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Insights into current physical, chemical and hybrid technologies used for the treatment of wastewater contaminated with pharmaceuticals

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ABSTRACT

The purpose of this article is to review the current physical, chemical and hybrid technologies practices employed in the removal of pharmaceuticals from liquid effluents originating from various resources including municipal waste, hospitals discharge with a focus on pharmaceutical manufacturing industry. Pharmaceutical pollutants are mostly persistent organic compounds that are not easily removed by conventional wastewater treatment processes. The literature reviewed shows that advanced oxidation processes are able to degrade these persistent pharmaceuticals. However, the oxidation may also introduce toxic oxidation intermediates/by-products if these processes are not properly monitored and operated. Physical treatments, like carbon adsorption and membrane filtration, can provide a barrier that prevents both parent compounds and toxic intermediates passing into treated wastewater. However, these processes are phase changing technologies in which contaminants are transferred from one phase to another hence, the retentate water and absorbent require further treatment, and properly managed disposal. The combination of different processes can be an ideal treatment scheme, for the retention and degradation of both parent and transformation compounds. Through hybrid technologies, the advantages of the methods are combined, leading to a maximization of contaminants removal. The review highlights the importance of installing combined wastewater treatment processes to reduce the amounts of pharmaceutical residues before the wastewater enters the environment. The use of advanced oxidation process, either as a pre-treatment or as a post-treatment combined with biological, adsorption, or filtration process is recommended as a promising option. Nevertheless, the optimum treatment methods for the pharmaceuticals-containing wastewater depends on the quality and quantity of wastewater, as well as on the pharmaceutical compounds residues and their hazardous effects.

1. Introduction: pharmaceuticals in aquatic environment

Contamination of the aquatic environment with pharmaceuticals is a serious global emerging concern. Pharmaceutical pollutants can find their way into this environment through wastewater expelled from households, farms, hospitals and industries, with the failure of wastewater treatment plants to eliminate them is identified as a major contributing factor. Pharmaceuticals can enter the natural environment due to human activities, today, more than 600 active pharmaceutical substances have been reported worldwide in many water bodies, even in drinking water (Eike et al., 2019). Although their occurrence is at low concentrations (nanograms to micrograms per liter), several studies have demonstrated that pharmaceutical active ingredients can cause significant risk on the environment and adverse effects on humans and aquatic life even at this minute level (Świacka et al., 2021).

The pharmaceutical industry has the potential to pollute water

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bodies with a wide range of hazardous pollutants as well as exhibiting a significant water footprint (Chaturvedi et al., 2017). The water treatment processes required to remove the residual pharmaceuticals from discharged water to acceptable standards may result in an increased cost of treatment. This might be an issue in bulk drug manufacturing units in developing countries. For example, studies from India demonstrated a high level of broad-spectrum fluoroquinolone antibiotics in surface water originating from manufacturing hubs of bulk drugs in the surrounding areas. The concentration of ciprofloxacin in Musi River reached 5015 μg/l while the levels found in sewage effluents around the world were less than 1 μg/l (Ritu and null, 2017).

The manufacture of pharmaceuticals can introduce harmful, biologically active and potentially persistent organic compounds into aqueous solutions (Prasanna et al., 2020). These may include, but are not limited to, antibiotics, non-steroidal anti-inflammatory drugs (NSAIDs), hormones, analgesics, and endocrine disrupting compounds (EDCs). Some of these are easily removed from the aqueous phase during conventional treatment processes, such as the activated sludge process (Tang et al., 2020), whereas others are very difficult to degrade and are thus found in the treated effluent of wastewater treatment plants (WWTPs).

The section below shows examples of the occurrence and consequence ecotoxicity of pharmaceuticals in aquatic environment around the world.

Non-steroidal anti-inflammatory drugs (NSAID)s are widely used medicines for human and veterinary use. Their occurrence in surface waters, wastewater, and sewage treatment plants was reported in many studies, which is attributed to their hydrophilicity and stability (Sousa et al., 2018). Diclofenac, for example, and its metabolites caused toxicity in vultures, mammals and aquatic organisms. It has been linked to the decline of three vulture species in India, Pakistan and Bangladesh (Prakash Prakash Reddy et al., 2006). This decline was attributed to the vultures' consumption of animals that had been treated with diclofenac. The importance of removing diclofenac from pharmaceutical waste streams is highlighted as this drug has been found to pass through conventional wastewater treatment processes relatively unaffected (Nguyen et al., 2019). Ibuprofen and salicylic acid have also been found to survive conventional WWTPs (Martín et al., 2012). Ibuprofen has been found to cause immunosuppression as well as impacting the physical development of fish (K. Zhang et al., 2020). Water or soil contamination with ketoprofen caused toxic damage to plants, namely rice seedlings, as well as affected the behaviour of some aquatic invertebrates (Bownik et al., 2020; H. Wang et al., 2020). NSAIDs have been demonstrated in literature to be persistent contaminants that are poorly removed by conventional wastewater treatment procedures. Therefore, advanced procedures are required to remove them.

Antibiotics present in wastewater have been found to be mostly degraded by conventional wastewater treatment processes, some however remain in very low aqueous concentrations after conventional treatment processes (Phoon et al., 2020). The residual antibiotics can pass through the WWTP and into the treated effluent, leading to the evolution of antibiotic resistance genes (ARGs). Micro-organisms in pharmaceutical wastewater treatment plants can therefore become exposed to antibiotics, increasing the chance that these organisms will develop antibiotic resistance. The ARGs that these organisms produce can be either suspended in water after cell wall lysis, included in replicating bacteriophages, or transferred to another bacterium via sexual pilus. Transduction is a mechanism in which a bacterium can acquire antibiotic resistance (Balcazar, 2014). The bacterium then incorporates this DNA into its chromosomal DNA resulting in an antibiotic resistant bacterium. Conjugation is a mechanism that involves bacterial contact via a sexual pilus, genetic material can be transferred along this pilus and incorporated into the recipient bacterial genome (McInnes et al., 2020). Finally, ARGs can become suspended in water after cell lysis. Subsequently, the naked DNA strands are taken by other bacteria via transformation, perhaps the most potent of the mechanisms by which bacteria gain antibiotic resistance (Lu et al., 2020). It is consequently highly important to remove both antibiotics, and ARGs from wastewater streams.

Endocrine disrupting compounds (EDCs) are responsible for altering the body's endocrine system in humans and animals. The presence of steroid hormones in aquatic water have been extensively reported including synthetic steroids, namely, ethinylestradiol (EE2) and mestranol (MeEE2), that are commonly used in oral contraceptives and hormone replacement therapy (Combalbert and Hernandez-Raquet, 2010; Baronti et al., 2000; Čelić et al., 2020; Torres et al., 2021). Despite the fact that steroidal hormones were detected at very low levels, their endocrine disturbing effects are harmful on human health and wildlife. Some of these compounds are poorly removed through a conventional wastewater treatment process (i.e. activated sludge process) (Aris et al., 2014). Hormones present in treated effluents which are disposed of into the aquatic environment can also lead to ecological problems, such as feminisation of male aquatic creatures (Darbre, 2019), or damage to or impact on the growth of fish population (Aris et al., 2020). The persistent nature of many of these compounds in domestic wastewater shows that advanced wastewater treatment processes are required for their removal.

Other groups of pharmaceutically active compounds were also detected in water bodies including antifungal drugs, antidepressants, beta-blockers and lipid-lowering agents such as statins (Assress et al., 2020; Lajeunesse et al., 2012; Loos et al., 2013; Mohapatra et al., 2016). Nevertheless, the current review will only focus on these three groups of medicines: NSAIDs, antibiotics and EDCs.

2. Wastewater treatment processes for the removal of pharmaceutical pollutants

Conventional wastewater treatment processes are focused on macropollutants including suspended solids, organic carbon, nitrogen, phosphorus and pathogens from wastewater; however, they are not designed to effectively remove micropollutants, such as recalcitrant pharmaceutically active compounds. In conventional systems, the efficiency of removing such compounds varies widely, from negative to complete removal, depending on the influent mass flow of the compounds, the compounds' physicochemical properties (size, concentration, functional group, polarity), and the environmental and operating conditions of the treatment scheme (Rout et al., 2021). Although during conventional wastewater treatment processes the pharmaceutical compounds are subjected to various physicochemical and/or biological processes, which mainly include mineralization, dispersion, dilution, photodegradation, and volatilization, the dominant removal mechanisms are biodegradation and biotransformation from microorganisms and sorption onto biosolids (Noutsopoulos et al., 2020; Koumaki et al., 2021).

Several pharmaceutical products have been found in surface water near suburban sites, while often the highest concentrations of these substances were detected in areas close to WWTP outfalls (Barber et al., 2015). This indicates that on one hand, the compounds survive conventional treatment processes and on the other hand, WWTPs are one of the main routes for their transfer into the aquatic environment. Fig. 1 displays how pharmaceuticals could possibly enter into water bodies (surface and underground) and soil though various routes originating from industrial, hospital discharges, excretion of drugs and their metabolites including human or veterinary medicines as well from the waste disposal for unused or expired medications.

The present paper reviews current physical, chemical and nature-based systems used in water treatment for removing pharmaceutical contaminants, either alone or as pre or post treatment to other technologies. There are other important technologies employed in wastewater treatments such as conventional biological treatments, but these are outside the scope of the current review. This review focuses first on widely used advanced oxidation processes (AOPs) which include

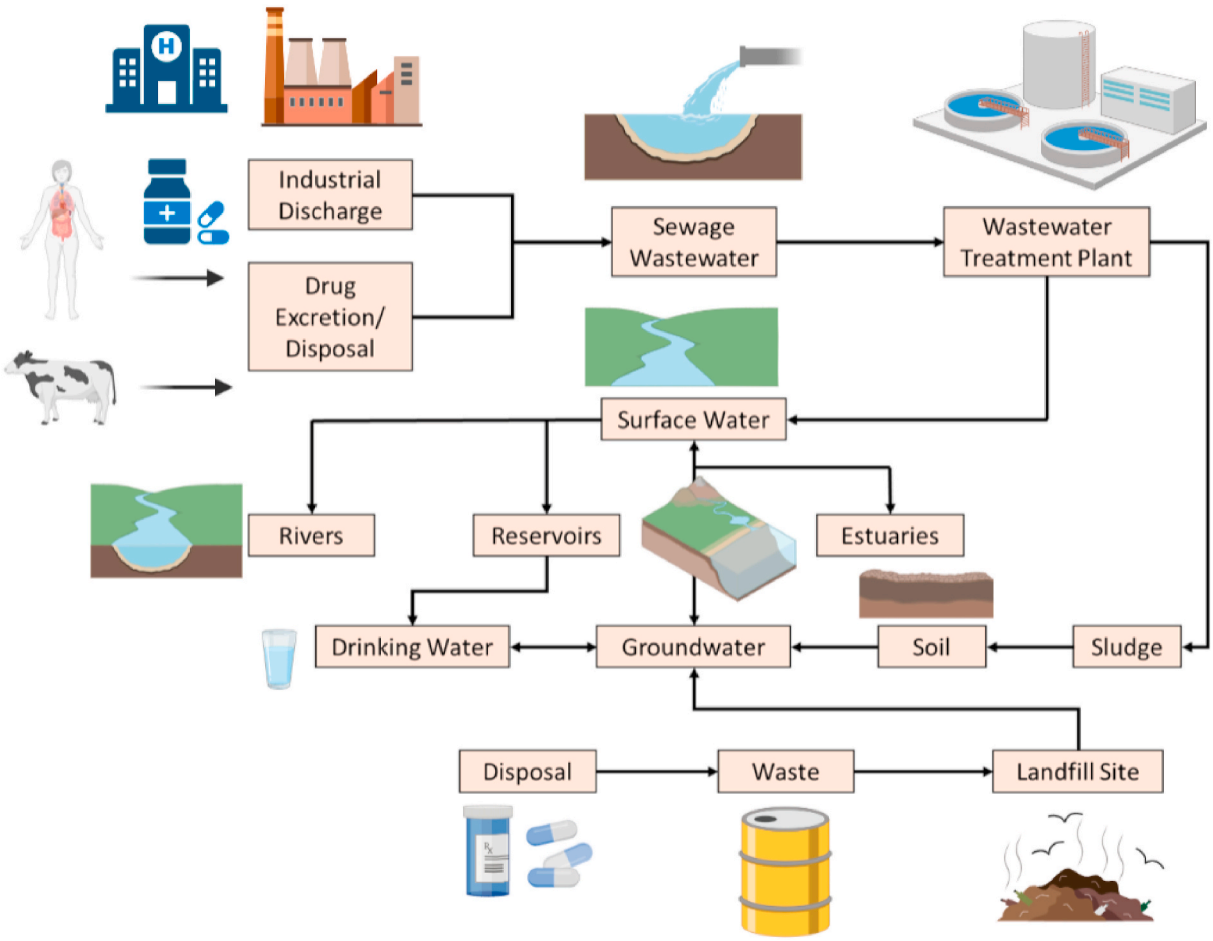

Fig. 1. Flowchart displaying possible pathways for pharmaceuticals entering into different water bodies and soil (created with BioRender.com).

ozonation and photocatalysis performed by the action of catalysts (TiO2 or Fenton's reagent); second, the physical treatments including adsorption on activated carbon and membrane separation such as nanofiltration and reserved osmosis, third on treatment through nature-based solutions and, finally, on the hybrid technologies which combine conventional and advanced treatment technologies (Fig. 2).

2.1. Advanced oxidation processes

2.1.1. Ozonation

Ozonation is a process that introduces ozone to water, this is usually done via bubbling ozone from the bottom of a tank through a sparger. Ozone has oxidation effects through direct reaction by ozone or indirect radical reactions through a chain of oxidative reactions. Ozone is a powerful oxidant on its own for certain organic compounds (Testolin et al., 2020). However, in the presence of water, ozone can react with available hydroxide ions to produce the less selective and consequently

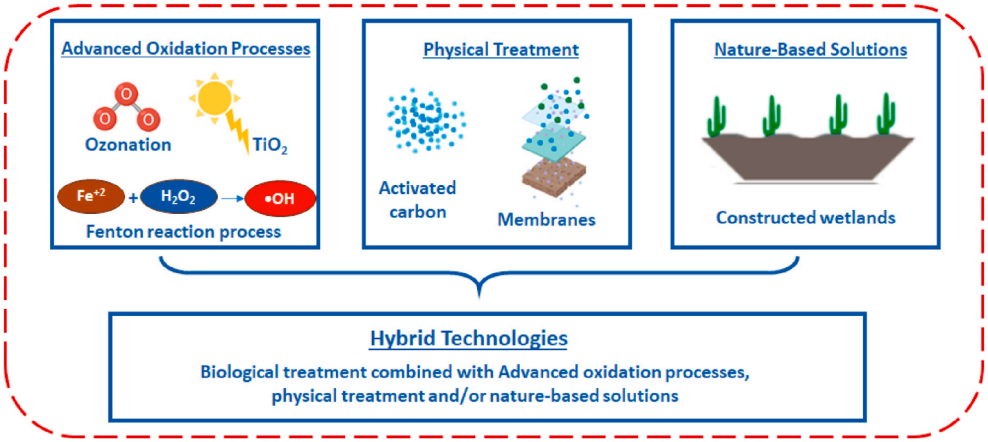

Fig. 2. Schematic presentation of treatment systems reviewed in the present article (created with BioRender.com).

more powerful oxidizing hydroxyl radical (HO•) (Silva, 2006). Studies showed that ozone can attack pharmaceutical aromatic compounds rich in electrons including sulfamethoxazole, ciprofloxacin, carbamazepine, azithromycin, clarithromycin, diclofenac, erythromycin and metoprolol (Kovalova et al., 2013; Lee et al., 2013; Altmann et al., 2014; Bourgin et al., 2018), and pharmaceuticals with deprotonated amine groups like trimethoprim at low pH (Dickenson et al., 2009; Gogate et al., 2020). On the other hand, HO• radicals, due to their quick action and their non-selective nature, oxidise a wide range of pharmaceuticals including those that are resistant to ozone in alkaline conditions (like primidone, loperamide, cephalexin and penicillin) (Dodd et al., 2006; Kovalova et al., 2013; Bourgin et al., 2018).

Ozone has been recently used widely as a tertiary treatment process for wastewater containing pharmaceuticals, taking advantage of its potent oxidation potential, compared to most traditional oxidants. However, one of the typical operational obstacles for implementing ozonation in wastewater treatment systems is the excessive presence of organic carbon and other oxidisable substances which means greater amounts of ozone are required for the full treatment of typical sewage (Farzaneh et al., 2020). Ozone is a difficult chemical to use, not easily stored and thus needs to be produced on site in almost all WWTPs. Ozone can be produced in several different ways. The method most frequently used in water treatment processes is the corona discharge method (Wu et al., 2021). It requires high voltage electricity to function; consequently, a pharmaceutical plant has to invest in the necessary equipment, such as power supplies and transformers in order to operate an ozonation system. Furthermore, excess ozone present in the water needs to be removed after the treatment process due to ozone's harmful nature, this can be achieved through the use of ozone destruction units. Intermittent operation of ozone generators could also reduce the amount of residual ozone whilst at the same time increase the energy efficiency of an ozonation process. However reduced removal rates of pharmaceutical compounds may be experienced using an intermittent ozonation regime (A.H. Khan et al., 2020).

Another important issue with implementing ozonation in pharmaceutical wastewater is the formation of by-products which in many cases present higher toxicity than the parent compounds (Tufail et al., 2020). Since the mechanisms taking place during ozonation depend on the pH, temperature as well as the ozone dose, their optimization plays a crucial role in the formation of these by-products. The typical ozone doses applied in wastewater treatment (0.4–0.6 gO_3/g DOC) usually do not result in mineralization and its toxicity increases temporarily after ozonation (Kharel et al., 2020). A typical example of drug's increased toxicity after ozonation includes carbamazepine. Although ozonation was effective in removing this drug from water, it caused toxicity in zebrafish resulting from the formation of by-products, manifested by behavioural changes in fish (Pohl et al., 2019). The ozonated carbamazepine also persistently induced embryotoxicity responses in zebrafish even over 2 week of storage, potentially illustrating environmental concern (Pohl et al., 2020).

A possible solution to this could be to increase the doses of ozone applied sufficiently so that the formed transformation products or

Table 1
Literature results concerning removal efficiencies of pharmaceuticals from water by ozonation.

	Compound initial concentration (mg/L)	Ozone dosage (mg/L)	Contact time (min)	Removal amount (%)	Source
Tetracycline	50	33	20	95 (pH:3)	(C. Wang et al., 2020b)
				99 (pH:9)	
Sulfaquinoxaline	0.5	5.5	1	99 (pH:3)	Urbano et al. (2017)
			1	95 (pH:7)	
			1	30 (pH:11)	
	0.5	2.8	Not stated	98 (pH:3)	
				62.7 (pH:7)	
				17.7 (pH:11)	
Sulfamethoxazole	1	2.3	2	80 (pH:2)	Garoma et al. (2010)
				80 (pH:7)	
				99 (pH:10)	
	1	3.2	2	90 (pH:7)	
Sulfamethizole	1	2.3	2	80 (pH:7)	
	1	3.2	2	95 (pH:7)	
Sulfathiazole	1	2.3	2	80 (pH:7)	
	1	3.2	2	99 (pH:7)	
Sulfadiazine	1	2.3	2	65 (pH:7)	
	1	3.2	2	99 (pH:7)	
Diclofenac	0.67–1.2	2.8–3.8	10	>99	Edefell et al. (2021)
		4.7–6.4		>99	
		6.5–8.9		>99	
		8.4–11.4		>99	
Ibuprofen	0.76–2.0	2.8–3.8	10	40	
		4.7–6.4		60	
		6.5–8.9		80	
		8.4–11.4		90	
EE2	0.1	5	1	99.9	Rokhina et al. (2012)
	0.1	5.5	Not stated	75–80	Si et al. (2018)
17α-Dihydroequilin (17αEQ)	0.1	5	1	99.2	Rokhina et al. (2012)
17α-Estradiol (17α)	0.1	5	1	100	
17β-Estradiol (E2)	0.1	5	1	99.9	
	0.1	5.5	Not stated	75–80	Si et al. (2018)
Estriol (E3)	0.1	5	1	99.5	Rokhina et al. (2012)
	0.1	5.5	Not stated	75–80	Si et al. (2018)
Estrone (E1)	0.1	5	1	99.7	Rokhina et al. (2012)
	0.1	5.5	Not stated	75–80	Si et al. (2018)
Equilin (EQ)	0.1	5	1	99.4	Rokhina et al. (2012)
Levonorgestrel (LN)	0.1	5	1	99.7	
Gestodene (GSD)	0.1	5	1	99.7	
Trimegestrone (TMG)	0.1	5	1	100	
Medrogestone (MN)	0.1	5	1	99.7	
Progesterone (P)	0.1	5	1	99.7	

oxidation by-products are completely mineralised. At the same time, this will increase the operating cost of the treatment process. An alternative solution is the implementation of hybrid technologies, such as ozone/H_2O_2, photocatalytic ozonation and heterogenous catalytic ozonation, or the combination of the biological wastewater treatment process with ozonation, thus leading to an optimized treatment scheme.

2.1.1.1. Ozonation of antibiotics. Ozonation has been used in literature to reduce both antibiotics and ARGs (Table 1). In many cases this treatment process has been found to be successful in the reduction of both antibiotics and ARGs (Wang et al., 2020a; Xia et al., 2020). Ozone, under an optimized contact time and ozone dose combination is able to deactivate antibiotic-resistant bacteria and remove ARGs, due to its reactivity with electron-rich functional groups, such as amines and activated aromatics. Ozone can damage the cell components including glycoproteins and glycolipids resulting in lysis of the bacterial cell. It also attacks the purine and pyrimidine bases of nucleic acids thus damaging the bacterial DNA in addition to the damage induced on the enzyme level through attacking sulfhydryl groups (Alonso et al., 2018). However, in some cases ozonation has been found to increase the concentration of ARGs in solution. The mechanism for these observations is not clear, one explanation is that the genes found to proliferate in effluent from ozonation treatments result in increased amounts of extracellular polymeric substances on the surface of the bacterial cell, these substances act in effect as armour against oxidative species such as ozone and superoxide anions. This increases the chances of survival for these bacteria and thus their likelihood to replicate, consequently increasing the amount of ARG material present in the treated water. This was found by Alexander et al. (2016) who found that, per 100 ng DNA extracted from samples before and after ozonation, vancomycin (vanA) and imipenem (blaVIM) resistance genes were found to increase in abundance due to the increased robustness of bacteria carrying these genes. In the study of Hu et al. (2019) the levels of sulphonamide (sul1, sul2) and macrolide (ermC) resistance genes remained high despite the pre-treatment, ozonation followed by a post-treatment. Whilst ozone is highly effective in the reduction of many antibiotics and ARGs, it can also result in the proliferation of some ARGs that offer some protection for certain bacterial communities against ozonation. Thus, it is important to remove these antibiotics from wastewater prior to their contact with bacteria, either in later biological wastewater treatment processes or in the environment.

2.1.1.2. Ozonation of NSAIDs. NSAIDs have been successfully degraded by ozonation (Table 1). However, it is important that degradation products are also analysed for their environmental harm, since some degradation products can be even more harmful than the parent NSAIDs from which they are derived (Pohl et al., 2019). Hama Aziz et al. (2017) found that acetate and oxalate ions developed during the ozonation of aqueous solutions containing diclofenac and ibuprofen. Some of the degradation products may be resistant to oxidation by ozone. This means that ozonation of NSAIDs should be monitored. Qiu et al. (2020) found that, whilst the intermediate products from the ozonation of diclofenac were more toxic, after further ozonation these intermediates were degraded into less harmful products. This shows the importance of monitoring the conditions of an ozonation process providing the correct hydraulic retention time for ozone to oxidise both parent compounds and their by-products. Additionally, promoting conditions for ·OH radical formation may also promote the complete degradation of NSAIDs, whilst encouraging the oxidation of ozone resistant intermediates and other by-products to less harmful compounds.

2.1.1.3. Ozonation of hormones, steroids and other EDCs. Ozonation can be used to oxidise hormones and other EDCs (Table 1). One of the most common EDCs found in wastewater and surface water is 17α-ethinylestradiol (EE2), which is an active ingredient in contraceptives (Islam et al., 2020). This hormone is known to interfere with sex determination and maturation, the toxicity of this compound is variable between species meaning that it can be highly impactful even at low concentrations (Porseryd et al., 2017). As is the case with the ozonation of NSAIDs, a question arises as to the toxicity of the ozonation by-products of EE2 and other pharmaceutical hormones and endocrine disruptors. Larcher et al. (2012) found that whilst the estrogenicity of EE2 was reduced by ozonation, the by-products produced had a large negative impact on testosterone secretion even after ozonation. This shows that whilst the intended effect of EDC substances can be reduced by ozonation, other unwanted effects can be heightened by the ozonation process. Lee et al. (2013) found that whilst the hydroxyl radical is a more powerful oxidant than ozone, its impact on EE2 in water treatment is not as strong as that of ozone. Due to the non-selective nature of the ·OH radical, it can be rapidly used up by many other contaminants that may be present in the water matrix such as alcohols, and other organic compounds, whereas ozone is more selective, being attracted to electron rich moieties (Lee and von Gunten, 2010). Oxidation by O_3 is the predominant process for EE2 degradation, it oxidises the phenol functional group which is responsible for the estrogenic activity of EE2 (Huber et al., 2004). The authors stated that it was impossible to get a full removal for the estrogenic activity as EE2 appeared again at a low level (0.1–0.2%) after the ozonation. Degradation products often further degrade and possibly produce other bioactive compounds.

2.1.2. Photocatalysis

Photocatalysis is another advanced oxidation process. This operates in a similar way to ozonation in that photocatalysis functions through the production of hydroxyl radicals (Jimenez-Relinque and Castellote, 2018). Unlike ozonation, hydroxyl radicals are formed through the interaction of water molecules with the surface of the illuminated catalyst. The catalyst that is commonly used for pharmaceutical photocatalytic studies is rutile TiO_2 due to its chemically and biologically inert nature, efficient photoactivity, cost-effectiveness and safety to the environment and humans. TiO_2 photocatalysis is explained by equations (1) and (2). In step 1 (Eq. (1)), the photocatalyst, represented in this case by TiO_2, absorbs a photon, increasing the quantum energy of an electron (e^-) and enabling its conduction from the valence band (VB) to the conductive band (CB), resulting in the production of an electron "hole" (h^+_{vb}) on the surface of the photocatalyst that serves as oxidizing sites. In step 2 (Eq. (2)) the lone pair on the oxygen in a water molecule is attracted to the positively charged hole on the surface of the photocatalyst, the water molecule donates an electron to the photocatalyst, neutralising the positively charged electron hole, this breaks one of the O–H bonds in the water molecule resulting in the production of a hydroxyl radical and an H^+ ion. In equation (3) (Step 3) a second reactive oxygen species is produced through the reaction of dissolved molecular oxygen and the conduction band electron. The O_2·-radical in Step 4 can react with further water molecules to produce more ·OH radicals, as well as hydrogen peroxide. The aqueous hydrogen peroxide reacts with conduction band electrons at the surface of the photocatalyst in Step 5 to produce more ·OH radicals.

Step 1 $TiO_2 + h\nu \rightarrow TiO_2(h^+_{vb} + e^-_{cb})$ (Eq. 1)

Step 2 $H_2O + h^+_{vb} \rightarrow H^+ + HO\cdot$ (Eq. 2)

Step 3 $O_2 + e^-_{cb} \rightarrow O_2\cdot^-$ (Eq. 3)

Step 4 $2H_2O + 2O_2\cdot^- \rightarrow H_2O_2 + 2HO\cdot + O_2$ (Eq. 4)

Step 5 $H_2O_2 + e^-_{cb} \rightarrow 2HO\cdot$ (Eq. 5)

The photocatalysis has lower operating costs and requires fewer procedures compared to ozonation. The difference is that photocatalysis

focuses on the production of the hydroxyl radical, a strongly oxidizing and non-selective radical, which oxidises almost any contaminant found in a water matrix. This means other pollutants present in the wastewater can be oxidised by ·OH radicals as well as the target pollutant. In terms of the removal or inactivation of target pollutants, for photocatalysis to be competitive with other methods, such as ozonation, these other pollutants could be removed by upstream conventional wastewater treatment processes (i.e. activated sludge process), allowing photocatalysis procedures to target the more persistent pollutants that pass through conventional processes largely unscathed (Carbuloni et al., 2020). Apart from the matrix effects that could limit the aspects for the application of photocatalysis, the efficiency of heterogenous photocatalysis depends on the irradiation, the ratio of catalyst amount to the initial concentration of the target compounds and environmental conditions such as pH. A catalyst load at a level lower than optimum one could lead to a limited generation of hydroxyl radical and therefore to insufficient removal of the target compounds. On the other hand, a higher level could augment solution turbidity and hence decrease the transmittance of the radiation. A more energy- and cost-effective alternative is a solar-driven photocatalysis application; however, the main obstacle of this process is the narrow overlap between the catalyst's and natural sunlight's absorption spectrum (Andreozzi et al., 1999).

2.1.2.1. Photocatalysis of antibiotics. Photocatalysts employed to reduce levels of antibiotics and ARGs in wastewater have been increasingly researched in recent years. The way in which photocatalysts remove antibiotics from water is very similar to the ozonation process, where the reactive oxygen species that are produced oxidise the antibiotics ideally

Table 2
Literature results concerning removal efficiencies of pharmaceuticals from water by photocatalysis.

Pharmaceutical	Photocatalyst	Pharmaceutical initial concentration (mg/l)	pH	Irradiation density (mW/cm^2)	Retention time (mins)	Removal amount (%)	Source
Imipenem	TiO_2 (Solar)	0.4 (river water)	8.5	–	45	80	Cabrera-Reina et al. (2019)
Meropenem	TiO_2 (Solar)	0.05 (river water)	8.5	–	30	70	
Ofloxacin	TiO_2 (Solar)	0.0002 (real wastewater)		–	360	77.8	Bernabeu et al. (2011)
Enrofloxacin	TiO_2 (Solar)	0.0002 (real wastewater)		–	360	90.4	
Clarithromycin	TiO_2 (Solar)	0.00003 (real wastewater)		–	360	69.7	
Levofloxacin	Inverse opal K-doped carbon nitride (0% K wt%)	10		–	60	48.8	Lei et al. (2020)
	Inverse opal K-doped carbon nitride (5% K wt%)	10		–	60	56.8	
	Inverse opal K-doped carbon nitride (7.5% K wt%)	10		–	60	100	
	Inverse opal K-doped carbon nitride (10% K wt%)	10		–	60	78.5	
				–		50.9	
Azithromycin Trimethoprim Ofloxacin Sulfamethoxazole	TiO_2 (UV LED)	0.1 (real wastewater)	7.2	–	180	100	Biancullo et al. (2019)
Naproxen	$ZnFe_2O_4$ magnetic nanoparticles coated with TiO_2 with copper support	10	4	–	120	80	Ahmadpour et al. (2020)
			5			70	
			7			60	
			9			45	
Naproxen	Nitrogen + Sulphur doped TiO_2 coated on polycarbonate	2.5	6	2	100	80.3	Eslami et al. (2020)
				11		85.3	
		10		2		82	
				11		70.1	
Ibuprofen	Nitrogen + Sulphur doped TiO_2 coated on polycarbonate	2.5	6	2	100	44	
		2.5		11		58	
		10		2		52	
		10		11		69	
EE2	TiO_2 grown on titanium-tungsten alloy	10	4	–	90	100	(Escudeiro de Oliveira et al., 2020)
EE2			4		2	53.4	
EE2	Sodium doped carbon nitride	10		–	120	92	Sudrajat (2018)
EE2	TiO_2	5	5.5		30	92	Nasuhoglu et al. (2012)
EE2	Graphitic carbon-nitride	3	7.3	–	45	68.5	Vinod et al. (2020)
EE2	Graphitic carbon-nitride heated at 180 °C for 9h with deionised water					88.4	
EE2	Graphitic carbon-nitride heated at 180 °C for 9h with ammonia					99.5	
EE2	Graphitic carbon-nitride heated at 180 °C for 9h with acetic acid					96	
E1			6		2	50	(Escudeiro de Oliveira et al., 2020)
Estrone	TiO_2	1	6–8		240	22	Sornalingam et al. (2018)
Estrone	1 wt% Gold:TiO_2	1	6–8		240	42	
Estrone	2 wt% Gold:TiO_2	1	6–8		180	100	
Estrone	4 wt% Gold:TiO_2	1	6–8		120	100	
Estrone	8 wt% Gold:TiO_2	1	6–8		180	100	
Levonorgestrel	TiO_2	50	5.5		30	97	Nasuhoglu et al. (2012)

to form mineralised carbon, water and other gaseous/mineral emissions.

Table 2 shows some results for antibiotic removal from the literature using photocatalysis. Wastewater from the pharmaceutical production process will probably contain concentrations of active ingredients, as well as other ingredients such as organic solvents which can impact the efficiency of the treatment. For instance, when methanol was added to photocatalysis treatment as carrier solvent, it acted act as a radical scavenger in the photocatalysis of the studied antibiotics (Biancullo et al., 2019). The addition of H_2O_2 while applying photocatalysis (using TiO2 under UVA) to degrade penicillin compounds in aqueous solution resulted an increase in ·OH, and thereby a complete degradation of amoxicillin, ampicillin and cloxacillin (Elmolla and Chaudhuri, 2010). The use of supramolecular organic photocatalyst (3D perylene diimide) under visible-light irradiation, increased the degradation of tetracycline-based antibiotics due to the adsorption and photocatalytic degradation (Q. Zhang et al., 2020).

Advanced oxidation process is efficient for ARGs removal. Some, however, are found to proliferate under oxidative stress. Dunlop et al. (2015) reported that bacterial regrowth when photocatalysis was at sub-lethal dose with an increase in ARGs transfer. Sub-lethal photocatalysis occurs when bacteria are not sufficiently exposed to hydroxyl radicals, consequently bacteria exposed to such conditions can survive the photocatalysis process. This highlights the importance of extending the photocatalysis procedure in order to achieve lysis of all cells in the wastewater. Additionally, Yin et al. (2019) discovered that E. Coli that had obtained antibiotic resistance through horizontal gene transfer had faster growth rates after sub-lethal photocatalysis compared to E. Coli that had no antibiotic resistance, and also bacteria that had gained antibiotic resistance through exposure. Thus, it seems likely that sub-lethal photocatalysis promotes the persistence of ARGs in the environment.

Silva et al. (2022) found that the degradation of some EU Watch List 2020/1161 pharmaceutical compounds (ciprofloxacin, sulfamethoxazole and trimethoprim) by applying TiO2/UV-LED based processes, led to an increase in the toxicity on Vibrio fischeri bacteria. Among these pharmaceuticals, transformation products of ciprofloxacin are more toxic than the native compound, while this work has shown that the toxicity mainly depends on the chosen irradiation (UV-A or UV-C) and the initial compounds in the matrix.

Bacterial and viral contamination in pharmaceutical plants is kept to a minimum, this means that effluents from antibiotic production processes will probably contain less bacterial and viral load than in other wastewaters. Indeed, whilst Shi et al. (2017) found that pharmaceutical wastewater contained high concentrations of chemical oxygen demand (COD), they also found that the major contaminants of pharmaceutical manufacture were solvents, residual pharmaceuticals, persistent organic matter and salts. Implementing a photocatalysis regime with other non-biological treatment processes, such as coagulation-flocculation and adsorption processes close to the point of disposal, may therefore be prudent for antibiotic production. This would result in the removal or destruction of residual antibiotics before their contact with bacteria, reducing the risk of ARG production by bacteria.

2.1.2.2. Photocatalysis of NSAIDs. With non-steroidal anti-inflammatory drugs (NSAID) being so ubiquitous, many studies have been conducted into the photocatalytic degradation of these substances. Again, the removal process is similar to that found in ozonation, where the hydroxyl radical produced at the surface of the photocatalyst oxidises bonds in NSAIDs. However, as is the case with ozonation, the intermediate and breakdown products produced by photo-catalysis may be more harmful than the parent NSAIDs. Diaz-Angulo et al. (2019) found that the photocatalysis of diclofenac produces the intermediates 2-(4-methylphenyl)indolizine, 2H-indol-2-one 1-(2,6-dichlorophenyl)-1, and (E)-4-((2,6-dichlorophenyl)imino)-3-(hydroxymethyl)cyclohexa-2, 5-dien-1-one. These compounds are known to be toxic or harmful in aquatic environments, and potentially acutely toxic if swallowed. In aquatic environments these could have a similar or even larger impact than the diclofenac parent molecule. Not much is known about these intermediates and by-products beyond their impact on aquatic environments, consequently further research is required to ascertain the exact environmental and health impacts of such compounds. Kanakaraju et al. (2015) found that some NSAIDs produce more stable intermediate products than others. For this reason, when implementing photocatalysis to remove such drugs from effluents, the amounts and toxicities of intermediates being produced should be monitored during photocatalysis.

2.1.2.3. Photocatalysis of hormones/steroids. Hormones and steroids can either be inactivated through partial degradation or can be completely degraded through oxidation by photocatalysis (Table 2). As is the case with NSAIDs, the photocatalysis of hormones and steroids such as those found in contraceptives and hormone blockers produces intermediates and by-products still potentially harmful to the environment. The photocatalysis of EE2 can result in the production of estrone, which, whilst less potent than EE2, still has similar effects as its parent compound (Sornalingam et al., 2018). A significant reduction in oestrogenicity of wastewater can thus still be achieved through the partial photocatalytic degradation of synthetic oestrogens such as EE2, where this hormone is known to be up to 1000 times more potent than oestrogens such as estrones and estradiols (Barnes and Levrant, 2007). Additionally, Narváez et al. (2019) found that more than 90% of levonorgestrel degraded during the photocatalysis. The by-products and remaining levonorgestrel have the potential of reducing β-hcG hormone levels in aquatic organisms and potentially in humans and poses a risk during pregnancy. Furthermore, whilst photocatalysis is found to be successful in the removal of both EE2 and Levonorgestrel, the efficiency of this removal is affected negatively by hydroxyl scavengers in the water (Nasuhoglu et al., 2012). Consequently, other treatment processes prior to photocatalysis, such as coagulation/flocculation, and biological processes including the activated sludge process and anaerobic digestion, may increase the performance of photocatalysis procedures directed towards the removal of hormones used in the manufacture of contraceptives, and other hormonal related medications.

Table 2 shows the removal efficiencies of some hormones, with details on conditions and the photocatalysts used. Carbon Nitride is of increasing interest towards its use in photocatalytic oxidation of organic pollutants due to its response to visual light, as well as its high surface area (Akhundi et al., 2020). Furthermore, Table 2 shows that through modification, the photocatalytic degradation of hormones such as 17α-ethynylestradiol can be improved. TiO_2 catalysts are also shown to be improved through the addition of other metals such as gold. The addition of gold to the TiO_2 photocatalyst reduces the recombination of conduction band electrons and electron holes formed by irradiation, where the gold acts as an electron sink (Sornalingam et al., 2018). This same phenomenon is also exhibited in other studies where additional materials act as electron sinks resulting in an improved removal of compounds by photocatalytic materials (Joo et al., 2016; Liang et al., 2017).

In addition to the degradation of hormones, if adequate time is allowed, degradation by-products can also be broken down using photocatalysts where the hydroxyl radical is capable of degrading most organic substances. To measure these effects, studies often use tertiary butanol as a hydroxyl radical scavenger (Vinod et al., 2020); phenolic rings are also known to scavenge hydroxyl radicals (Lipinski, 2011). This makes photocatalysis potentially more promising than ozonation for pharmaceutical wastewater treatment, where harmful oxidation by-products are also likely to be reduced by the photocatalysis process.

Based on the process effectiveness, the use of TiO_2 photocatalysis can be considered as a state-of-the-art treatment process for pharmaceutical wastewater. However, the operating conditions for complete

mineralization of the formed by-products need to be optimized in terms of treatment time and accumulative energy compared to other oxidation processes (like ozonation and photo-Fenton) (Badia-Fabregat et al., 2018). Furthermore, despite the high efficiency of UV/TiO2 in the degradation of pharmaceutical compounds in pilot-scale studies, they do not yet find application at full scale due to some technical obstacles. Passing radiation through wastewater could be hard depending on the wastewater quality while recovering the used catalyst after treatment is also a challenge. Physically separated photocatalytic and membrane units, photocatalytic membranes and fixed bed photocatalytic reactors have been studied to circumvent this issue; however, their application in wastewater effluents has not been investigated yet (Rizzo et al., 2019).

2.1.3. Fenton reaction processes

A low-cost and high-efficiency process extensively used for the degradation of pharmaceuticals is the Fenton process. Fenton's oxidation process involves reactions of hydrogen peroxide (H_2O_2) with iron ions (Fe^{+2}) (Fenton's reagent) via a free radical chain reaction to produce hydroxyl radicals (Eq. (6)). Fe^{+2} serves as a catalyst, whereas other iron sources have been also used for the degradation of pharmaceuticals (Fe_3O_4, Ce–Fe-graphene, FeS_2) (Gadipelly et al., 2014; Liu et al., 2018). The Fenton reaction takes place under acidic conditions, equation (7). The reaction presented in equation (8) shows that the catalytic behaviour of Fe^{3+}/Fe^{2+} propagates the Fenton reaction because Fe^{3+} is immediately reduced to Fe^{2+}. Only a small quantity of Fe^{3+} is needed for the regeneration of Fe^{2+}, thus helping in the continued sustenance of the process. However, at the same time, the presence of Fe^{3+} hinders the continuous generation of hydroxyl radicals, leading to a slow decomposition of H_2O_2 and generating the unpleasant (due to its lower oxidation power) superoxide radical ($HO_2^{\bullet}$), while, also, the generation of Fe^{2+} according to Eq. (9) is slower than that in Eq. (8) (Jain et al., 2018). Therefore, the introduction of modified versions of the Fenton process is reasonable and they include many homogenous (like photo-Fenton, sono-Fenton, electro-Fenton, photo-electro-Fenton) and heterogeneous (like solid-solution-based Fenton) reactions.

$$Fe^{2+} + H_2O_2 \rightarrow Fe^{3+} + \cdot OH + OH^- \quad (6)$$

$$Fe^{2+} + H_2O + H^+ \rightarrow Fe^{3+} + H_2O + \cdot OH \quad (7)$$

$$Fe^{3+} + H_2O_2 \rightarrow Fe^{2+} + HO_2^{\cdot \leq} + H^+ \quad (8)$$

$$Fe^{3+} + HO_2^{\cdot} \rightarrow Fe^{2+} + O_2 + H^+ \quad (9)$$

$$Fe^{3+} + hv + H_2O \rightarrow Fe^{2+} + \cdot OH + H^+ \quad (10)$$

$$O_2 + 2H^+ + 2e^- \rightarrow H_2O_2 \quad (11)$$

$$Fe^{3+} + e^- \rightarrow Fe^{2+} \quad (12)$$

In the last few years, the use of the classical Fenton process coupled to radiation (photo-Fenton) or electrochemistry (electro-Fenton) has been investigated for wastewater treatment, due to its high effectiveness for the elimination of pollutants present in complex aqueous matrices and recalcitrant wastewaters, such as pharmaceutical wastewater (Dolatabadi et al., 2019; Rahim Rahim Pouran et al., 2015; Sirés and Brillas, 2012). In the photo-Fenton process, irradiation with UV or UV/Vis light can assist the reduction of Fe^{3+} to Fe^{2+} a reaction which produces hydroxyl radicals and regenerates Fe^{2+} ions (Eq. (10)) that can further react with H_2O_2 (Eq. (6)) and generate hydroxyl radicals. These reactions increase the amount of Fe^{2+} and the Fenton reaction is accelerated and continues indefinitely, as long as the system remains illuminated (reacting again with H_2O_2). In the electro-Fenton process, hydrogen peroxide is generated under acidic pH via oxygen reduction (Eq. (11)) and then it reacts with Fe^{2+} ions resulting in the production of hydroxyl radicals and Fe^{3+} ions (Eq. (6)). A small amount of Fe^{2+} is initially needed for the reaction with electrochemically generated H_2O_2 and to carry out recycling of Fe^{3+} to Fe^{2+}, thus minimizing the operating cost by avoiding the continuous addition of hydrogen peroxide to the solution. Fe^{2+} ions and H_2O_2 are produced simultaneously by cathodic reduction of Fe^{3+} (Eq. (12)) and O_2 (Eq. (11)), ensuring an adequate catalytic concentration in the solution.

The efficiency of the classical Fenton and photo-Fenton processes heavily depends on several operating parameters, such as the dose of H_2O_2 and Fe^{2+}, pH, and inorganic/organic content of the wastewater matrix (Kumar et al., 2019). The optimum initial pH range for Fenton processes is approximately between 2 and 4, under which the maximum amount of hydroxyl radicals is generated, and iron precipitation is avoided (Tekin et al., 2006). To minimize this drawback, iron complexes are used, since they permit the process to work at near-neutral conditions. However, some treatment plants such as pharmaceutical wastewater treatment plants produce acidic effluents, the favourable pH for Fenton reactions without adjustment (Ouyang et al., 2019).

The main drawbacks of the Fenton processes are the formation of toxic by-products from the oxidation of the dissolved effluent organic matter (Michael et al., 2019), the pH dependency, the iron sludge production and the energy consumption. The toxic compounds formation can be mitigated when optimal operational conditions, regarding reagent dose and reaction time, are applied, while the complete oxidant conversion is necessary to enhance the organic compounds removal and not to increase toxicity (Martínez et al., 2018). Furthermore, the Fenton reagent apart from the oxidation function has also a coagulation function, by the formation of ferric hydroxy complexes, and thus is capable of both substituting the coagulation process in primary treatment with a reduced sludge formation and serving as a polishing step through removing the remaining pollutants after Fenton's oxidation (Tekin et al., 2006).

Several studies have demonstrated that Fenton processes can be successfully applied as a pre-treatment step prior to biodegradation to treat wastewater with different organic loads to enhance the biodegradability of the wastewater (Sirtori et al., 2009; Mansour et al., 2015; Ramteke and Gogate, 2016; Vidal et al., 2018; Changotra et al., 2019; Gogate et al., 2020).

Fenton reaction processes have been shown to be effective not only in oxidizing various antibiotics, NSAIDs, hormones/steroids and EDCs (Table 3) but also in deactivating the bacteria by damaging their nucleic acids and membranes through hydroxyl radicals attack (Hou et al., 2019). Based on the Fenton reaction mechanisms, it can be anticipated that the higher the ratio of H_2O_2 to pollutants, the more extensive the removal; while also a higher Fe^{2+} concentration in the solution results in higher pollutant degradation. However, the excessive increase of the added Fenton reagent could cause an adverse effect by slowing the oxidation process due to the self-inhibition effect of OH radicals by Fe^{2+}. As discussed above, in the presence of excess H_2O_2, the hydroxyl radicals are recombined forming hydroperoxyl radicals which have a lower oxidation potential. In fact, Ioannou-Ttofa et al. (2019) found that when the H_2O_2 concentration increased above a threshold, the efficiency of oxidizing some antibiotics decreased (Table 3). In addition, increasing iron concentration could increase sediment concentration in the solution, thus affecting water quality. Ahmed et al. (2020) found that an increased concentration of Fenton's reagent, during the photo-Fenton process, did not increase bacterial disinfection efficiency and this was attributed to the scattering of the radiation by the iron sediments, resulting in bacteria protection against solar photons. Furthermore, the use of inappropriate reagent concentrations could result in high operating costs and difficulties in removing the excess reagent, to achieve the effluent standards either for disposal or reuse.

Although the effect of Fenton's reagent and catalyst concentration on the degradation kinetics of various pharmaceutical compounds has been investigated by several previous studies, each study recommended different optimum doses. This is because the optimal reagent dose heavily depends on the compound's initial concentration, water matrix, reaction time, pH applied and chemical structure of the compound.

Table 3
Oxidation of some pharmaceuticals by different Fenton reaction processes.

Pharmaceutical	Compound initial concentration (mg/l)	Reaction conditions and/or Catalyst concentration	Contact time (min)	Removal amount (%)	Source
Ampicillin	0.1	Solar photo-Fenton	20	100	Michael et al. (2019)
Trimethoprim		$FeSO_4{\cdot}7H_2O$: 5 mg/l		80	
Ofloxacin		H_2O_2:100 mg/l		80	
Tetracycline		(pH:2.8–2.9)		80	
Erythromycin				40	
Sulfamethoxazole				40	
Clarithromycin				40	
Ampicillin	0.1	Solar photo-Fenton	20	100	
Tetracycline		$FeSO_4{\cdot}7H_2O$: 5 mg/l		80	
Erythromycin		H_2O_2:100 mg/l		<20	
Ofloxacin		(pH:7.5–8.0)		<20	
Sulfamethoxazole				<20	
Trimethoprim				<20	
Tetracycline	0.1	Solar photo-Fenton	20	100	
Ampicillin		$FeSO_4{\cdot}7H_2O$: 5 mg/l		95	
Trimethoprim		H_2O_2:50 mg/l		95	
Erythromycin		(pH: 2.8–2.9)		80	
Sulfamethoxazole				65	
Ofloxacin				65	
Clarithromycin				40	
Ampicillin	0.1	Solar photo-Fenton	20	100	
Tetracycline		$FeSO_4{\cdot}7H_2O$: 5 mg/l		70	
Clarithromycin		H_2O_2:50 mg/l		<20	
Erythromycin					
Sulfamethoxazole		(pH:7.5–8.0)		<20	
				<5	
Ofloxacin				<5	
Ampicillin	0.1	Solar photo-Fenton	5	85	Ioannou-Ttofa et al. (2019)
		$FeSO_4{\cdot}7H_2O$: 5 mg/l	20	100	
		H_2O_2 : 75 mg/l			
		(pH:3.0)			
	0.1	Solar photo-Fenton	5	75	
		FeSO4·7H2O: 5 mg/l	20	90	
		H2O2 : 100 mg/l	50	100	
		(pH:3.0)			
	0.1	FeSO4·7H2O: 5 mg/l	90	100	
		H2O2 (50 mg/l)			
		(pH:3.0)			
	0.1	$FeSO_4{\cdot}7H_2O$: 5 mg/l	60	100	
		H_2O_2 (75 mg/l)			
		(pH:3.0)			
Amoxicillin	138	Fe^{2+}:H_2O_2 = 2.0	1	100	Elmolla and Chaudhuri (2011)
Cloxacillin	84	(pH:3.0)			
Lincomycin	25	Photo-Fenton	60	65	Bautitz and Nogueira (2010)
		Fe^{2+}:H_2O_2 = 0.06			
		(pH: not stated)			
Metronidazole	70	Electro-Fenton reaction	30	92	Rahmatinia and Rahmatinia (2018)
		Nano–Fe_2O_3 : 1 g/l			
		(pH:3.0)			
Amoxicillin	20	Electro-Fenton reaction	60	98	Kalantary et al. (2018)
		Nano–Fe_2O_3 : 1 g/l			
		(pH:3.0)			
Sulfamethizole	25	Electro-Fenton reaction	15	100	Puga et al. (2020)
		$FeCl_3$–modified perlite			
		(pH:6.0)			
Etodolac	511	$FeSO_4{\cdot}7H_2O$	30	100	Vergili and Gencdal (2015)
		Fe^{2+}:H_2O_2 = 0.05			
		(pH:3.0)			
Diclofenac	5	Photo-Fenton	120	99	Miró et al. (2013)
		Fe^{2+}:H_2O_2 = 1			
		(pH: 3.5)			
	140	Electro-Fenton reaction	120	95	Rosales et al. (2019)
		Fe_2O_3–modified chitosan (20 g/l)			
		(pH:6.0)			
	50	electro-Fenton reaction	8	98	Yu et al. (2020)
		Pyrite (8 g/l)			
		(pH:7)			
	4100	$FeSO_4{\cdot}7H_2O$	90	97.5	Badawy et al. (2009)
		Fe^{2+}:H_2O_2 = 0.02			
		(pH:3.0)			
Ibuprofen	20	Fe^{2+}:H_2O_2 = 48 (Fe^{2+}:7.5 mg/l)	180	100	Adityosulindro et al. (2017)
		(pH:3.0)			
		Fe^{2+}:H_2O_2 = 48 (Fe^{2+}:3.7 mg/l)			

(*continued on next page*)

Table 3 (*continued*)

Pharmaceutical	Compound initial concentration (mg/l)	Reaction conditions and/or Catalyst concentration	Contact time (min)	Removal amount (%)	Source
		(pH:3.0)	180	50	
17α-Ethinylestradiol	1	Fenton-reaction	10	70	López-Velázquez et al. (2021)
		Fe2+:28 mg/l	30	90	
		Fe2+:H2O2 = 1:10			
17β-estradiol (E2)	1	Electro-Fenton reaction	25	100	Naimi and Bellakhal (2012)
	5	Na_2SO_4: 7.1 g/l	30	100	
	10	Fe^{2+}: 11 mg/l	40	100	
		(pH:3.0)			

Michael et al. (2019) showed that macrolide antibiotics, due to their high molecular weight and saturated structure, present slower degradation rates, whereas ampicillin, was completely degraded even under the least favourable pH conditions (pH:7.5–8.0) due to its ionization state at this pH and to its existence in deprotonated form. The same trend was reported in the case of NSAID diclofenac, where 100%, 95% and 80% removal were obtained at pH 3, 5 and 7, respectively, after 120 min of irradiation (Alalm et al., 2015). The relatively high efficiency even at neutral pH could be attributed to physicochemical properties of the compound, such as solubility and pKa value. Diclofenac's pKa is approximately 4.15, indicating that at pH 3, which is favourable for Fenton reaction, it is insoluble and exists in its unionised form, whereas when the pH is higher than pKa, the compound exists almost entirely in the ionized form and it is very soluble, leading to its degradation (Mirzaei et al., 2017). Other antibiotics, such as amoxicillin were also examined under natural pH and a very limited degradation was observed even after 120 min of treatment, confirming that the optimum pH for the degradation of pharmaceuticals by Fenton processes is at acidic range, achieving the best performance (Liu et al., 2018). Regarding removal of hormones from water, its use for the elimination of estrogen from aqueous solutions is extremely limited. Naimi and Bellakhal (2012) have investigated the removal of estrogens (i.e. 17β-estradiol) through the electro-Fenton process. In their study, the electro-Fenton process was performed in an aqueous-acetonitrile mixture, using a carbon felt cathode and platinum anode, and 17β-estradiol's complete removal was attained after 25, 30 and 40 min of treatment, depending on estrone's initial concentration (Table 5); however, the toxicity of the treated solution was not determined, questioning the viability of the technique.

Apart from the removal of antibiotics and other pharmaceutical residues, a key parameter for the treatment method is the capability of reducing the toxicity of the solution and of inactivating ARBs and degrading ARGs. In a recent study, Hou et al. (2019) found that among different AOPs tested for the treatment of pharmaceutical wastewater, photo-Fenton and Fenton oxidation were the most efficient approaches for simultaneous removal of both 16S rRNA and ARGs, with the photo-Fenton technique being slightly more efficient in reducing ARGs than that of Fenton oxidation alone. The high efficiency of the photo-Fenton process in inactivating ARBs and degrading both extracellular and intracellular ARGs (e-ARGs and i-ARGs, respectively) has been also reported by others (Giannakis et al., 2018; Michael et al., 2019; Ahmed et al., 2020). In particular, Ahmed et al. (2020) found that the photo-Fenton process reduced e-ARGs of both short- and long amplicons through shearing the extracellular DNA into short DNA fragments, whereas, as compared with e-ARGs, a higher dosage of Fenton reagent was required to damage i-ARGs. Furthermore, a 6.17 log ARB inactivation was achieved under neutral pH conditions after 30 min of irradiation, and no bacterial regrowth occurred after 48 h even in the absence of residual H_2O_2, demonstrating permanent disinfection of ARBs. However, their experiments were conducted at a relatively high Fenton's reagent dose (i.e., Fe^{2+}: 28 mg/l and H_2O_2: 340 mg/l), which limits the application of the technique in real conditions. Not only the reagent dose but also the reaction time play crucial roles in the ARB and ARG removal. In fact, it has been shown that the removal of ARGs and 16S rRNA gene increased significantly with the increase of Fenton dose or reaction time (Hou et al., 2019), confirming that both removal efficiency of ARGs and the cost of reagents should be considered in the process design.

Several studies have reported the formation of pharmaceutical intermediates, the majority of them demonstrated the reduction of the overall solution toxicity, indicating that the by-products induced less toxic effects compared to the parent compounds (Tufail et al., 2020). Michael et al. (2019) evaluated the toxicity of photo-Fenton treated wastewater and found that even though the treatment led to increased aqueous toxicity, the toxic effects were ascribed to the dissolved organic matter and its associated oxidation products and not to the antibiotics' transformation products. Similar results were observed by Ioannou-Ttofa et al. (2019) after the Fenton and photo-Fenton treatment of wastewater in the presence of the ampicillin antibiotic. It is consequently important, on one hand, to choose and apply the optimum dose of Fenton's reagent and, on the other hand, to either remove the remained dissolved effluent organic matter from the wastewater prior to their treatment via Fenton driven processes or to remove the Fenton-formed toxic by-products afterwards.

2.2. Physical treatment technologies

2.2.1. Activated carbon adsorption

Adsorption is a phase changing technology in which compounds are transferred from one phase (aqueous phase) to another (solid phase - adsorbent). Activated carbon (AC) is a suitable material, and the most extensively used adsorbent, due to its high adsorption capacity, attributed to its high porosity, large surface area (over 1000 m^2/g) and high degree of surface interactions (Dhangar and Kumar, 2020). AC is classified as powder activated carbon (PAC) and granular activated carbon (GAC) based on particle size and pore diameter, macroporous (≥50 nm), mesoporous (2–50 nm), and microporous (2−more than 0.8 nm). Other materials, such as carbon nanotubes and biochars, have also been extensively used (Lu et al., 2020). The adsorption characteristics of these materials depend on the source of the raw material used during their manufacturing and the activation process (Rodriguez-Narvaez et al., 2017).

PAC is an amorphous carbon material which is usually applied as a slurry feed. GAC is commonly applied in packed bed filters, and it can also be used as a replacement for anthracite media in conventional filters, providing both adsorption and filtration. GAC's stationary application ensures that saturation of the material can be achieved, whereas for PAC applications this can be reached only through its internal recirculation due to the long contact times needed to reach adsorption equilibrium (Kårelid et al., 2017). Another shortcoming of PAC's feed is its separation from the treated effluent, and therefore it usually needs to be followed by a filtration unit.

The adsorption process has several advantages, including the high efficiency of removal of some pharmaceutical compounds (Table 4) from water and wastewater (Kårelid et al., 2017; Mansour et al., 2018; Rizzo et al., 2019; Rout et al., 2021), the reduced sensitivity to toxic pollutants and the lack of toxic transformation products. Nonetheless, AC is not cost-effective due to high production and regeneration costs, whilst the

Table 4
Adsorption of some pharmaceuticals by activated carbon.

Pharmaceutical	Pharmaceutical initial concentration (mg/L)	Method	Rejection rate (%)	Source
Sulfamethoxazole	50–500	PAC (commercial)	90	Chu and Wang (2017)
Ciprofloxacin	1.0	PAC (biochar)	94	Kim et al. (2020)
Amoxicillin	100–500	GAC	96.5	Awwad et al. (2015)
Diclofenac	10–30	APC from cocoa pod husks	76–94	De Luna et al. (2017)
Carbamazepine	2.0	PAC (commercial)	93	Baghdadi et al. (2016)
Naproxen	1.0–30.0	PAC (plus magnetite)	67–90	İlbay et al. (2015)
17aethinylestradiol	0.025–0.1	GA Charcoal	68–78	Kumar and Mohan (2011)
17b-estradiol	2	GAC	20–97	Ifelebuegu et al. (2015)
Atenolol	5–900	GAC (commercial)	88	Haro et al. (2017)

frequency of its regeneration, replacement and disposal are environmental considerations among its drawbacks. Furthermore, it has been reported that for industrial purposes, adsorption often suffers from reduced effectiveness and increased adsorbent material consumption resulting from the presence of background organic matter (Margot et al., 2013). The presence of a high amount of organic matter in wastewater (>20 mg/l of dissolved organic matter) interferes in compound removal efficiency by competing for adsorption active sites on the adsorbent.

The removal efficiencies of the pharmaceutical compounds vary widely and depend on both their physicochemical properties (molecular size, polarity, functional group, octanol/water partition coefficient, adsorption-desorption distribution coefficient, pKa) and environmental and operating conditions. The adsorption of ionizable compounds is strongly pH-dependent and since many of the pharmaceuticals are readily protonated or deprotonated in neutral water, depending on their pKa, AC adsorption does not seem efficient for their removal (Badia-Fabregat et al., 2018). As electrostatic interactions between the functional groups of the pollutants and the AC cannot be predicted from the physicochemical characteristics, the removal efficiency for specific compounds needs to be evaluated. For instance, the highly polar negatively charged antibiotic sulfamethoxazole is only partially adsorbed on the positively charged PAC and GAC surface (Altmann et al., 2015; Bourgin et al., 2018), whereas the negatively charged NSAID diclofenac exhibited high adsorption (Knopp et al., 2016; Streicher et al., 2016; Serrano et al., 2011). In contrast, the positively charged clarithromycin was satisfactorily removed (>95%) from the wastewater through adsorption onto PAC and GAC (Kårelid et al., 2017; Bourgin et al., 2018). The neutral hormones EE2 and E2 were effectively adsorbed onto PAC and GAC (Sun et al., 2017; Grover et al., 2011).

Pollutant removal is also correlated by the applied AC dose and contact time, whereby generally higher initial concentrations require greater carbon dosages (Mansour et al., 2018). However, this is not consistent for all pharmaceuticals. Strongly absorbing compounds, like diclofenac, can be eliminated by more than 90% at low PAC doses (5–10 mg/l)(Mailler et al., 2015), while weakly absorbing pharmaceuticals, like sulfamethoxazole, require essentially higher PAC doses up to 10–50 or even 100 mg/l (Altmann et al., 2014). Rizzo et al. (2019) reported that the mean PAC dose needed to be applied is about 1.5 g PAC/g DOC when PAC is recycled to the activated sludge treatment, whereas when PAC is applied directly to the activated sludge treatment, the mean dose increases to 2–3 g PAC/g DOC.

In addition, studies examining competitive adsorption have noted that not only the presence of other pharmaceuticals, contained as a mixture in wastewater, but also other organic and inorganic material might adversely affect the effectiveness of the process (Mansour et al., 2018). Consequently, with respect to pharmaceutical compounds removal, adsorption onto AC could be a suitable and cost-effective alternative for pharmaceutical effluents, depending on the specific compound or mixture to be removed and the operating conditions, when these are pre-treated, and the majority of the organic matter load and suspended solids have been significantly eliminated.

2.2.2. *Membrane processes: Reverse osmosis and nanofiltration*

Reverse osmosis makes use of pressure to overcome the natural osmotic pressure that exists between one side of a reverse osmosis membrane and the other. The most well-known application of reverse osmosis is its use in producing drinking water from seawater or brackish water, however it can also be used to produce ultrapure water from water sources of a lower quality. Typically, the source water has already undergone several other treatment processes to improve the efficiency and lifetime of a reverse osmosis membrane. These processes, such as rapid or slow sand filtration, microfiltration, ultrafiltration, and powdered or granular activated carbon adsorption, remove substances that lead to membrane fouling and damage. Such substances include bacteria and extra-cellular polymeric substances (Weinrich et al., 2016; Nagaraj et al., 2018), minerals and colloids, and non-biological organic compounds (Fortunato et al., 2020). However, as suggested in the previous section on photocatalysis, the wastewater produced by a pharmaceutical production plant, depending on the products manufactured, will probably contain much lower levels of biological matter than is the case for other wastewater such as domestic wastewater. This makes the use of reverse osmosis for the treatment of pharmaceutical wastewater more favourable than is the case for other wastewaters, since the risk of membrane fouling due to biological activity is much lower because of the reduced presence of microbes, and the corresponding extra-cellular polymeric substances that these organisms produce (Jeong et al., 2016; Tran et al., 2007). As mentioned already, fouling is not just biological, colloidal as well as other non-biological substances cause fouling, therefore it is still wise to employ some prior treatments such as coagulation-flocculation, microfiltration and ultrafiltration and biological treatment before a RO process to ensure that it runs efficiently.

2.2.2.1. Reverse osmosis of water contaminated with antibiotics. Reverse osmosis can reduce amounts of antibiotics as the membrane is an absolute barrier and does not allow large molecules including antibiotic molecules to pass (Table 5). This results in permeate water practically devoid of antibiotics and a retentate water that contains concentrated residual antibiotics unless an additional treatment technique is applied to reduce antibiotic concentrations in the retentate as well (Khanzada et al., 2020).

Unlike other treatment methods such as ozonation and photocatalysis, the pollutants are not destroyed in reverse osmosis, they are retained on the retentate side of the membrane. Reverse osmosis permeate will contain lesser concentrations of antibiotics than the influent, however the retentate water will contain higher concentrations of antibiotics than the influent. This water containing higher concentrations of antibiotics also requires treatment, so simply applying reverse osmosis techniques to pharmaceutical wastewater does not eliminate antibiotics. Consequently, research has begun to focus on the combination of photocatalysis, ozonation and biological treatment with reverse osmosis (Benner et al., 2008; Racar et al., 2020).

As well as antibiotics, any ARGs may also be prevented from passing into the permeate water. Indeed, Slipko et al. (2019) found that ARGs were reduced by filtration techniques including reverse osmosis, nanofiltration and ultrafiltration. Specifically, their results demonstrated that

Table 5
Pharmaceutical removal in several studies using reverse osmosis and nanofiltration.

Antibiotic	Antibiotic initial concentration (mg/L)	Trans-membrane pressure (bar)	pH	Filtration Method	Rejection rate (%)	Source
Ciprofloxacin	0.05	–	–	Reverse osmosis	98.7	Alonso et al. (2018)
	0.1				97.9	
	0.2				99.6	
Amoxicillin	0.164	–	–	Reverse osmosis	~100	(Egea-Corbacho Egea-Corbacho Lopera et al., 2019)
Penicillin	0.213	–	–		~100	
Azithromycin	0.000792	–	–	Reverse osmosis	99.57–100	Rodriguez-Mozaz et al. (2015)
Erythromycin	0.000413	–	–		99.03–99.39	
Ofloxacin	0.000412	–	–		100	
Sulfamethoxazole	0.000615	–	–		99.19–100	
Trimethoprim	0.000135	–	–		99.12–100	
Ibuprofen	30	15.5	8	Reverse osmosis	97.9	Huang et al. (2011)
Paracetamol	130	15.5	8		94.3	
Ibuprofen	100	–	–	Nanofiltration	80.54	Maryam et al. (2020)
	100	–	–		9.7	
	10	5	5		97	Licona et al. (2018)
	10	10	5		97.5	
	10	15	5		98	
	10	20	5		98.5	
	10	5	4		94.5	
	10	5	7		92	
Diclofenac	100	–	–	Nanofiltration	43.31	Maryam et al. (2020)
		–	–	Nanofiltration	9.1	
Paracetamol	100	–	–	Nanofiltration	26.00	
	100	–	–	Nanofiltration	8.1	

the retention of free DNA molecules is mainly based on a size exclusion mechanism, while, also, surface charging of the membrane and adsorption holds a pivotal role in the prevention of free DNA permeation. When negatively charged membranes are employed for preventing adsorption of organic matter, adsorption of free DNA was reduced, due to the repulsion between free DNA and the membrane surface, thus, the membrane may not be an efficient barrier for ARGs encoded in free DNA, as predictions would be based only on the molecular weight cut off. This makes reverse osmosis as well as other membrane techniques attractive water treatment processes for plants that manufacture antibiotic medication. Despite the high logarithm (log) removal rate of ARGs in treated wastewater by both reverse osmosis and nanofiltration downstream steps, literature shows that ARGs can still be detected in the final treated water. For example, Lan et al. (2019) found that the abundance of ARGs in constructed wetlands after the reverse osmosis steps was significant. Nevertheless, the same study also noted a marked reduction in ARGs between the influent raw water and the treated effluent from the final constructed wetlands treatment. Thus, the authors (Lan et al., 2019) showed that ARG reduction can be achieved in pharmaceutical manufacturing wastewater using reverse osmosis and nanofiltration.

2.2.2.2. Reverse osmosis and nanofiltration of NSAIDs. NSAIDs have been successfully removed by reverse osmosis, however, as is the case with reverse osmosis for antibiotics, the process results in elevated NSAID concentrations in the retentate (Nguyen et al., 2020). Again, many studies have been conducted in recent years to evaluate the combination of different water treatment techniques with reverse osmosis to treat the retentate. Additionally, different membrane materials have also been investigated, with nanofiltration becoming increasingly of interest in recent years.

Table 5 shows several facts relating to pharmaceutical removal using reverse osmosis and nanofiltration. The importance of molecular weight cut off (MWCO) is shown by Maryam et al. (2020) where the nanofiltration membrane with the lower MWCO exhibits greater rejection rates. Furthermore, results reported by Licona et al. (2018) show that conditions such as transmembrane pressure and solution pH are significant factors in the removal of ibuprofen from water where the rejection rate of ibuprofen by nanofiltration was found to increase with transmembrane pressure between 5 and 20 bar. In addition, the pH was found to impact the rejection of ibuprofen across both nanofiltration and reverse osmosis membranes, with the optimal pH close to 5.

As is shown in Table 5, NSAID pollution can be successfully rejected by nanofiltration with <1000 Da MWCO, or reverse osmosis.

Radjenovic et al. (2011) applied an advanced oxidation process known as electrochemical oxidation to further treat retentate containing NSAIDs including diclofenac, naproxen and ibuprofen, achieving removal rates between 20 and 100%. The removal of pharmaceuticals from reverse osmosis concentrate using granular activated carbon has also been applied and found to reduce the concentration of ibuprofen to 90.9%, diclofenac to 85.9% (Jamil et al., 2019).

2.3. Nature-based solutions

2.3.1. Constructed wetlands

Constructed wetlands (CWs) are a low-cost and eco-technological wastewater treatment solution. Basically, a CW is a small semi-aquatic ecosystem that mimics natural wetlands system, in which organisms and natural vegetation proliferate allowing a variety of physicochemical reactions occur to treat wastewater. CWs are mainly classified into three types depending on the regime of the feed flow and flow through the CW: the free surface flow, the horizontal subsurface flow, and the vertical subsurface flow (Sharma et al., 2016). The dominating removal mechanisms in CWs are biodegradation, sorption on organic matter and phytoremediation, hydrolysis, and photodecomposition.

In a comprehensive and critical analysis of the overall removal of pharmaceuticals in CWs, which included 260 CWs with 148 drugs sorted according to their therapeutic classes into 33 groups and 25 transformation products, Ilyas et al. (2020) found that the average removal efficiency ranges between 7% and 100% (for 131 out of 148 compounds), with the most widely studied pharmaceuticals (34 compounds) ranging from 21% to 93%, while some cases of negative removal also occurred (17 out of 148). The median removal range was approximately 30%–70%. They also reported that biodegradation, in conjunction with the other mechanisms, is responsible for the removal of most pharmaceuticals, with the easily biodegradable ones exhibiting the highest removal efficiencies, and the ones where removal is governed by mechanisms such as adsorption, photodegradation, or plant uptake presenting moderate to low removals. Comparable results were observed by He et al. (2018) in a field study of three full-scale operating

CWs (i.e., two free water surface flow CWs (SF-CWs) and one vertical subsurface flow CW (VSF-CW) serving as tertiary treatment of wastewater treatment plants. Among the detected 14 pharmaceuticals; erythromycin, sulfamethoxazole, propranolol, and metoprolol were largely removed (>75%) in the compartments of the CWs, whereas diclofenac, naproxen, and lincomycin were moderately removed (30%–60%). The fate of the pharmaceuticals depends on the physicochemical properties of the compounds which play a crucial role in their removal efficiency. A compound that exists in the dissociated form or has a high hydrophobicity, expressed by log Kow and log Koc, tends to be sorbed onto sediments and plants (Zhang et al., 2018). Ilyas et al. (2020) demonstrated that log Kow, log Koc and molecular weight could be set as predictors of pharmaceutical removal efficiency and, accordingly, could be used for predicting their potential removal by CWs.

In another comprehensive study by Ilyas and van Hullebusch (2020), where the efficiency of four types of CWs to remove 29 pharmaceuticals and 19 transformation products were reviewed, biodegradation was identified as the major removal mechanism for 16 out of 29 compounds, besides the influence of other processes (e.g., adsorption/sorption, plant uptake, and photodegradation). Among the four CW types studied, hybrid CW worked slightly better followed by vertical flow, horizontal flow, and free water surface CW. It was shown that hybrid CWs exhibited better performance due to the coexistence of aerobic and anaerobic conditions and longer hydraulic retention time, while in free water surface CW the main removal pathway was photodegradation and only photo-unstable pharmaceuticals were removed. Moreover, the authors highlighted the importance of by-product nature, because, in some cases, when they were persistent or non-biodegradable, they can be retransformed into their parent compound, leading to poor or negative removal. Overall, the median removal efficiencies for the majority of the parent compounds did not exceed 60%, denoting the moderate efficacy of CWs in removing pharmaceuticals, while the removal of pharmaceuticals is also governed by many design and operational factors, including the large space, high hydraulic time, low flow and the less wastewater load (Ilyas and van Hullebusch, 2019).

Auvinen et al. (2017) assessed the performance of a pilot-scale aerated subsurface-flow CW treating hospital wastewater, in terms of common macropollutants and 10 pharmaceuticals, during both continuous and intermittent aeration. Their results confirmed the low and moderate removal of the target compounds under both aeration conditions. The beta-blockers: atenolol and bisoprolol were moderately removed (>75% and >50%, respectively), thus high remaining concentration was observed in the effluent (up to 0.5 μg/l). Carbamazepine, diclofenac, sotalol and gabapentin showed only a limited removal (<50%), while sulfamethoxazole's and tramadol's removals were mostly negative.

Besides the moderate efficacy of constructed wetlands (CW) in the removal of most of the pharmaceutical substances, a mixed performance against ARG removal has been also reported. Previous studies found that CWs are able to reduce the concentration of ARGs, whereas, in some others, a significant increase was observed after CW treatment, either in absolute concentrations or relative concentrations. The mixed results are mainly attributed to the flow pattern and redox conditions prevailing in CWs. For instance, it has been reported that a surface flow CW could be more efficient than a subsurface flow CW. The relatively high removal efficiency could be due to sunlight penetration and a higher oxidation state created in the surface water, that result in enhanced aerobic biodegradation and photodegradation under these conditions (Sharma et al., 2016). In contrast, when a vertical flow or subsurface flow regime is applied, ARGs are not significantly reduced. Ávila et al. (2021) investigated the occurrence and removal of 11 ARGs in two vertical subsurface flow CWs (an unsaturated (UVF) and a partially saturated (SVF) unit) operating in parallel and treating urban wastewater. High removal rate (greater than 90%) was observed for some of the tested antibiotics like sulfamethoxazole, ofloxacin, metronidazole and trimethoprim in SVF. The removal efficiency of ARGs showed a high variability (from 21% to 93%) between sampling days, while the mean removal of ARGs showed no statistical differences between the two wetlands. Furthermore, in both CWs, even though the absolute concentrations of ARGs in the effluent were lower than those measured in influent wastewater, the differences were not statistically significant. However, when concentrations were normalized by the bacterial abundance in both CWs' gravel media, some differences between the two CWs were shown, which suggest that conditions in the unsaturated wetland might not favor the colonization of gravel particles by bacteria carrying ARGs. In the same study, samples were taken from the top and bottom layer of both CWs and the distribution of the studied ARGs was similar, suggesting a homogeneous distribution of ARGs across the filter bed. Overall, the removal of ARGs from wastewater in both absolute and relative terms showed that the CWs studied were not able to significantly reduce either the bacterial load of the influent wastewater or the prevalence of most ARGs within the bacterial community.

Mixed results were also reported from He et al. (2018) in a study where the performances of one vertical subsurface flow CW (VSF-CW) and two free water surface flow CWs (SF-CWs) were evaluated. The influent wastewater of the two SF-CWs consisted of mixed domestic and industrial/hospital wastewater after being pre-treated by an activated sludge with sand filter and an oxidation ditch, respectively. The total bacteria increased in all the investigated CWs, while, relative to the total bacteria, most -but not all- ARGs remained stable or showed a decrease after CW treatment. The increased concentrations of ARGs in the SF-CWs, as well as the increase of total bacteria in all CWs, may relate to regrowth of resistance-carrying bacteria. Meanwhile, the vertical subsurface flow CW tested revealed ARG removal ranging from 57% (*Intl1*) to almost 100% (*ermB*).

Positive removals of ARGs have been also demonstrated by other researchers (Song et al., 2018; Chen et al., 2019); however, many studies have shown that CWs may enhance the spread of antibiotic resistance genes, due to the long-time exposure of antibiotics that resulted in harboring abundant ARGs even with increasing abundances over time (Song et al., 2018; Chen et al., 2019; Z. Y. Lu et al., 2020). Thus, the results highlight the dynamic variation of ARGs in CW media and note that the ARG removal performance by CWs may be dramatically changed by many factors, including their flow structure, age, type, hydraulic retention time (HRT), seasonality, influent dynamics and water quality (Li et al., 2021).

2.4. Hybrid technologies

Hybrid technologies are a combination of two or more conventional/advanced treatment technologies for achieving the maximum, or even complete, removal of micropollutants or recalcitrant compounds. The need for hybrid technologies arises from the fact that none of the single-treatment technologies, neither biological nor AOPs, appears to be efficient in ensuring high removals for all parent compounds and transformation products. Therefore, the degradation and mineralization of some persistent pollutants can be enhanced with the combination of two or more processes due to synergistic effects and using the advantages of the individual treatment methods. In the last few years, several advanced and hybrid treatment schemes have been investigated (Grandclément et al., 2017; Mohapatra and Kirpalani, 2019; Dhangar and Kumar, 2020). For instance, in a study Hou et al. (2019) employed a lab-scale simulation reactor for simultaneous removal of 18 antibiotics and 10 ARGs from real pharmaceutical wastewater through combining up-flow anaerobic sludge bed (UASB), anoxic-oxic tank (A/O), and four separate AOPs including UV, Ozonation, Fenton, and Fenton/UV. Their results showed complete elimination of antibiotics through the reactor, with UASB providing the greatest contribution (85.8 ± 16.1%) followed by A/O unit (6.2 ± 6.6%), while in contrast, the abundance of all ARGs increased through UASB and A/O units, indicating that biological processes might enhance resistance proliferation. ARGs were mainly removed by AOPs, of which the Fenton/UV combination was the most

effective for the removal of both 16S rRNA and ARGs, whereas UV and ozonation held only limited elimination potential.

2.4.1. Combined advanced oxidation processes

Conventional wastewater treatment plants are designed to remove readily biodegradable and settleable compounds (Anandan et al., 2020). In biological processes, the presence of toxic pollutants can limit or inhibit the metabolic activities of microorganisms, hence restricting the performance of biological treatments (Kanafin et al., 2021). On the other hand, although AOPs have been successfully applied for the removal of refractory pollutants, through their oxidation by hydroxyl radicals, the main drawbacks hindering their wide application, as explained previously, are the frequent production of more stable and toxic by-products and the elevated operational costs. The limitations of the individual processes can be overcome by combining physical and/or chemical methods with biological treatment, where AOPs can be used either as pre-treatment or post-treatment to biological techniques (Nidheesh et al., 2020).

2.4.1.1. Post-treatment with AOPs. As a post-treatment, AOPs are usually applied as a polishing step to remove the remaining pharmaceuticals (Hou et al., 2019) and, in some cases, to reduce the toxicity in the effluent. Sirtori et al. (2009) evaluated the use of oxidation (photo--Fenton process) followed by a biological treatment, namely; Immobilized Biomass Reactor with the addition of H_2O_2 on samples of real wastewater containing nalidix acid (a quilonone antibiotics). The drug had completely disappeared suggesting that this combination can be effective if used at a specific conditions (Sirtori et al., 2009). The treatment of hospital discharged water with combined biological (membrane bioreactor) and AOPs found that pharmaceuticals were eliminated by ozonation or PAC as a post treatment (Kovalova et al., 2013).

However, many studies pointed out the opposite results, noting that more toxic by-products are formed after the oxidation processes, thus requiring either process optimization or a further treatment step that will act as a barrier (Tang et al., 2019; Hong et al., 2020; Poelmans et al., 2020). For instance, the addition of an activated carbon step can enhance the elimination of poorly or non-biodegradable compounds by adsorption. Patel et al. (2020) employed a combined approach of ozone-based advanced oxidation ($O_3 + H_2O_2$) followed by adsorption through a bed of GAC for the treatment of a real pharmaceutical industrial effluent obtained from a pharmaceutical manufacturing unit in India. They demonstrated that the hybrid process applied is suitable for the treatment of wastewater that contains complex organic compounds, chemical oxygen demand (COD) removal and water quality parameters were significantly reduced (>73% removal) during ozonation and subsequently the degradation compounds produced were removed by adsorption. Although this study lacked toxicity measurements, the application of adsorption on GAC as post-treatment of AOPs (solar photo-Fenton) has been successfully demonstrated to provide almost complete removal of the resulting increased toxicity and elimination of remaining antibiotics, ensuring wastewater decontamination (Michael et al., 2019).

2.4.1.2. Pre-treatment with AOPs. With regard to the application of AOPs as a pre-treatment step, the main aim is the complete contaminant mineralization or the improvement of wastewater biodegradability through the conversion of pollutants into more degradable products (Jurczyk and Koc-Jurczyk, 2017; de Wilt et al., 2020; Nidheesh et al., 2020). Considering the recalcitrant nature of some pharmaceuticals, a reasonable alternative would be the improvement of their biodegradability through their oxidation, but this might also result in toxic by-products. The sequence of the processes includes initially the breakdown of the organic contaminants' strong bonds *via* AOPs, and then this organic load is reduced *via* biological processes. The combination of these processes has higher synergistic effects resulting in biodegradability enhancement and toxicity reduction (Su et al., 2019), and once optimized, it can also reduce the cost and energy consumption.

Nevertheless, it should be highlighted that the efficiency of the AOP pre-treatment method may vary according to the chosen AOP process, the wastewater characteristics, and the target compounds. The high toxicity of the non-biodegradable pollutants in the influent has been outlined by Ma et al. (2016). Specifically, in their study, Ma et al. (2016) evaluated the conventional pollution parameters and toxicity of wastewater collected at different treatment stages from a pharmaceutical industrial park wastewater treatment plant and they observed that the toxicity in the influent affected the efficiency of the biological treatment processes - inhibiting the metabolic activity of microbes and even poisoning the microbes to death - indicating the significant impact of the influent acute toxicity in the pharmaceutical industry treatment plants. Moreover, they found that the toxicity of the effluent samples after biological treatment was greater than the influent toxicity, a phenomenon that might be caused by the generation of more persistent and toxic degradation products.

The potential of UV photolysis as a pretreatment method for antibiotic decomposition and elimination of their antibacterial activity was investigated by Ding et al. (2020). The UV photolysis pretreatment eliminated the antibacterial activities of five antibiotics contained in wastewater through the photodecomposition mechanism consisting of photoinduced dehalogenation, hydroxylation, hydrolysis, decarboxylation and oxidation of their main functional groups. This demonstrated that UV photolysis could be adopted as a pretreatment step for the source control of antibiotic antibacterial activity before the biological treatment unit.

Besides UV photolysis, the Fenton oxidation process has also been proven to be effective in removing pharmaceuticals at a two-step chemical/biological treatment. In a recent study, Changotra et al. (2019) investigated the performance of the sequential Fenton applications including dark-Fenton, solar-driven photo-Fenton and electro-Fenton and biological treatment (i.e., aerobic activated sludge) of real pharmaceutical industrial wastewater with high and low strength organic loads. Among the different Fenton processes, photo-Fenton treatment significantly enhanced the biodegradability and reduced the organic load, whilst, coupled with biological treatment, it led to effective degradation, mineralization, and detoxification of wastewaters. Similar results were established when electro-Fenton and photo-electro-Fenton processes are combined with biological treatments. In particular, the antibiotics nafcillin and sulfamethazine were almost completely eliminated by photo-electron-Fenton/anaerobic digestion processes and electro-Fenton/activated sludge processes, respectively (Mansour et al., 2015; Vidal et al., 2018). Likewise, Talwar et al. (2018) confirmed the increased biodegradability and non-toxicity of real pharmaceutical wastewater after its treatment by TiO_2-photocatalysis and rotating biological contractor, achieving 96.5% overall degradation, of which 67% corresponded to TiO_2-photocatalysis and 30% to biological treatment. These results show that combined AOP applications as pre-treatment technology and biological treatment are a more effective approach in comparison to single-step treatment either by Fenton or biological process to treat industrial pharmaceutical effluents. However, it should be noted that, since the optimum AOP application requires acidic pH conditions of around 3, the pH should be readjusted to neutral values prior to the contact of the effluents with the microorganisms present in the biological treatment plant.

2.4.2. Biological treatment combined with membrane processes

Biological treatments such as activated sludge (AS) and anaerobic digestion, are known for being cost effective and environment friendly. Membrane bioreactors (MBRs) are non-conventional treatment processes that have been used for the removal of pharmaceuticals (Rezaei et al., 2020; Zhang et al., 2021). In brief, the MBR system is the combination of a membrane process with a biological treatment process,

where the pollutants are removed through physical retention and microbial biodegradation on the membrane surface, while the membrane restricts the movement of higher molecular weight compounds. Although MBR resulted in sufficient removal of many EDCs, it showed mixed performance for pharmaceuticals and this is mostly attributed to the compounds' physicochemical properties (solute molecular weight, size, geometry, charge, and hydrophobicity) and membrane properties and operating conditions (membrane pore size, porosity, charge, and pressure) (Kim et al., 2018). MBR treatment is mainly effective for the removal of hydrophobic and readily biodegradable trace organics, whereas it exhibits limited removal of hydrophilic and persistent compounds (Nguyen et al., 2012). In contrast, the retention of relatively hydrophilic compounds by NF and RO membranes is generally high due to electrostatic interactions (i.e., repulsion) arising from the negative surface charge of the membranes, and steric hindrance (retention of molecules larger than that of the pore size) (Kim et al., 2018; Dhangar and Kumar, 2020). Therefore, the combination of these two technologies could achieve enhanced pollutant removal. Wastewater will initially be treated by MBR to eliminate the hydrophobic and easily biodegradable substances and then the effluent will be treated by a membrane system to retain and remove the remaining hydrophilic and poorly biodegradable compounds. For instance, it has been reported that the integration of MBR followed by membrane filtration techniques (RO/NF) can almost completely remove a broad range of pharmaceutical compounds (or reduce concentrations below the limits of detection), achieving removals greater than 95% for EDCs, hormones, beta-blockers, NSAIDs, antibiotics, ARBs and ARGs (Nguyen et al., 2013; Wang et al., 2018; Jian Lu et al., 2020; Rizzo et al., 2020).

Wang et al. (2015) investigated the performance of an MBR–NF process for the treatment of antibiotic production wastewater with the recycling of the NF concentrate to the MBR. The MBR–NF process was shown to be effective for the removal (>95%) of the two antibiotics, spiramycin and new spiramycin, contained in the wastewater, while also the acute toxicity was drastically reduced, excellent water quality and a high-water yield of 92% was achieved. In summary, when choosing and designing these hybrid systems, parameters such as wastewater and pollutant characteristics, membrane specifications (molecular weight cut-off and charge), fouling and energy demand should be considered (Slipko et al., 2019; Racar et al., 2020).

Another hybrid system, which includes the MBR and the adsorption processes (PAC addition), is used to treat pharmaceutical wastewater. The hybrid PAC-MBR scheme would achieve an effective removal of pharmaceuticals *via* adsorption and biodegradation in a single step, while, following PAC addition, toxic effects of inhibitors may reduce by adsorbing non-biodegradable, toxic and inhibitory organic matter (Asif et al., 2020). Studies showed that with highly biodegradable pharmaceuticals, the addition of PAC does not seem to further increase the removal, however, for relatively non-biodegradable pharmaceuticals, the addition of PAC has been shown to be useful in order to achieve good removal efficiencies (Alvarino et al., 2017; Asif et al., 2020; Kaya et al., 2016). The removal efficiency is influenced by the properties of the compounds, such as the distribution coefficient value of the pharmaceutical (which is the pH-corrected log Kow), while the saturation of PAC depends on the ionic charge of the pharmaceutical (Alvarino et al., 2017). Moreover, regarding the membrane fouling, a restricting factor in operating MBR systems, Kaya et al. (2016) in a study carried out using high organic load rate wastewater obtained from a pharmaceutical company showed that the hybrid PAC-MBR system led to a reduced amount of membrane fouling; probably because some of the high-molecular-weight compounds are adsorbed onto the PAC pores instead of the membrane surface.

Regarding the combination of MBR treatment with AOPs, in a recent study, Khan et al.(M.F. Khan et al., 2020) evaluated the efficacy of combined AOPs (O_3 and O_3/H_2O_2) with MBR and CW in decontaminating hospital effluents before their discharge into the sewage treatment plant. MBR and CW exhibited 100% elimination of ibuprofen, carbamazepine, frusemide and ofloxacin, with the MBR-O_3 process proving to be the optimal approach, among those tested for hospital effluent pre-treatment. Similar positive results were demonstrated also by Mascolo et al. (2010) where the enhanced removal of the antiviral drug acyclovir from real pharmaceutical wastewater was obtained by employing a hybrid MBR-O_3 system. The tested hybrid system was placed in the recirculation stream of the MBR effluent, obtaining 99% acyclovir removal after the MBR step while the ozonation process allowed further removal of 99% of the residual concentration in the MBR effluent. The MBR-O_3 system also effectively removed the ozonation by-product detected in the effluent as it was recirculated and removed in the MBR. Kaya et al. (2017) investigated the treatability of the NSAID etodolac chemical synthesis wastewater from the pharmaceutical industry by applying a hybrid ozonation-Anaerobic MBR (AnMBR) system. The need to employ ozonation as pre-treatment arose, because, although the AnMBR was successfully operated up to 7500 mg/l of COD with 85–90% removal, the presence of high sulfite concentration in the raw wastewater (i.e., 3000–5250 mg/l) caused inhibitory effects on the microbial population including methanogens, acedogens and sulphate reducing bacteria. This problem of high sulfite concentration was resolved by pre-ozonation process that allowed the oxidation of sulfite to sulphates. In addition, pre-ozonation was also effective in obtaining a high etodolac removal efficiency of up to 99% followed by the formation of three metabolites which were removed after AnMBR treatment. The combination of electro-oxidation (EO) and the MBR for the treatment of simulated hospital wastewaters, injected with four pharmaceuticals, was studied by Ouarda et al. (2018). In this study, the EO process was applied either as pre-treatment or post-treatment to MBR. Even though MBR treatment alone shows high removal for ibuprofen and estradiol (90%), for carbamazepine and venlafaxine a low elimination was observed (<20%). Therefore, the use of EO as a pre-treatment stage aimed at increasing the biodegradability of wastewaters, whereas the use of EO as a post-treatment/polishing step aimed at eliminating non-biodegradable persistent compounds. In detail, the EO-MBR system improved the removal of venlafaxine, however its overall reduction did not exceed 50%. In contrast, when the MBR-EO system was applied, high removal was achieved for all four pharmaceuticals (>95%). Considering both the high efficacy of pharmaceutical removal and the reduced toxicity (except at 100% v/v) to *Daphnia manga*, the MBR-EO system was chosen as the most suitable to produce high-quality effluents. The effective combination of MBR and AOPs as a polishing step has also been proved in the case of MBR combination with the UV oxidation process. Nguyen et al. (2013) confirmed the enhanced overall removal efficiency of pharmaceuticals when MBR permeate is treated by UV-photolysis, observing high removals (85%–100%) for several pharmaceuticals including easily- and non-biodegradable compounds. For instance, the refractory pharmaceutical carbamazepine showed almost 35% removal after MBR and direct UV oxidation treatment alone, while when these two processes were combined, the overall removal was elevated to more than 96%. MBR treatment and AOPs can remove pollutants through different degradation mechanisms and a hybrid system involving both these technologies can take advantage of their complementary nature. It is essential that MBR effluent has low background organic matter and suspended solids concentration, thus making it suitable for post-treatment *via* AOPs, because the presence of the organic matter may absorb and scatter UV light, in the case of photolysis, and compete for hydroxyl radicals in general.

2.4.3. Combined constructed wetlands

In order to achieve higher efficiencies for a wide range of pharmaceuticals during CW treatment, the processes that take place in the wetlands have been combined with other treatment technologies. The most used configuration is that where CWs are applied as a post-treatment stage. For instance, the combination of an upflow anaerobic sludge blanket (UASB) reactor with CWs was assessed for treating urban

wastewater, in terms of pharmaceutical removal. Sakurai et al. (2021) evaluated the effectiveness of a treatment comprising a UASB coupled with a horizontal subsurface flow (HSSF) CW, followed by a vertical subsurface flow (VSSF) CW, in removing organic matter, nutrients, microorganisms, and 12 antibiotics. They found that none of the 12 antibiotics was detected in the effluents of the final CW system and also efficient reduction of the indicative parameters, namely, chemical oxygen demand (COD), biochemical oxygen demand (BOD), total nitrogen, total phosphorus and microorganisms count (74%, 93%, 50%, 61% and 97% (E. *coli*) respectively) was achieved. The removal of all tested macropollutants and microorganisms from HSSF-CW was significantly higher than the removal observed by VSSF-CW and this is possibly attributed to both the flow regime at the two CWs and the higher hydraulic retention time (HRT) applied to HSSF-CW compared to VSSF-CW (Auvinen et al., 2017; Petrie et al., 2018). Contrary results were reported by Reyes-Contreras et al. (2011) where the seasonal variability in three NSAID (ibuprofen, naproxen, ketoprofen) and carbamazepine removal from urban wastewater treated by UASB and surface/subsurface CW was investigated. Low to medium removals were observed, with the removal efficiency shown to be dependent on the compound (Sharma et al., 2016), temperature (Nivala et al., 2019) and sunlight (Nuel et al., 2018; Zhang et al., 2018), which is consistent with the fact that biodegradation, plant uptake and photodegradation are the predominant removal mechanisms for these compounds. Another treatment combination has been studied by Kharel et al.(2021), where the removal of carbamazepine, tramadol and diclofenac and their main metabolites (epoxy-carbamazepine, di–OH–carbamazepine, N-Desmethyl tramadol and hydroxy-diclofenac) was investigated after ozonation followed by vertical flow CW treatment, which operated downstream of a conventional activated sludge. The concentrations of all target metabolites showed a very limited, even negative, reduction after CW treatment indicating its low performance, compared to the GAC filter that was employed in the same study as an alternative.

Given the persistent nature of some pharmaceuticals under CW treatment, the photo-Fenton process has been applied to examine the possibility of their removal enhancement. Casierra-Martinez et al. (2020), evaluated the performance of a coupled system integrated by a horizontal subsurface flow (HSSF) CW and solar photo-Fenton at laboratory scale under tropical conditions for the removal of diclofenac from domestic wastewater. For this hybrid system, significant removal was achieved for diclofenac using Fe^{2+}:H_2O_2 at a ratio of 0.1 (15 min retention time). Specifically, the individual treatment units showed 56 ± 21% removal after HSSF-CW and 92% removal after solar photo-Fenton process for diclofenac, indicating that the implementation of this technological coupling has potential benefits for the removal of pharmaceuticals from wastewater.

3. Conclusion

Pharmaceuticals occurrence in aquatic environment is ubiquitous issue that is gaining more attention due to their health hazard and deleterious ecotoxicological effects. Contaminations could occur through various routes and one of the important routes is pharmaceutical industry. Industrial wastewater varies in quality and quantity (different pharmaceutical compounds, pollutant concentration, wastewater matrix, volume) and it also depends on the raw materials and the processes used in the production procedures. Hence it is challenging to indicate a particular treatment scheme for such a diversified industry. After the treatment processes applied, even when the removal of the pharmaceuticals is relatively high, but no complete mineralization is performed, it is important to quantify the remnant concentrations of pharmaceuticals, which may pose a harmful effect when disposed of or reused. In addition to the effluent quality, the treatment cost should also be taken into account when designing these treatment plants, as these technologies need to be viable for relevant industries and also affordable for low-income countries.

Owing to the persistent character of some pharmaceuticals and their low biodegradability, one treatment method is not enough for complete eradication. Physical processes, like adsorption and membrane processes, have the advantages of high removal efficiency and short treatment duration. However, these processes are phase changing technologies and produce concentrated retentate water which requires further treatment prior to its disposal due to the increased concentrations of persistent contaminants, while process complexity, cost of adsorbent preparation, regeneration, disposal and membrane operation cost and fouling should not be disregarded.

Biological treatments have the advantages of low price and relatively easy handling; however, they also have some disadvantages due to the long treatment time, the low removal rate of the biologically stable compounds, highly impacted by environmental and operational conditions and the possible toxicity due to the relatively high pollutants' concentrations on the microorganisms used resulting in the failure of the process.

AOP removal efficacy is higher than that of traditional oxidation processes due to the generation of powerful oxidizing agents. However, AOPs such as ozonation and photocatalysis can produce intermediates and by-products that are more toxic than the parent compounds. Furthermore, some antibiotic resistance genes may be promoted by non-lethal exposure to reactive oxygen species.

Therefore, the combination of different processes could be an ideal for degrading both parent and transformation compounds. Hybrid technologies have been proven to be a suitable strategy to improve the efficiency of pharmaceutical removal. These findings were also recommended by previous relevant reviews (Gadipelly et al., 2014; Priya et al., 2022). Combined technologies of physical and physicochemical separation technologies (adsorption on activated carbon and membrane separation) and advanced oxidation processes (AOPs) may be appropriate for the removal of many persistent compounds that remained in treated wastewater after a biological treatment system. The employment of AOPs, either as pre-treatment or as post-treatment, and their combination with other processes, like biological, adsorption, and filtration processes, have arisen as promising options. Ozonation has been also applied as an oxidation process, however, the presence of dissolved organic matter in the wastewater may lead to the production of toxic transformation products. Therefore, the employment of an activated carbon packed bed filter as post-treatment has been proven to be efficient in reducing toxicity in the effluents. An interesting alternative to AOP application could be photolysis performed under natural sunlight, which lowers the operational cost.

Physical processes, like adsorption and membrane processes such as reverse osmosis, and/or nanofiltration, can be applied in instances where AOPs are not completely effective. Biological treatment processes coupled with membrane systems have been shown also to be promising technologies for pharmaceutical removal.

In short, as the quality and quantity of the pharmaceuticals-containing wastewater and the nature of target substances play important roles in choosing the optimum process for the treatment scheme to be applied, the specific characteristics of the wastewater of the respective source should be evaluated in order to determine the effectiveness of different processes in removing the compounds. AOPs and their combination with physicochemical processes are promising options for degrading and removing both parent and transformation compounds to achieve a better eradication of pharmaceutical contaminants.

CRediT authorship contribution statement

Heba Ghazal: Conceptualization, Methodology, Writing – original draft, Writing and Editing. **Elena Koumaki:** Original Draft- Writing. **John Hoslett:** Original Draft- Writing. **Simos Malamis:** Writing – review & editing. **Evina Katsou:** Methodology. **Damia Barcelo:** Writing – review & editing. **Hussam Jouhara:** Conceptualization, Writing – review & editing.

Declaration of competing interest

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

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