization rate (DOC removal of 98%) with more efficient consumption of H ₂ O ₂ . Initial degradation rate was 3.50 × 10 ⁻³ mM/min.	Méndez-Arriaga et al., 2009
Photocatalytic ozonation	Diclofenac and amoxicillin	Aqueous solution (not specified) and urban wastewater	Complete mineralization (TOC abatement) was achieved with TiO ₂ photocatalytic ozonation for amoxicillin and diclofenac after 30 min and 120 min, respectively.	Moreira et al., 2015
Ozone/TiO ₂ /UVB, UVB/TiO ₂ , O ₃ /UVB and single systems (UV, O ₃)	Mixtures of nine pharmaceuticals	Water (not specified)	Ozone/TiO ₂ /UVB (313 nm) yielded the highest TOC removal of 95% within 120 min for the pharmaceutical mixtures (each 10 ppm).	Rivas et al., 2012
Electro-peroxone	Venlafaxine	Milli Q water, secondary effluent from wastewater treatment plant	Compared to single ozonation and electrolysis treatment, electro-peroxone efficiently degraded 20 mg/L of venlafaxine within 3 min of reaction time, when the applied current was increased from 50 mA to 300 mA and the O ₃ concentration was fixed at 40 mg/L.	Li et al., 2015
Ozone and ultrasound	Amoxicillin	Distilled water and ultrapure water	Coupling of ozonation and ultrasound resulted in a higher pseudo-first-order degradation rate of 2.5 min ⁻¹ at pH and higher TOC removal (45%) than single ozonation treatment with 1.97 min ⁻¹ at similar pH.	Kıdık and Doğan, 2018

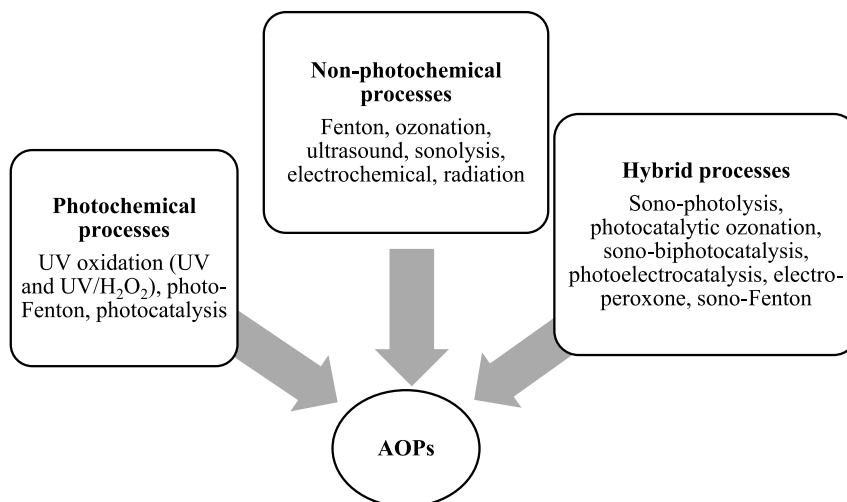


Fig. 2. Types of AOPs for pharmaceutical wastewater treatment.

O₃ with H₂O₂ (O₃/H₂O₂), and O₃ with UV (O₃/UV) have been applied to pharmaceuticals in water as a single oxidation method or pre-oxidation and/or disinfection step before other treatments (Almomani et al., 2016; Andreozzi et al., 2005; Ikehata et al., 2006; Kidak and Doğan, 2018). Various parameters such as pH, ozone dose and temperature affected the conversion and mineralization of pharmaceuticals in these treatments. The short life time of ozone renders this method to be expensive and its high-energy demand has been identified as a potential drawback for real applications (Ikehata et al., 2006).

Many studies have reported low mineralizations, despite high removal efficiencies of investigated APIs due to persistent by-products formed during ozonation (Almomani et al., 2016). This finding highlights the necessity to evaluate the toxicity before and after treatment by ozonation. Low doses of ozone have been reported to achieve complete abatements of target APIs, but with incomplete mineralization rates. A study by Zhao et al. (2017) reported that ozonation resulted in the complete degradation of the anti-inflammatory drug indomethacin within 7 min using 4 different ozone doses (2–35 mg/L), while only 50% of TOC was removed at the highest ozone dose (35 mg/L) in 30 min. Two studies performed by Dantas et al. (2011) and Wang et al. (2011) found that high removals of the APIs, propranolol and tetracycline, were achieved. However, TOC or COD (35% after 90 min) indicated the formation of stable intermediates or in the case of tetracycline, the resistance of the parent API to ozonation. Addition of H₂O₂ and irradiation have been suggested to enhance the degree of mineralization. Toxicity assessments revealed that toxicity of the ozonated or ozone-treated solution can be eliminated despite incomplete mineralization.

Operation parameters such as pH, dose of ozone, water matrix, and presence of organic matter and their effects on the removal efficiency of pharmaceuticals have been studied. Alharbi et al. (2016) suggested that although all four investigated APIs (diclofenac, carbamazepine, sulfamethoxazole and trimethoprim) required different doses of ozone for their degradation, ozonation can be regarded as an efficient treatment for these compounds. Kidak and Doğan (2018) reported the dependence of the ozonation process on pH (e.g. pH 3, 7 and 10) in removing amoxicillin. An alkaline pH (pH 10) produced the highest reaction rate (1.970 min⁻¹) compared to acidic and neutral conditions due to the formation of higher amounts of HO[•] radicals formed through ozone decomposition. In contrast, the degradation of salicylic acid was reported to be

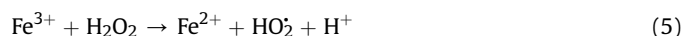
optimal at acidic pH (pH 4) with about 40–50%, compared to only 10–20% under basic conditions (pH 8 and 10), when the molar ratio between ozone and salicylic acid was approximately 3. Although it is known that the concentration of HO[•] radicals increases with increasing pH, the degradation of salicylic acid was driven by direct ozone oxidation instead (Hu et al., 2016). The effect of ozone dose and pH (acid and neutral) was investigated by Almomani et al. (2016) for the degradation of four groups of pharmaceuticals, including antibiotics and oestrogen, in three types of water matrices (synthetic, WWTP effluent and surface). Compared to synthetic wastewater, a higher ozone dose (222.3 mg/h) was needed to effect the degradation of pharmaceuticals in WWTP effluent and surface water due to the presence of natural organic matter (NOM). The effect of organic matter in secondary effluents from two WWTPs (Dihua and Neihu in Taiwan) on the ozonation efficiency was determined by comparing the rate constants (Cai and Lin, 2016). It was concluded that the observed difference in the inhibition rate constant was due to functional groups such as carboxyl, aliphatic hydroxyl and aryl groups present in the organic matter in the Dihua WWTP. Although organic matter in both secondary effluents displayed a similar reactivity towards ozonation, discrepancies occurred on their reactivity towards HO[•] radicals, which subsequently impacted on the inhibition rate.

Current research showed that the integration of ozonation with an activated sludge system (Domenjoud et al., 2017) and the combination of multistage ozonation with aerobic biodegradation (Marcelino et al., 2017) are effective when dealing with real pharmaceutical wastewater such as raw hospital water and urban wastewater. These processes are effective in reducing high levels of organic matter. The high operating costs of ozonation may be overcome by combining this treatment method with other technologies.

3.2. Fenton and photo-Fenton

The Fenton reaction is based on the use of a mixture of iron salts (Fe²⁺) and H₂O₂, generating HO[•] radicals under mild acidic conditions (Eq. (4)). The Fe²⁺ catalyst can be regenerated as shown in Eq. (5) or through reactions of Fe³⁺ with other intermediates (Bautista et al., 2008).





Both Fenton and photo-Fenton processes have been found to be effective for the degradation of pharmaceuticals. Despite having similar restrictions as the thermal Fenton process, the photo-Fenton reactions can be enhanced by UV–Vis radiation to initiate additional HO[•] radicals (Andreozzi et al., 1999; Legrini et al., 1993). Solar photo-Fenton has been demonstrated for the treatment of various pharmaceuticals such as antibiotics, anti-inflammatory, analgesic and antineoplastic drugs (Alalm et al., 2015; Klammer et al., 2010b; Sirtori et al., 2011; Trovó et al., 2011). For example, Trovó et al. (2011) reported on the efficiency of photo-Fenton using a solar simulator for the degradation of amoxicillin in the presence of two different iron species, ferrioxalate complex and FeSO₄. Complete removal of amoxicillin was achieved in the presence of the ferrioxalate complex within 5 min, while 15 min were needed when FeSO₄ was applied in the presence of 120 mg/L H₂O₂. Nevertheless, the ferrioxalate complex was found to demonstrate higher toxicity particularly for *Daphia magna* bioassays. Low concentrations of Fe²⁺ (5 mg/L) and H₂O₂ (75 mg/L) have been shown to efficiently degrade 100 µg/L of loxacin and trimethoprim under solar photo-Fenton conditions (Michael et al., 2012). Sirtori et al. (2011) performed the solar photo-Fenton on nalidixic acid in different water matrices (i.e. demineralized water, saline water and simulated industrial effluent). The efficacy of the solar photo-Fenton process was greatly affected by the water composition, in particular for DOC removal. DOC removal from the simulated industrial effluent was the lowest with 20% after 240 min, followed by 73% reduction in the saline water after 107 min and 86% in the demineralized water after 92 min. Koltzaidou et al. (2017) explored the solar photo-Fenton (Fe³⁺/H₂O₂) degradation of 5-fluorouracil by varying the concentrations of H₂O₂ (0–90 mg/L) and Fe³⁺ (0–15 mg/L). At pH 3, the optimum concentrations of H₂O₂ and Fe³⁺ were 60 mg/L and 4.5 mg/L, respectively. This study chose a lower concentration of Fe³⁺, 4.5 mg/L, despite the higher concentration providing a slightly higher degradation rate, due to the increased need for iron sludge removal if a higher concentration were to be applied.

A recent study has reported that a ferrioxalate-based photo-Fenton reaction using UVA-light emitting diodes (LEDs) successfully led to complete degradation of antipyrine in 2.5 min, 93% of TOC removal in 60 min and a reduction in the amount of H₂O₂ (Davididou et al., 2017). The near monochromatic irradiation at 365 nm, which was close to the maximum absorbance of the ferrioxalate complexes, was suggested to be the crucial factor (Davididou et al., 2017). A minimal amount of H₂O₂ (100 mg/L) was found optimal to degrade 50 mg/L of antipyrine. Excess H₂O₂ exhibited scavenger effects thus reducing the availability of HO[•] radicals needed for API degradation (Veloutsou et al., 2014).

Although the Fenton process is not as energy intensive as other AOPs such as UV and O₃, it requires low acidic pH (3–5) conditions (Malato et al., 2002) with pH significantly influencing the Fenton reaction (Perini et al., 2018). At a pH higher than 3, Fe³⁺ precipitates as Fe(OH)₃, while at even higher pH values, the formation of Fe(II) complexes leads to a decline in Fe²⁺ concentration. Much progress has been made in operating Fenton and photo-Fenton processes at a neutral or near-neutral pH to deal with large-scale operations or real wastewater samples (e.g. hospital wastewater) (Giraldo-Aguirre et al., 2017; Perini et al., 2018). The removal of oxacillin was performed at pH-6 (Giraldo-Aguirre et al., 2017), while the removal of mixtures of micropollutants by means of photo-Fenton was performed at pH 6–7 (De la Cruz et al., 2013b). A 203 µmol/L solution of oxacillin was completely eliminated after 50 min in the presence of 90 µmol/L of Fe²⁺, 10 mmol/L of H₂O₂ and irradiation with a 30 W light source (365 nm) at pH 6 (Giraldo-Aguirre et al.,

2017). The potential use of iron ligands or complexing agents such as oxalate, citric acid and ethylenediaminedisuccinic acid has been investigated when performing photo-Fenton reactions at a neutral pH (Klammer et al., 2010a; Miralles-Cuevas et al., 2014).

In addition to working at non-conventional pHs, different sources of iron species have also been investigated to compare their effects on the degradation efficiency of APIs. de Lima Perini et al. (2013) investigated the potential of iron citrate, iron oxalate, and iron nitrate on the conversion of ciprofloxacin. Iron citrate and iron oxalate resulted in the highest conversion of ciprofloxacin (25 mg/L) at pH 4.5, but iron citrate was superior based on the highest TOC removal (0.699). A low reactivity between iron nitrate and H₂O₂ was suggested to be the cause of the poor degradation of ciprofloxacin.

Overall, researchers are constantly investigating approaches to overcome the low acidic condition requirements of Fenton and photo-Fenton reactions. By modifying 'conventional' conditions, a better insight in the efficiency is obtained and sluggish degradation kinetics are overcome. However, more studies need to be performed and optimized at a wide pH range using natural and wastewater matrices.

3.3. UV and UV/peroxide processes

The effectiveness of UV processes for the removal of pharmaceuticals depends strongly on the UV absorption of the pharmaceutical (Kim et al., 2009). The critical parameters determining the degradation kinetics of direct UV photolysis furthermore comprise the rate constants, *k*_{UV}, quantum yield (*φ*), and molar extinction coefficient (*ε*) (Luo et al., 2018). UV combined with H₂O₂ (UV/H₂O₂) generally provides better removal efficiencies for pharmaceuticals with poor UV absorption. UV/H₂O₂ processes are governed by the H₂O₂ concentration, rate of HO[•] radical formation, UV light intensity, water constituents, chemical structure of the pharmaceutical (Yuan et al., 2009) and also the solution pH (Baeza and Knappe, 2011).

A study of UV photolysis (254 nm) revealed that sulfasalazine was photostable, while this technique was able to degrade its two human metabolites, sulfapyridine and 5-aminosalicylic acid. The reported quantum yields for sulfapyridine and 5-aminosalicylic acid were $(8.6 \pm 0.8) \times 10^{-3}$ and $(2.4 \pm 0.1) \times 10^{-2}$ mol Einstein⁻¹, respectively. However, addition of peroxides, H₂O₂ and peroxydisulfate to the UV system attained 93.1% and 96.2% removal of sulfasalazine as a result of the highly reactive free radicals HO[•] and SO₄^{•-} (Ji et al., 2018). A study by Jung et al. (2012) also reported an enhanced degradation rate when amoxicillin was degraded with UV light in the presence of 10 mM of H₂O₂, compared to direct UV alone. A study by Li et al. (2017) reported on the degradation rates of three non-steroidal anti-inflammatory drugs (NSAIDs), ketoprofen, diclofenac and carprofen when exposed to UV irradiation (254 nm). Results indicated that carprofen exhibited the highest degradation rate of 1.54×10^{-4} s⁻¹, followed by ketoprofen at 5.91×10^{-5} s⁻¹ and diclofenac at 7.78×10^{-6} s⁻¹. A recent study by Markic et al. (2018), which compared the effectiveness of UVC/H₂O₂ and UVC/S₂O₈²⁻ treatments on the degradation of 17α-ethinyl estradiol, 17β-estradiol, azithromycin, carbamazepine, dexamethasone, erythromycin and oxytetracycline in a mixture (in the absence of NOM), revealed that first-order reaction rates for UVC/S₂O₈²⁻ were higher than UVC/H₂O₂. The observed results were attributed to the different reaction mechanisms of the HO[•] and SO₄^{•-} radicals with the pharmaceuticals and also due to the discrepancies in their optical properties (e.g. quantum yield and molar absorption coefficients).

A study by Perisic et al. (2016) compared the efficiency of UVC/H₂O₂ with UVA/TiO₂ for the degradation of diclofenac. Complete

degradation of diclofenac (29.62 mg/L) was achieved within 2 min under UVC/H₂O₂ conditions (H₂O₂ = 16.78 mM), which was substantially faster compared to UVA/TiO₂ (TiO₂ = 1.306 g/L), which took 156 min. UVC/H₂O₂ also resulted in a higher pseudo-first-order rate constant for mineralization ($3.92 \times 10^{-4} \text{ s}^{-1}$), while for UVA/TiO₂, the rate constant was $8.72 \times 10^{-5} \text{ s}^{-1}$. The effects of the molar extinction coefficient (ϵ), quantum yield (ϕ), and degradation kinetics of ibuprofen and sulfamethoxazole were examined at varying pHs (3 and 7.55) and by employing experimental and modelling approaches (Luo et al., 2018). The ϕ values for ibuprofen at pH 3 and 7.55 were 0.0161 and 0.1030 mol Einstein⁻¹, respectively, while for sulfamethoxazole the values were 0.0885 and 0.0236 mol Einstein⁻¹, respectively. The discrepancies of the ϕ values obtained in this study compared to other existing studies were attributed to the experimental conditions such as the volume and geometry of the reactor and the light source. The developed model was suggested to be used in optimizing photolysis effects on pharmaceuticals at different pHs and in real wastewater.

As UV photolysis is highly dependent on the chosen irradiation intensity, the response of APIs and the quantum yield, the addition of peroxides to generate reactive radicals has been shown to improve the degradation of APIs. UV/H₂O₂ has also shown to reduce the required UV energy in accomplishing degradation of pharmaceuticals (Kim et al., 2009), as the degradation is no longer dependant on direct absorption by the API.

3.4. Sonolysis

Another AOP which has gained popularity is ultrasound irradiation, also known as sonolysis. This technique is based on the production of HO[•] radicals from water pyrolysis due to the high intensity of acoustic cavity bubbles (Guyer and Ince, 2011).



where))) refers to the ultrasound irradiation.

The efficiency of this AOP to degrade APIs is significantly affected by the power and frequency of the applied ultrasound (Ince, 2018; Kidak and Doğan, 2018; Méndez-Arriaga et al., 2008b). The influence of frequency on the degradation of ciprofloxacin has been studied (De Bel et al., 2011). The results obtained revealed that among the three frequencies investigated (544, 801 and 1081 kHz), the lowest at 544 kHz produced a high degradation rate constant of 0.0067 min⁻¹ when degrading 15 mg/L of ciprofloxacin at 25 °C. Naddeo et al. (2013) reported that increasing the power density (100–400 W/L) successfully enhanced the degradation of diclofenac and carbamazepine. Likewise, a recent study by Lianou et al. (2018) also reported that the investigated power densities (20–60 W/L) enhanced the degradation of piroxicam, due to the formation of HO[•] radicals and higher mixing intensity. Furthermore, cavitation activity also critically controls the efficiency of sonochemical treatment (Ziylan-Yavas and Ince, 2018). Ultrasonic power increases the degradation rate linearly as a result of the high number of active cavitation bubbles, subsequently generating more HO[•] radicals (Madhavan et al., 2010).

The addition of radical promoters also contributes to the performance of sonolysis (Rayaroth et al., 2016). The effects of other pharmaceutical ingredients or additives such as mannitol and calcium carbonate on the ultrasound degradation of oxacillin and elimination of antimicrobial activity were investigated by Serna-Galvis and co-workers (Serna-Galvis et al., 2016). The addition of

these additives did not alter the degradation kinetics of oxacillin and the antimicrobial elimination kinetics, confirming the effectiveness of sonolysis to selectively degrade pharmaceuticals and to eliminate antibiotic activity, even in the presence of other pharmaceutical ingredients. The obtained degradation rates for an initial concentration of 47.23 μmol/L oxacillin and 250 kHz of ultrasound for oxacillin only, oxacillin and mannitol and oxacillin and calcium carbonate showed similar values of 1.4 ± 0.0 , 1.3 ± 0.1 , and $1.4 \pm 0.1 \text{ μM min}^{-1}$, respectively, while the antimicrobial kinetics were 0.0145, 0.0144, and 0.0146 min⁻¹, respectively. Another study investigated the effect of the addition of Fe-containing additives, namely Fenton's reagent, zero-valent iron and super paramagnetic iron oxide nanoparticles, on the sonochemical degradation of diclofenac (Guyer and Ince, 2011). Among the three Fe-additives, super paramagnetic iron oxide nanoparticles produced the highest estimated relative efficacy, 41.54 μM mg⁻¹ at a frequency of 861 kHz due to the large surface area and excess cavitation nuclei, confirming the contribution of paramagnetic iron oxide nanoparticles in ultrasound treatment.

Although sonolysis principally does not require additional chemicals, this technique is rather energy demanding, results in low mineralization and is limited to lab-scale. To overcome these drawbacks, it may be coupled with other AOPs to reduce the operating costs and to benefit from the synergistic effects of the AOPs for both, API oxidation and mineralization. The mechanisms involved in the degradation of pharmaceuticals should be further established to elucidate the contribution of the chosen AOP to sonolysis.

3.5. Electrochemical oxidation

Electrochemically-based AOPs have appeared as an attractive option for pharmaceutical removal as they generate reactive species via electricity and without the need for chemicals and thus without secondary waste (García-Segura et al., 2018). A review by Sires and Brillas (2012) highlighted research findings related to this technology, which can be classified as electrochemical separation technologies (such as electrodialysis and electrocoagulation) and degradation technologies (such as anodic oxidation). Two oxidation mechanisms are involved in the electrochemical oxidation process. Firstly, there is the direct oxidation at the anode whereby direct charge transfer occurs between the pharmaceutical compound and the anode surface. Indirect oxidation occurs via *in-situ* generation of reactive oxygen species by oxidants at the surface of the electrode (Feng et al., 2013).

Compared to conventional anodes such as Pt, IrO₂ or PbO₂, boron-doped diamond (BDD) anodes are popular in the electrochemical oxidations of pharmaceuticals due to their stability to corrosion, high oxygen-over potential (to generate more HO[•] radicals) and inert surfaces (García-Espinoza et al., 2018; Švorc et al., 2017). Several studies have confirmed the effectiveness of BDD anodes in degrading pharmaceuticals. The degradation of diclofenac, sulfamethoxazole, iopromide and 17- α -ethinylestradiol in a real hospital effluent and in synthetic wastewater was compared using electrochemical oxidation with a BDD anode (Loos et al., 2018). Flow rates (125, 250 and 500 L/h) did not significantly affect the pseudo-first-order rate constants for sulfamethoxazole and iopromide, while the rate constants increased for diclofenac and 17- α -ethinylestradiol with increasing flow rate in the simulated wastewater at an applied current of 0.9 A. In the real hospital wastewater, an increase in the applied current from 0.9 to 3.1 A positively enhanced the degradation of all four compounds instead. Degradation of carbamazepine was greatly influenced by current and treatment time applied during the electrochemical degradation mediated by chloride ions and using a Nb/BDD anode

(performed better than Ti/IrO₂) (García-Espinoza et al., 2018). Acute toxicity testing using *Vibrio fischeri* showed an increase in toxicity levels after 20 min and 90 min of treatment time from 11.35 TU (toxicity unit) to 30.44 TU. This was linked to residual reactive chlorine species and not to any toxic by-products. Electrochemical oxidation using BDD was also reported to be more efficient than Fenton oxidation in degrading real pharmaceutical wastewater sampled from a pharmaceutical plant, due to its reliability and robustness (Pérez et al., 2017).

Although electrochemical oxidation is known for its advantages, the effectiveness of electrochemical processes is greatly controlled by the electrode surface whereby it tends to reduce over-treatment as a result of the formation of products. Research should be directed towards the fabrication of novel electrodes to overcome such limitation and more studies are needed on pilot scale rather than commonly conducted lab-scale scales.

3.6. Radiation

A recent review has shown that solution pH, dose rate and water matrices contribute to the effectiveness of ionizing irradiation in degrading pharmaceuticals and personal care products (Wang and Chu, 2016). Compared to UV-based AOPs, gamma irradiation has shown better penetration and subsequently increased formation of hydroxyl radicals and hydrated electrons (e_{aq}^-) to facilitate the degradation of pharmaceuticals. Wang and Wang (2018) investigated single gamma irradiation to induce activation of peroxy-monosulfate for the degradation of carbamazepine. Although increasing the dose of single gamma irradiation resulted in increased degradation of carbamazepine, the addition of peroxy-monosulfate caused its complete degradation, attributed to the presence of hydroxyl radicals, perhydroxyl radicals and superoxide radical anions. Another study on carbamazepine investigated the efficiency of combining electron beam irradiation and hydrogen peroxide (Liu et al., 2016). The authors revealed that a degradation of carbamazepine of up to 90% could be achieved using an electron beam irradiation dose of 1 kGy in the absence of H₂O₂. In the presence of 10 mM of H₂O₂, the degradation increased to 95%. A further increase of the H₂O₂ concentration to 50 and 200 mM led to a decrease in the degradation rate, indicating that an appropriate concentration of H₂O₂ is essential. Zheng et al. (2014) also investigated the efficiency of electron beam radiation on the degradation of carbamazepine in the presence of different ions (e.g. SO₄²⁻, HCO₃⁻, NH₄⁺, Cl⁻ and Na⁺) and water matrices. Among the active species, HO[•], H[•] and e_{aq}^- , HO[•] was determined as the most contributing species based on experiments performed using carbamazepine solutions saturated with either N₂, N₂O or *tert*-butanol with N₂. Degradation of carbamazepine in river water both, in the presence and absence of suspended solids was slower than in pure water, when the adsorbed dose was varied from 0 to 5 kGy due to the presence of dissolved organic matter and ions.

The effect of two types of ionizing radiation on the degradation of multi-class pharmaceuticals in an influent of a WWTP was studied by Reinholds et al. (2017). Comparing electron beam radiation and gamma radiation, the former was found advantageous in reducing these pharmaceuticals, as noted from a reduced exposure time of more than 35 times. Silva et al. (2016) examined the degradation of fluoxetine by means of electron beam irradiation and found that a low irradiation dose, 0.5 kGy, was sufficient to achieve almost 90% removal, despite an incomplete mineralization (12.5%) at a similar dose. The acute toxicity for *Daphnia similis* (86.8%) compared to only 9.6% for *Vibrio fischeri* was linked to residual amounts of the parent compound fluoxetine and not of any by-products. Electron beam treatment (using a linear electron accelerator) has proved successful in antibiotic resistance

management in a wastewater treatment plant. This has been demonstrated by Szabó et al. (2018) for the elimination of the antimicrobial activity of piperacillin present in an environmentally relevant concentration.

Radiation has been reported as a clean process as there is no requirement of additional chemicals to initiate the reaction, the energy cost is minimal and the process can be performed at various temperatures (Darwis et al., 2015; Kim et al., 2017). Beside the degradation kinetics deriving from radiation-induced degradations, studies should focus on the radiolytic degradation products, mineralization and also toxicity, which have been generally lacking in the above studies. In addition, the potential ionizing irradiations such as electron-beam radiation and gamma radiation should be investigated at environmentally-relevant concentrations.

3.7. Combined AOPs

Although the treatment of pharmaceuticals typically revolves around single AOP methods, recent developments in AOP hybrid techniques have attracted considerable interest. Hybrid AOPs have been studied in various combinations as shown in Fig. 2 and Table 1. The increased removal of pharmaceuticals in hybrid systems compared to single AOP is due to the synergistic effect and the increase in the amount of reactive species, which also produces better mineralization. To maximize the degradation efficiency, APIs in real or synthetic wastewaters are either treated sequentially or simultaneously.

The combinations of AOPs, choices of AOPs and orders of treatment vary from study to study and there is no clear agreement on this aspect. Márquez et al. (2014) performed ozonation to treat pharmaceutical wastewater followed by solar TiO₂ photocatalytic oxidation. Although substantial TOC removal (60% for synthetic secondary effluent and 80% for distilled water) was observed compared to the single treatment, the study failed to justify the order of the treatment and it was recommended to pursue an investigation of both techniques simultaneously. Coupling of ultrasonic and Fenton was performed by Adityosulindro and co-workers to remove and improve TOC removal of ibuprofen in distilled water and municipal wastewater from a treatment plant (Adityosulindro et al., 2017). Combinations of sonolysis with ozonation and photolysis have also been examined. For diclofenac, carbamazepine and sulfamethoxazole, Naddeo et al. (2015) studied the effect of ultrasound introduction on an ozonation system at varying flow rates of ozone (e.g. 1.3 g/h, 2.4 g/h and 3.3 g/h). Although an enhancement was observed in the removal percentage, the applied ozone flow rate markedly affected the removal efficiencies for the single APIs as well as their mixtures. The application of ozonation in combination with ultrasound enhanced the degradation of APIs due to the improved ozone mass transfer, but depended on the hydrophobicity of the compound. A study investigated the potential of sonolysis and photolysis (UV/H₂O₂), referred to as sono-photolytic, for the degradation of synthetic pharmaceutical wastewater (mainly comprising of chloramphenicol, diclofenac, salicylic acid, and paracetamol) by measuring TOC levels (Ghafoori et al., 2015). Sono-photolysis led to 91% TOC removal compared to only 3% under sonolysis alone and 8% under photolysis (UV) alone, respectively. The preference of combining sonolysis with other AOPs is mainly driven by the aim to increase the mineralization level, which is not readily achieved using sonolysis alone (Méndez-Arriaga et al., 2009; Naddeo et al., 2015). The combination of ozonation with TiO₂ photocatalysis also facilitated complete mineralization for amoxicillin and diclofenac (Moreira et al., 2015). The same effect was reported by Rivas et al. (2012) for the combination of ozone/TiO₂/UVB for the degradation of pharmaceutical mixtures. Furthermore, electro-peroxone

that combines ozonation and electrolysis treatment also effectively degraded venlafaxine and provided better TOC removal when compared to ozonation only (Li et al., 2015).

As the majority of hybrid and integrated techniques perform superior compared to single treatments, more studies are being directed towards this area of research (Table 1). Although it is evident that various AOPs are efficient in removing pharmaceuticals, most AOPs are generally labelled as expensive methods. To overcome this drawback, the coupling of advanced oxidation treatment with existing conventional water treatment methods has been suggested to be more cost-effective and also to enhance the efficiency of the process (Oller et al., 2011; Schröder et al., 2016). Coupling of AOPs has been reported to improve the quality of the effluent prior to discharge into the environment, as shown by a recent study that found “safer” effluent when ozone and sonolysis were coupled for the degradation of amoxicillin in water (Kıdık and Doğan, 2018).

In most of the hybrid studies summarized above, the order of the coupled treatment was neither specified nor justified in the experimental section. Future studies should provide a justification to help with the selection of multiple treatment combinations for pharmaceutical wastewater treatment. Although coupled AOPs provide better mineralization, studies should support this finding by identifying intermediates to ascertain that the coupled AOP-effluent possesses minimal or less environmental risk than the single AOPs.

4. TiO₂ photocatalytic degradation of pharmaceuticals

Photochemical degradation of pharmaceuticals by means of TiO₂ photocatalysis is undertaken (i) to investigate the kinetics and optimize the conditions of the applied process, (ii) to determine mineralization of the parent compound and to achieve high biodegradability, (iii) to identify possible degradation products formed during HO[•] radical mediated treatment and (iv) to evaluate the toxicity of the treated water to ensure safety. With these four general aims, the application of TiO₂ photocatalysis for the removal of various APIs has been examined extensively. Studies using UV/TiO₂ catalyzed oxidation on different therapeutic drug classes such as NSAIDs and analgesics, antibiotics, anticonvulsants, lipid regulators, β -blockers and psychiatric drugs are summarized in Table 2. Important aspects observed in these studies are also summarized in this section.

TiO₂ photocatalysis has resulted in the successful degradation of a variety of drugs treated, thus leading to an increasing interest in its application for the removal of pharmaceuticals in water and wastewater. The API selection in most studies is either driven by their high consumption, which correlates with the high probability of detection in the environment, or by an existing gap or scarcity of available studies on these compounds. For example, antibiotics (e.g. sulfamethoxazole, amoxicillin, tetracycline) and NSAIDs (e.g. diclofenac, ibuprofen, naproxen) are frequently investigated due to their high consumption rates (Kanakaraju et al., 2015; Pereira et al., 2014; Zhu et al., 2013), while the removal of psychotropic drugs such as benzodiazepines and antidepressants represents a knowledge gap, despite their increased usage (Trawiński and Skibiński, 2017).

TiO₂ photocatalytic studies frequently investigate the effects of operational parameters such as catalyst loading, initial concentration of substrate, type of TiO₂ photocatalyst, pH of the solution, wavelength/light intensity and water matrix on the degradation kinetics of the pharmaceutical (Carbajo et al., 2016). Besides these common parameters, effects of stirring speed, temperature and gas sparging rates were also examined. Several studies comprehensively investigated the effect the operational parameters on the

kinetics of the chosen APIs (Kanakaraju et al., 2014b; Van Doorslaer et al., 2012; Villegas-Guzman et al., 2015) while studies that only focused on selected parameters are also available (Fukahori et al., 2012; Giraldo et al., 2010) (Table 2). It is widely accepted that the design and geometry of the photoreactor used also effects the degradation rate of APIs (Carbajo et al., 2016; Friedmann et al., 2010; Malato et al., 2009). Variations in these numerous parameters within different studies make a direct comparisons of results difficult, even for the same API.

The effects of initial concentrations, TiO₂ P25 concentration, stirring speed, temperature, and sparging rates (oxygen, nitrogen and pure air) were examined for the degradation of moxifloxacin (Van Doorslaer et al., 2012). The study concluded that photocatalytic degradation of moxifloxacin can generally occur at ambient temperature upon sparging, with the other parameters greatly influenced the degradation rate. A study by Villegas-Guzman et al. (2015) reported that the applied light power (30 W and 150 W) had a significant effect on the degradation kinetics of dicloxacillin at low TiO₂ concentrations (0.05 g/L), while natural pH enhanced the degradation rate in contrast to acidic (pH 3) or basic pHs (7 and 9), which inhibited the degradation. The effect of various operational parameters such as TiO₂ loading, solution pH, TiO₂ type, type of water, and initial concentration of diclofenac were systematically investigated for the degradation of diclofenac by Kanakaraju et al. (2014b). The water matrix significantly affected the degradation of diclofenac, due to the presence of ions and other NOM.

The material properties of TiO₂ such as surface, electronics and structure also play an important role in governing the overall photocatalytic activity (Carbajo et al., 2016). The choice of the TiO₂ type also varies between studies with demonstrated differences in photocatalytic activity towards organic compounds. Variations in photocatalytic performance are explained by the differences in the morphology, crystal phase, specific surface area, surface charge, particle size distribution, porosity, band gap and surface hydroxyl density control (Carp et al., 2004). TiO₂ P25, Hombikat UV 100 and Ti (IV) oxide (Aldrich) have been commonly used. Table 3 displays a comparison of the properties of these common photocatalysts. The efficiency of five different TiO₂ materials, namely P90, P25, Hombikat UV 100, PC500 and ST01, was tested for the degradation of carbamazepine (Carabin et al., 2015). The most efficient photocatalyst was P90 followed by P25 with removal efficiencies of 69% and 60%, respectively. Mixtures of crystalline phases of anatase and rutile in these photocatalysts were attributed to the observed photocatalytic activity. Another study investigated the effect of eight different TiO₂ materials, namely Degussa P25, Hombikat UV 100, Millennium PC50, Millennium PC100, Millennium PC105, Millennium PC500, Tronox AK1 and Aldrich Anatase AA, on the degradation of the antibiotic amoxicillin (Dimitrakopoulou et al., 2012). P25 resulted in maximum API degradation, which was linked to its slower electron-hole recombination rate and its favourable composition of anatase and rutile. A recent study investigated the degradation of paracetamol and aspirin mixtures in deionized water using micro-sized TiO₂ K1077 (by Kronos) and TiO₂ P25 (Bianchi et al., 2017). P25 provided complete degradation (after 6 h) and a mineralization efficiency of 90% (after 6 h). In contrast, TiO₂ K1077 demonstrated a lower photocatalytic activity particularly for aspirin and a poor mineralization of 40% after 4 h. The different properties of these TiO₂ materials did not correlate to these findings. While TiO₂ K107 was composed of a larger crystalline size (130 nm) and anatase/rutile composition (100%), it shows a lower band gap (3.15 eV) compared to TiO₂ P25 (3.21 eV).

The influence of the water quality on TiO₂ photocatalysis is critical to establish its suitability for real wastewater treatment. Pharmaceuticals, spiked in distilled water and Milli-Q water, are

Table 2Selected recent studies of TiO₂ photocatalytic oxidation of pharmaceuticals.

Therapeutic class/ compound	Water matrix	Experimental conditions	Results	Reference
Antibiotics Oxolinic acid	Milli-Q water	Black lamp (14 W/m ² ; 365 nm)	Experimental conditions of pH 7.5 and 1.0 g/L of TiO ₂ favoured between 80 and 100% of oxolinic acid degradation. About 20% of oxolinic acid was adsorbed on TiO ₂ under dark conditions.	Giraldo et al., 2010
Trimethoprim	Milli-Q water, distilled water and simulated seawater	Solar simulator (1.5 kW Xenon arc lamp) and compound parabolic collector	Trimethoprim demonstrated high stability to direct photolysis and degradation did not follow first-order kinetics. Solar TiO ₂ photocatalysis improved the degradation of trimethoprim with rate constants of 0.22 min ⁻¹ in distilled water and 0.081 min ⁻¹ in simulated seawater.	Sirtori et al., 2010
Amoxicillin	Ultra-pure water and secondary effluent from a municipal WWTP	UVA lamp (9 W; 350–400 nm)	Photocatalytic degradation of amoxicillin (10 mg/L) consumed only 20 min in ultra-pure water compared to 60 min in spiked secondary effluent at pH 7.5.	Dimitrakopoulou et al., 2012
Moxifloxacin	Deionized water	UVA lamp (365 nm)	Maximum degradation rate of moxifloxacin was achieved in the presence of 5 g/L TiO ₂ and air sparging of 60 mL/min. Ambient temperature (298 K) was reported to be sufficient for degradation of this compound.	Van Doorslaer et al., 2012
Dicloxacin	Distilled water	Black lamp (30–150 W; 365 nm)	Effects of TiO ₂ concentration and power were investigated on the removal of low (3 ppm) and high (800 ppm) concentration of dicloxacin. Degradation rates increased with the TiO ₂ loadings (0.05–2.0 g/L) and applied power. Highest dicloxacin removal rate, 62.82 × 10 ⁻⁸ M s ⁻¹ was obtained using 2 g/L TiO ₂ and 150 W for 800 ppm.	Villegas-Guzman et al., 2015
NSAIDs and analgesics Diclofenac (and amoxicillin)	Milli-Q water	Solar simulator (250–765 W/m ²)	TiO ₂ photocatalysis produced 96% degradation of diclofenac at an irradiation level of 400 W/m ² , while 80% was achieved with direct photolysis.	Kockler et al., 2012
Naproxen (and diclofenac)	Distilled water, river water and drinking water	Medium pressure Hg lamp (200–600 nm)	TiO ₂ photocatalytic degradation rate of naproxen in river water decreased from 0.21 min ⁻¹ to 0.10 min ⁻¹ and 0.11 min ⁻¹ when phosphate alone and mixture of phosphate and chloride anions, respectively was added into river water samples.	Kanakaraju et al., 2015
Ibuprofen	Ultra-pure water	Medium pressure Hg lamp (125 W)	Degradation of ibuprofen was more pronounced under TiO ₂ photocatalysis using artificial UV light compared to solar UV irradiation. 92% of ibuprofen was removed, while TOC removal of 78% was obtained under artificial UV light (medium pressure Hg lamp).	Candido et al., 2016
Aspirin and Paracetamol	Milli-Q water and tap water	UVA lamp (315–400 nm; 75 W/m ²)	The photocatalytic degradation of aspirin and paracetamol mixture (12.5 mg/L each) using 0.1 g/L TiO ₂ P25 produced better removal and mineralization compared to similar amount of TiO ₂ K1077.	Bianchi et al., 2017
Ibuprofen	Ultrapure water, municipal wastewater and pharmaceutical industry wastewater	UV-LED (4 × 10 W; 382 nm)	TiO ₂ photocatalytic degradation of ibuprofen in ultrapure water (60 mg/L) increased with the number of LEDs used whereby 4LEDs produced complete degradation after 30 min of treatment time.	Jallouli et al., 2018
Anticonvulsants Carbamazepine (and ibuprofen)	Milli-Q water and wastewater from WWTP	Solar simulator (1000 W) Phillip Xe lamp and UVA lamp (9 W Radium lamp)	Degradation under UVA irradiation in pure water was sensitive to TiO ₂ P25 loading. Solar and UV-A photocatalysis appear to be efficient for carbamazepine degradation.	Achilleos et al., 2010
Phenobarbital	Milli-Q water	High pressure Hg lamp (365 nm)	Photocatalytic degradation rate constant of phenobarbital increased from 0.012 min ⁻¹ at pH 3 to 0.027 min ⁻¹ for pH 5, 7 and 9 (all three having similar values). Degradation of phenobarbital decreased from 95% to 79% when the initial concentration was increased from 50 µM to 100 µM.	Cao et al., 2013
Carbamazepine	Distilled water	UVA lamp (3 × 8 W; 365 nm)	Carbamazepine was degraded up to 99% in the presence of 1.5 g/L TiO ₂ photocatalyst P90 after 90 min of treatment using a UVA lamp (365 nm).	Carabin et al., 2015
Carbamazepine	Milli-Q water	Solar simulator (1000 W Xe short-arc lamp)	Addition of TiO ₂ improved the degradation rate of carbamazepine to 0.015 min ⁻¹ compared to only 0.0005 min ⁻¹ during photolysis after 120 min of treatment. The presence of natural organic matter (lignite humic acid) at low concentrations increased the degradation of carbamazepine.	Drosos et al., 2015
Lipid regulators Bezafibrate	Doubly distilled water	Solar simulator (1500 W xenon arc lamp)	Bezafibrate was completely degraded within 200 min following pseudo-first-order kinetics with rate constant, of 2.81 × 10 ⁻² min ⁻¹ .	Lambropoulou et al., 2008
β-blockers Metoprolol and propranolol	Milli-Q water	Solar simulator (Xe-OP lamp; 1 kW)	Maximum removals of both compounds were achieved with 0.4 g/L TiO ₂ P25. Almost 55% of TOC and COD removal was achieved after 360 min of irradiation.	Romero et al., 2011
Propranolol	Milli-Q water	Solar simulator (Xe-OP lamp; 1 kW) and solar compound parabolic concentrators	Higher pseudo-first-order kinetic constants were obtained in laboratory solar device (k = 0.0090–0.01085 min ⁻¹) than pilot solar device (k = 0.00492–0.00785 min ⁻¹).	De la Cruz et al., 2013a
Metoprolol	Deionized water	Solar box (Xe lamp; 1 kW)		

(continued on next page)

Table 2 (continued)

Therapeutic class/ compound	Water matrix	Experimental conditions	Results	Reference
Others			TiO ₂ photocatalytic degradation of metoprolol followed first order kinetics, where the degradation rate constants increased from 0.0061 min ⁻¹ to 0.12 min ⁻¹ for 0.05 g/L and 0.4 g/L TiO ₂ , respectively. TiO ₂ concentration of 0.4 g/L also produced the highest TOC removal (45.6%).	Romero et al., 2015
Crotamiton (anti-pruritic drug)	Milli-Q water	UV lamp (0.25–2.0 mW/cm ²)	The studied pH range of 3–9 did not show great influence on the degradation rate. Pseudo-first-order rate constant increased with UV intensity.	Fukahori et al., 2012
Chlorhexidine (antimicrobial)	Ultra-pure water	UVA lamp (10 W)	TiO ₂ loading of 200 mg/L removed the highest percentage of chlorhexidine (68.2%) within 1 h of treatment at pH 10.5. TiO ₂ Aeroxide P25 performed slightly better than TiO ₂ pure anatase in removing the chlorhexidine.	Das et al., 2014
Methamphetamine (central nervous system stimulant)	Effluent from sewage treatment plant, deionized water	UV lamp (9W; 365 nm)	The apparent rate constant of 100 µg/L methamphetamine increased from 0.12 to 2.34 min ⁻¹ when the TiO ₂ loading was varied from 0.01 to 0.1 g/L. The degradation rate dropped when 0.4 g/L and 0.7 g/L TiO ₂ was used in the photocatalytic degradation.	Kuo et al., 2015
Methotrexate (antineoplastic agent or chemotherapeutic drug)	Milli-Q water	UVA lamp (8W; 352 nm)	The half-life of methotrexate (100 µg/L) in the TiO ₂ photocatalytic treatment was 13.8 min. Addition of HCO ₃ ⁻ (400 mg/L) in the TiO ₂ photocatalytic treatment reduced the half-life to 1.8 min.	Lai et al., 2017
Venlafaxine (antidepressant)	Ultra-pure water	UVA lamp (9W/78; 340–400 nm)	Degradation rate of venlafaxine increased from 0.1 min ⁻¹ at the TiO ₂ concentration of 0.2 g/L to 0.2 min ⁻¹ at 0.6 g/L and decreased when 0.8 g/L was used (pH = 4.0). Complete elimination of 2.5 mg/L venlafaxine was attained after 20 min in the presence of 0.4 g/L TiO ₂ .	Lambropoulou et al., 2017

Table 3

Characteristics comparing of TiO₂ P25 to other commercial photocatalysts.

Properties	TiO ₂ P25	Hombicat UV 100	Ti (IV) oxide (Aldrich)
Brunauer-Emmett-Teller (BET) surface area, m ² /g	50	>250	190–290
Particle size, nm	21	5	15
Crystal form	80% Anatase; 20% Rutile	100% (or >99%) Anatase	100% (or >99%) Anatase

commonly used in TiO₂ photocatalytic oxidation studies as shown in Table 3. Real water matrices such as wastewater effluents, river or lake water and drinking (tap) water have likewise been utilized in TiO₂ photocatalytic degradation, although in general these studies are less common. The presence of radical scavengers such as carbonate ions, HCO₃⁻ and CO₃²⁻ and natural NOM both in spiked and real wastewater samples typically impacts on the degradation efficiencies. The effect of carbonate species (HCO₃⁻ and CO₃²⁻) has been reported to either inhibit or enhance the degradation rate of pharmaceuticals. The influence of HCO₃⁻ in pure water on the UV/TiO₂ photocatalytic degradation efficiency has been studied for methotrexate. The initial reaction rate was found to increase with increasing HCO₃⁻ concentration (20–400 mg/L) due to the reduced self-recombination rate and longer life time of CO₃²⁻ compared to HO[•] radicals (Lai et al., 2017). The degradation of clofibric acid in four different environmental water matrices (tap water, river water, mineral water and recycled wastewater) showed a >90% decrease in the degradation efficiency compared to pure water due to the presence of organic matter, anions such as chlorides, sulfates and carbonates or in the case of recycled wastewater, due to the presence of alkaline, alkaline earth and heavy metals (Rioja et al., 2016). Antonopoulou et al. (2016) also reported a decrease in the TiO₂ photocatalytic degradation efficiency of three transformation products of tramadol, namely *N*-desmethyl- (*N*-DES), *N,N*-bidesmethyl (*N,N*-Bi-DES) and *N*-oxide-tramadol (*N*-OX-TRA), in secondary-treated wastewater compared to ultra-pure water, owing to the presence of inorganic ions and organic carbon that scavenged the reactive radical species.

The effect of NOM such as humic acid and fulvic acid on TiO₂ photocatalysis has been reported to either (i) inhibit the

photodegradation due to its ability to absorb light or by acting as a quencher for the photo-excited molecules, or (ii) promote photodegradation by acting as a photosensitizer. The effect of NOM on the degradation of carbamazepine was evaluated by Drosos et al. (2015). This study reported that low concentrations of NOM enhanced the photocatalytic degradation of carbamazepine as a result of adsorption of the NOM onto the TiO₂ surface, which maintained sufficient contact for photocatalysis to occur. However, higher concentrations of NOM were reported to impede the adsorption of the pharmaceuticals onto TiO₂. In another study, the effect of NOM, humic acid and tannic acid, on the TiO₂ photocatalytic degradation of carbamazepine and three of its derivatives (carbamazepine epoxide, acridine and acridone) was reported to vary and to be dependent on the type and concentration of NOM (Haroune et al., 2014). The degradation of acridine was observed to decrease with an increasing concentration of tannic acid, while the results for the other compounds were inconclusive due to the noisy data.

Furthermore, studies have shown that filtered or unfiltered wastewater samples influence the degradation rate of UV/TiO₂ photocatalysis to different extents. For example, the photocatalytic degradation rate of moxifloxacin was reported to be 2 times slower in unfiltered hospital wastewater than in demineralized water. Despite this, a comparison of the photocatalytic degradation of moxifloxacin in unfiltered and filtered hospital wastewaters revealed no significant difference, implying that suspended particulate matter did not inhibit the degradation (Van Doorslaer et al., 2015). In a separate study, the TiO₂ photocatalytic degradation of naproxen in unfiltered river water and in the presence of phosphate and chloride anions markedly decreased the degradation rate

(0.10–0.11 min⁻¹) compared to a higher degradation rate in their absence (0.21 min⁻¹) (Kanakaraju et al., 2015). Light filtering effects and competitive adsorption by NOM were held responsible for these findings.

Researchers predominantly perform laboratory-scale experiments with artificial UV light over pilot scale operations with sunlight, as conditions are easier to control. Often, there is no direct correlation between results from both protocols as shown by De la Cruz et al. (2013a) for the degradation of propranolol. Factors such as light intensity, available wavelengths and the photoreactor configuration contribute to these differences. However, pilot scale studies are more realistic and more relevant for real high-volume wastewater applications. Compound parabolic collectors (CPC) are commonly chosen for large-scale solar photocatalytic investigations, as these devices can harvest both non-concentrating and concentrating radiation (Blanco-Galvez et al., 2007).

One important purpose of TiO₂ photocatalytic treatment is the improvement of the biodegradability of persistent pharmaceuticals. In most cases, complete degradation of the parent pharmaceutical does not correspond directly with the mineralization rate, indicating the formation of more stable intermediates during the degradation processes. A non-biodegradable fraction frequently remains in the treated solution. The degree of mineralization is usually reported as dissolved organic carbon (DOC) and total organic carbon (TOC) removal or chemical oxygen demand (COD) and tends to vary based on the nature of the water matrix. Hybrid methods, however, are commonly more effective in improving mineralization rates as well as biodegradability. For example, sonophotocatalysis of ibuprofen showed a higher TOC removal of up to 92% compared to the individual process, sonolysis or TiO₂ photocatalysis, which only achieved 16% and 88%, respectively, after 3 h (Madhavan et al., 2010).

The transformation products generated during UV/TiO₂ photocatalyzed oxidation may potentially be more toxic than the parent compound itself. Accordingly, the incorporation of a toxicity evaluation in pharmaceutical degradation studies is important. Toxicity experiments to measure antibiotic activity using bacterial strains such as *Escherichia coli* and *Enterococcus faecalis*, inhibition test using bacteria such as *Vibrio fischeri* and bioassay tests to determine EC₅₀ or LC₅₀ have been reported. The presence of toxic by-products during or after the treatment has been generally reported as the main factor contributing to toxicity (Calza et al., 2006; Méndez-Arriaga et al., 2008a). In most cases, toxicity was found to be high during the initial period of the treatment and to decrease towards the end, demonstrating the potential detoxification ability of photocatalysis. Recent research showed that by-products generated during the UV/TiO₂ treatment of methotrexate in the presence of HCO₃⁻ anions increased toxicity for 12 h of treatment, while no toxicity was observed in the absence of HCO₃⁻ anion (Lai et al., 2017). Likewise, it has been reported that a photoproduct of diclofenac, i.e. 8-chlorocarbazole-1-yl- ethanoic acid, displayed higher toxicity than the parent compound (García-Araya et al., 2010). Therefore, attention must be paid to ensure that there are no more toxic or more persistent products formed compared to the parent pharmaceutical being degraded. Emphasis on the identification of transformation products has been lacking in the literature, especially when real wastewater samples were involved. A few possible reasons for this neglect are: (i) difficulties in separating and identifying the often large number of transformation products formed, (ii) lack of or non-existent analytical standards to determine the identity of these transformation products and (iii) requirements for more than one analytical technique or sample preparation technique due to their diverse physicochemical properties (Agüera et al., 2005; Fatta-Kassinos et al., 2011b). Despite this, transformation products and degradation pathways have been proposed in various studies,

especially when dealing with single APIs (Jallouli et al., 2018; Lambropoulou et al., 2017). Lai et al. (2017) attempted to compare the degradation products formed during the UV/TiO₂ and UV/TiO₂/HCO₃⁻ degradation of methotrexate. As the identification of degradants naturally becomes more complicated for multiple APIs, studies tend to neglect this aspect as one of their objectives. A study by Kanakaraju et al. (2016) attempted to identify the main degradants generated during solar TiO₂ photocatalysis of a diclofenac and naproxen mixture by means of liquid chromatography mass spectrometry (LC-MS) and Fourier transform-ion cyclotron resonance-mass spectrometry (FT-ICR-MS). More studies, however are needed to address the identification of degradants formed when more than one API is present in the water or wastewater.

Existing data suggest that TiO₂ photocatalysis appears to be an excellent choice of AOP for pharmaceutical removal in pure or wastewater. However, limited information is available on the efficiency of this process for the removal of pharmaceuticals in mixtures, particularly in real wastewater. Various APIs belonging to different therapeutic groups may be present in real wastewater leading to additive, synergistic and antagonistic effects or interactions. In addition, as pharmaceuticals may occur in concoctions with other pollutants such as dyes and heavy metals, future studies should attempt to fill this knowledge gap. Nevertheless, simulated wastewater containing known mixtures of pollutants may be used to investigate important aspects of TiO₂ photocatalysis (e.g. toxicity, kinetics, degradation products) as interactions of multi-pollutants in real wastewater are highly complex due to the presence of other substances such as anions and organic matter.

5. Conclusions and future outlook

This review has demonstrated the potential application of AOPs for the removal of pharmaceuticals in wastewater.

Current research demonstrates that pharmaceuticals are a persistent type of pollutant in aquatic media with increasing environmental and health concerns. Many studies have revealed that conventional WWTPs are the main entry point of APIs to surface waters in trace quantities. The role of an abiotic process involving biological degradation remains unclear due to contradicting evidence. Various factors dictate the behaviour of APIs towards biological degradation. Gathered evidence on the effects of pharmaceuticals' presence and detection signify the seriousness of these pollutants. More risk assessment studies investigating the ecological effects of pharmaceuticals and their metabolites should be performed. To address the limitations of conventional WWTPs, AOPs should be considered as alternatives or add-ons as they often offer better removal efficiencies.

Researchers have applied different AOPs in order to degrade or remove pharmaceuticals in water or wastewater. Typically, most AOP studies on pharmaceuticals deal with (i) the degradation kinetics by investigating the effect of operational parameters, (ii) mineralization measurements using indicators like TOC, DOC or COD, (iii) toxicity studies and (iv) the profiling or identification of degradants. Although it is evident from most of the reviewed studies that AOPs are efficient in the degradation of pharmaceuticals, the identification of transformation products and toxicity levels are equally crucial as these products can be more biologically active or toxic than their parent compounds, thus imposing even greater hazards to the environment. Although synthetic wastewater samples have generally been used for degradation studies, more studies are being carried out using real wastewater samples. As a result, more useful information is becoming available for the application of AOP in real industrial settings. As the matrix of real wastewater sample is complex due to the presence of organic and inorganic substances and due to variations of the wastewater

characteristics, a reliable AOP protocol needs to be chosen to ensure its effectiveness. Moreover, the complex nature of wastewater samples makes the identification of degradation products challenging and difficult. Besides single AOP techniques, hybrid or combined techniques are also becoming popular to achieve high removal efficiencies.

Future studies should consider developing AOP degradation protocols on mixtures of pharmaceutical, given that they do not occur individually in water bodies. Such an effort would also be more practical for future applications and implementations. In addition, environmentally relevant conditions (e.g. water matrices or environmental concentration of APIs) should be considered when planning experimental designs for pharmaceutical degradations. Further research should also be undertaken to explore the usage of UV-LEDs instead of mercury based lamps for TiO₂ photocatalysis and TiO₂/hybrid oxidation techniques, as the former have long life times, are robust, consume less energy and do not require unnecessary warming up times. Hybrid photocatalysts using either commercially available TiO₂ photocatalysts and traditional adsorbents (e.g. TiO₂/zeolite (Pan et al., 2014), TiO₂/alginate (Kanakaraju et al., 2017) and TiO₂/activated carbon (Basha et al., 2011)) and combined AOP techniques can be applied for the degradation of pharmaceutical mixtures in wastewaters. Likewise, the fabrication of novel TiO₂ photocatalysts with enhanced visible light absorbing capacity would facilitate TiO₂ photocatalytic oxidation studies under direct sunlight or visible light (Schneider et al., 2014). As the complexity of the water matrix is critical for TiO₂ photocatalysis, systematic investigations to compare real and simulated wastewaters should be performed, in particularly for pharmaceutical mixtures and with other types of organic or inorganic pollutants. TiO₂ photocatalytic oxidation studies and other AOPs should more closely examine the quality of treated effluents, particularly the toxicity level, which could be affected due to oxidation by-products, and implement subsequent treatment (e.g. biological treatment) in their design to meet discharge limits.

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