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Review

Removal of Pharmaceuticals from Water by Adsorption and Advanced Oxidation Processes: State of the Art and Trends

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Abstract: Pharmaceutical products have become a necessary part of life. Several studies have demonstrated that indirect exposure of humans to pharmaceuticals through the water could cause negative effects. Raw sewage and wastewater effluents are the major sources of pharmaceuticals found in surface waters and drinking water. Therefore, it is important to consider and characterize the efficiency of pharmaceutical removal during wastewater and drinking-water treatment processes. Various treatment options have been investigated for the removal/reduction of drugs (e.g., antibiotics, NSAIDs, analgesics) using conventional or biological treatments, such as activated sludge processes or bio-filtration, respectively. The efficiency of these processes ranges from 20–90%. Comparatively, advanced wastewater treatment processes, such as reverse osmosis, ozonation and advanced oxidation technologies, can achieve higher removal rates for drugs. Pharmaceuticals and their metabolites undergo natural attenuation by adsorption and solar oxidation. Therefore, pharmaceuticals in water sources even at trace concentrations would have undergone removal through biological processes and, if applicable, combined adsorption and photocatalytic degradation wastewater treatment processes. This review provides an overview of the conventional and advanced technologies for the removal of pharmaceutical compounds from water sources. It also sheds light on the key points behind adsorption and photocatalysis.

Keywords: pharmaceutical products; wastewater; advanced oxidation technologies; adsorption

1. Introduction

In the past three decades, pharmaceutical residues have been discovered in almost all environmental matrices on every continent [1]. Approximately 3000 pharmaceutical substances are used in the European Union. Pharmaceuticals have been detected in groundwater, urban wastewater, surface water, and drinking water in a range of ng to µg per litre [2–6]. Because of their low biodegradability and high hydrophilicity, pharmaceuticals are difficult to eliminate from water systems using conventional wastewater treatment techniques [7]. Therefore, their disposal in wastewater treatment plants is a major concern [6,8]. Indeed, pharmaceuticals are considered the most significant groups of environmental pollutants of special concern. The most consumed type of pharmaceutical products may differ from one country to another. For example, in Spain, antihistamines, analgesics, and antidepressants are the most consumed based on the National Health System [9]. However, in Italy, antibiotics, sulphamethoxazole, ofloxacin and ciprofloxacin, β-blocker atenolol, antihistaminic ranitidine, diuretics furosemide, hydrochlorothiazide, and steroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen

are the most detected pharmaceuticals in sewage treatment plants [10]. Klein et al. [11] reported that Tunisia was considered the second-highest consumer of antibiotics in 76 countries analyzed between the years 2000–2015, and consumption was estimated at around 47 defined daily doses per 1,000 inhabitants per day.

Many studies have shown that wastewater treatment plants (WWTPs) do not totally remove pharmaceutical compounds [9]. More than 100 different drugs have been found in the aquatic environment [3,12]. Antibiotics and NSAIDs were reported in surface water samples from various countries at concentrations ranging from 5 to 150 µg/L [9,13,14]. Castiglioni et al. [10] noted that there is a difference in concentrations in pharmaceutical compounds in WWTPs between winter and summer. This is mainly due to greater attenuation and lower use of pharmaceuticals in summer. Thus, pharmaceuticals and their metabolites are detected regularly in aquatic and terrestrial environments [15,16]. Hence, tertiary treatment is needed to eliminate these emerging pollutants. Today, countries are facing high COVID-19 pandemic incidence rates and struggling to manage the dramatic increase in medical waste production by healthcare facilities, in particular with respect to pharmaceutical products. For instance, Wuhan inhabitants in China (~11 M) produced ten times more daily medical waste than the previous average (200 tons on a single day, 24 February 2020). A drastic increase in medical waste was also reported in other parts of the world, such as in Catalonia, Spain, and in China, with increments of 350% and 370%, respectively [17]. Recent studies indicated that the COVID-19 pandemic has led to an increase in waste generation by an average of 102.2% in both private and public hospitals [18]. In addition, the hazardous waste volume in the hospitals' investigations has increased by an average of 9% in the amount of medical waste and by 121% compared to the first wave and before the epidemic COVID-19 [19,20].

The hydrophobic/hydrophilic nature of pharmaceutical compounds facilitates their interaction with microplastics, frequently present in surface water and playing the role of a vector of pharmaceuticals within aqueous environments through π - π interactions [21]. The literature cites about 160 pharmaceutical compounds that have been recently found in the water surface and wastewater [21]. There are already approaches and strategies for minimizing this issue that proved their efficiencies and estimates to be implemented and prioritized in the near future. Currently, the accuracy of techniques for pharmaceutical removal from wastewater differs from drugs to other (80–100%). With this purpose, the development of new technology such as combined techniques based on an in situ census is still needed.





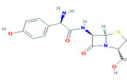
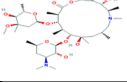
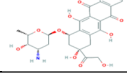
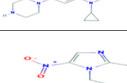
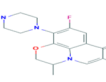

The main focus of this review is an in-depth compilation and discussion of the treatment options investigated for the removal of pharmaceuticals, including methods of detection and removal of pharmaceutical products from water sources. To this point, the information gathered in this review provides a clear concept in a single report to enable a fast understanding of the current status of the pharmaceutical detection field. This paper summarizes the methodological, socio-economic, and technological factors in both the short and long term influencing the pharmaceutical loading and removal from wastewater. A critical discussion of these approaches for implementation in wastewater treatment processes is also presented. So far, there are still major gaps between laboratory and field-scale research that need to be overcome in order to assess the viability of real applications.

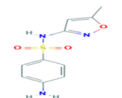
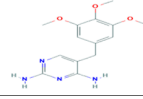
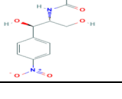
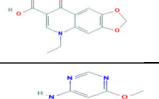
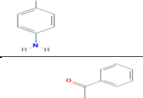
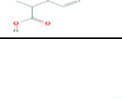
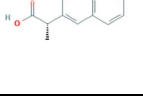
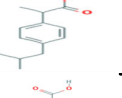
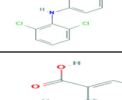
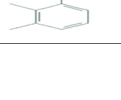
The ultimate goal of this review is to provide a platform on the recent development in the coupling of adsorption and advanced oxidation processes for the removal of PPCPs from the aquatic environment. The pharmaceutical adsorption capacity by adsorption and advanced oxidation process and their combination is discussed, and their efficiencies on the concentration of pharmaceuticals removed are described in this review. Continuing efforts in the following areas will strengthen the potential of the coupled process AOPs/adsorption in PPCPs removal from source water.

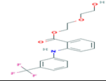
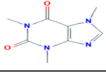
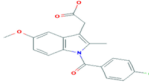
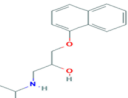
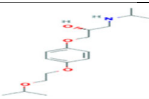
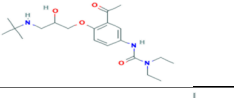
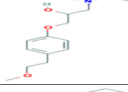
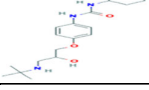
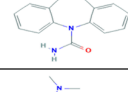
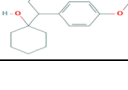
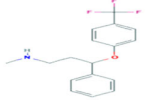
2. Commonly Used Pharmaceuticals: Their Classes, Chemical Structures, and Therapeutic Applications

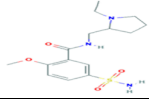
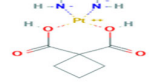
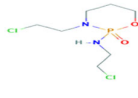
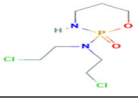
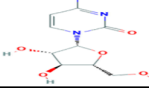
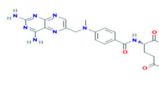
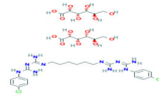
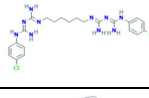
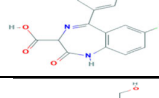
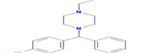
Approximately 3000 pharmaceutical substances are used in the European Union. The most widely used molecules are antibiotics for human and veterinary medicine, their consumption has reached 12,500 tons per year over the last decade. Non-steroidal anti-inflammatory drugs (NSAIDs) such as acetylsalicylic acid (aspirin), diclofenac, and ibuprofen are inhibitors of the two isoforms of cyclo-oxygenase (cox-1 and cox-2) enzymes, involved in prostaglandin synthesis. Ibuprofen, scientifically named 4-isobutylphenyl-2-propionic acid, is one of the most widely used NSAIDs worldwide. Additionally, there are other types of drugs, such as analgesics like paracetamol, that are considered antipyretic (Table 1). It appears to inhibit cyclo-oxygenase in the central nervous system without peripheral action, which is the reason why it does not have anti-inflammatory effects. Naproxen (NPX) is one of the most effective analgesics, a non-steroidal anti-inflammatory drug (NSAID), and it has been found in both surface water and wastewater at concentrations ranging from 20 ng/L to several mg/L [22]. Additionally, it is detected in wastewater treatment plants in the range of 250 to 1.5 µg/L, and its removal has been estimated at around 71% [23]. NPX has an excellent cardiac profile; however, it has been reported that people who ingest trace amounts of NPX have a higher risk of heart attack or a higher potential of urinary bladder cancer [24–26]. Depending on the development of their health services, the type and the concentration of drugs in sewage systems vary in each country. As an example, in Table 1, major pharmaceutical products used in Tunisia are shown with a predominance of antibiotics and analgesics. In Northern countries, synthetic and natural hormones, such as 17- α -ethinylestradiol (EE2) and 17- β -estradiol (E2), are present in wastewater at a non-negligible level [27].

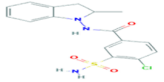
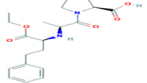
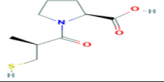
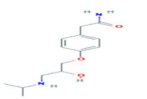
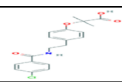
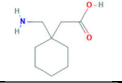
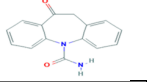
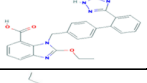
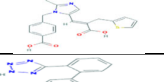
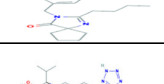
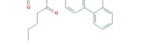
Table 1. Class and chemical structure of the most used pharmaceutical products in Tunisia.

Class	Pharmaceuticals	Chemical Formula	Molecular weight g/mol	Uses	Structure
Analgesic/ antipyretic	Acetaminophen	C ₈ H ₉ NO ₂	151.16	Used for mild-to-moderate pain and fever.	
	Aspirin	C ₉ H ₈ O ₄	180.16	Used in the prevention of arterial and venous thrombosis.	
	Lamotrigine	C ₉ H ₇ Cl ₂ N ₅	256.09	Used antiseizure medication that is a rare but well-known cause of idiosyncratic liver injury that can be severe and even fatal.	
	Tramadol	C ₁₆ H ₂₅ NO ₂	263.37	Used as a narcotic analgesic for severe pain.	
Antibiotic	Amoxicillin	C ₁₆ H ₁₉ N ₃ O ₅ S	365.4	Used in the treatment of mild-to-moderate bacterial infections such as sinusitis, bronchitis, otitis media, cellulitis, and community acquired pneumonia.	
	Azithromycin	C ₃₈ H ₇₂ N ₂ O ₁₂	749	Related for the rare instances of acute liver injury.	
	Doxorubicin	C ₂₇ H ₂₉ NO ₄	543.5	Used in the therapy of several forms of lymphoma, leukemia, sarcoma, and solid organ cancers.	
	Ciprofloxacin	C ₁₇ H ₁₈ FN ₃ O ₃	331.34	Used in the therapy of mild-to-moderate urinary and respiratory tract infections caused by susceptible organisms.	
	Metronidazole	C ₆ H ₉ N ₃ O ₃	171.15	Used in the treatment of many anaerobic and certain protozoan and parasitic infections.	
	Ofloxacin	C ₁₈ H ₂₀ FN ₃ O ₄	361.4	Used in case of rare instances of acute hepatocellular injury	

	Sulfamethoxazole	$C_{10}H_{11}N_3O_3S$	253.28	Used in combination with trimethoprim	
	Trimethoprim	$C_{14}H_{18}N_4O_3$	290.32	Used for mild-to-moderate bacterial infections and as prophylaxis against opportunistic infections	
	Chloramphenicol	$C_{11}H_{12}Cl_2N_2O_5$	323.13	Now used rarely and reserved for severe, life-threatening infections for which other antibiotics are not available.	
	Oxolinic acid	$C_{13}H_{11}NO_5$	261.23	Used in urinary tract infections.	
	Sulfamonomethoxine	$C_{11}H_{12}N_4O_3S$	280.31	It is a sulfonamide and a member of benzenes.	
NSAIDs	Ketoprofen	$C_{16}H_{14}O_3$	254.28	Used in the treatment of acute pain and chronic arthritis.	
	Naproxen	$C_{14}H_{14}O_3$	230.26	Used for the reduction of pain, fever, inflammation, and stiffness caused by conditions such as osteoarthritis, kidney stones, rheumatoid arthritis, psoriatic arthritis, gout, ankylosing spondylitis, menstrual cramps, tendinitis, bursitis, and for the treatment of primary dysmenorrhea.	
	Ibuprofen	$C_{13}H_{18}O_2$	206.28	Treatment of rheumatism and arthritis.	
	Diclofenac	$C_{14}H_{11}Cl_2NO_2$	296.1	Used for the therapy of chronic forms of arthritis and mild-to-moderate acute pain.	
	Mefenamic acid	$C_{15}H_{15}NO_2$	241.28	Used in case of rare instances of clinically apparent, acute liver injury.	

	Etofinamate	$C_{18}H_{18}F_3NO_4$	369.3	Used to treat muscle and joint paint.	
	Caffeine	$C_8H_{10}N_4O_2$	194.19	Caffeine is the most widely consumed psychostimulant drug in the world and is mostly consumed in the form of coffee.	
	Indomethacin	$C_{19}H_{16}ClNO_4$	357.8	Used for chronic inflammatory arthritis.	
β_blockers	Propranolol	$C_{16}H_{21}NO_2$	259.34	Used for the therapy of hypertension, cardiac arrhythmias, angina pectoris, and hyperthyroidism.	
	Bisprolol	$C_{17}H_{29}NO_4$	311.4	Used to counteract the effect of bradycardia through reduced reflection wave. (b)	
	Celiprolol	$C_{20}H_{33}N_3O_4$	379.5	Used for the management of mild to moderate hypertension and effort-induced angina pectoris.	
	Metoprolol	$C_{15}H_{25}NO_3$	267.36	Used in the treatment of several diseases of the cardiovascular system.	
	Talinolol	$C_{20}H_{33}N_3O_3$	363.5	It has been investigated for the basic science of gastrointestinal motility disorder.	
Tricyclic antidepressants TCA	Carbamazepine	$C_{15}H_{12}N_2O$	236.27	Used in therapy of epilepsy and trigeminal neuralgia.	
	Venlafaxine	$C_{17}H_{27}NO_2$	277.4	Can be associated with transient asymptomatic elevations in serum aminotransferase levels.	
	Fluoxetine	$C_{17}H_{18}F_3NO$	309.33	Used to treat major depressive disorder (MDD), moderate-to-severe bulimia nervosa, obsessive-compulsive disorder (OCD), premenstrual dysphoric disorder (PMDD), panic disorder with or without agoraphobia, and, in combination with olanzapine, for treatment-resistant or bipolar I depression.	

				sion.	
	Sulpiride	$C_{15}H_{23}N_3O_4S$	341.4	Used therapeutically as an antidepressant, antipsychotic, and as a digestive aid.	
Antineoplastic	Carboplatin	$C_6H_{12}O_4Pt$	371.25	Used as a chemotherapeutic agent for the treatment of various cancers, mainly ovarian, head and neck and lung cancers.	
	Ifosfamide	$C_7H_{15}Cl_2N_2O_2P$	261.08	It is associated with minor transient serum enzyme elevations and has been linked to cases of acute liver injury, including acute cholestatic hepatitis and veno-occlusive disease.	
	Cyclophosphamide	$C_7H_{15}Cl_2N_2O_2P$	261.08	It is associated with minor transient serum enzyme elevations and has been linked to rare cases of acute liver injury.	
	Cytarabine	$C_9H_{13}N_3O_5$	243.22	Used largely in the therapy of acute leukemia.	
	Methotrexate	$C_{20}H_{22}N_8O_5$	454.4	It has been associated with frequent but mild elevations in serum liver enzymes and, more importantly, with development of chronic liver injury, progressive fibrosis, cirrhosis, and portal hypertension.	
	Digluconate (chlorhexidine)	$C_{34}H_{54}Cl_2N_{10}O_{14}$	897.8	It is used in various applications, including wound care, hand washing, preoperative body shower, oral hygiene, and general disinfection.	
Antiseptic	Chlorhexidine	$C_{22}H_{30}Cl_2N_{10}$	505.4	Used as a topical antiseptic and in dental practice for the treatment of inflammatory dental conditions caused by microorganisms.	
Anti-convulsant	Clorazepate	$C_{16}H_{11}ClN_2O_3$	314.72	Used as an anticonvulsant as adjunctive therapy in management of epilepsy and as an anxiolytic for therapy of anxiety and alcohol withdrawal.	
	Hydroxyzine	$C_{21}H_{27}ClN_2O_2$	374.9	Used largely for symptoms of itching, nausea, anxiety, and tension.	

	Indapamide	$C_{16}H_{16}ClNO_3$	365.8	Antihypertensive agent and a diuretic.	
	Enalapril	$C_{20}H_{28}N_2O_5$	376.4	Used in the therapy of hypertension and heart failure.	
	Captopril	$C_9H_{15}NO_3S$	217.29	Used in the therapy of hypertension and heart failure.	
	Atenolol	$C_{14}H_{22}N_2O_3$	266.34	Used as an antihypertensive, hypotensive, and antiarrhythmic, Atenolol acts as a peripheral, cardioselective beta-blocker specific for beta-1 adrenergic receptors, without intrinsic sympathomimetic effects.	
	Bezafibrate	$C_{19}H_{20}ClNO_4$	361.8	Used for the treatment of hyperlipidemia.	
	Gabapentin	$C_9H_{17}NO_2$	171.24	Used as adjunctive therapy in the management of epilepsy and for neuropathic pain syndromes.	
	Oxcarbazepine	$C_{15}H_{12}N_2O_2$	252.27	It is a potent anticonvulsant used alone or in combination with other agents in the therapy of partial seizures.	
Antihypertensive	Candesartan	$C_{24}H_{20}N_6O_3$	440.5	Used widely in the therapy of hypertension and heart failure.	
	Eprosartan	$C_{23}H_{24}N_2O_4S$	424.5	Used for the treatment of high blood pressure.	
	Irbesartan	$C_{25}H_{28}N_6O$	428.5	It has been linked to rare instances of acute liver injury.	
	Valsartan	$C_{24}H_{29}N_5O_3$	435.5	Used alone or in combination with other agents to treat hypertension and reduce cardiovascular mortality after myocardial infarction.	

Data adopted from pubchem ^(b) [28].

3. Concentration of Pharmaceuticals in Water Environment

Numerous pharmaceutically active compounds have been discovered in water since the first discovery of such contaminants in aquatic systems in the 1980s [1]. Human drug residues occur mainly in hospital effluents and, in the case of urban medicine, in sewage systems containing patient discharge. These effluents loaded with residues are treated in the treatment plant before reaching the aquatic environment. Residual pharmaceuticals may introduce toxicity into our population, ecosystems, or the ecosphere [29]. The presence of pharmaceutical compounds in the environment, in the form of non-modified active ingredients, has been known since the first studies on a few compounds in the effluents of wastewater treatment plants or aquatic environments [30]. They can reach surface water, groundwater, and then drinking water [9].

In general, NSAIDs are the most consumed all over the world because of their availability without medical prescription [9]. For example, ibuprofen is still detected at $\mu\text{g/L}$ concentrations [31–34]. Despite the fact that the removal rate of this medicine is very high, it is always detected in the river downstream. Likewise, two additional compounds have been detected: acetaminophen (paracetamol) and aspirin (acetyl-salicylic acid) [9]. Akhtar et al. [35] indicated that only 20% to 30% of pharmaceuticals for anti-inflammatory, β -blockers, and analgesics could be removed, which was in contrast to antibiotics, where 50% can be eliminated from the effluent water.

According to Moslah et al. [27], in Tunisia, antibiotic and β -blockers are the most observed groups in wastewater, which means that these compounds are resistant to biological WWTPs. For antibiotics, their concentrations in the effluent ranged from 35 ng/L to 1.2 $\mu\text{g/L}$. Moslah et al. [27] reported that the pharmaceutical products that represent the most consumed drugs in Tunisia are paracetamol, mefenamic acid, and ibuprofen. Moslah et al. [27] also reported that other pharmaceuticals such as antibiotics and β -blockers were detected in the effluents of WWTPs, and their concentration ranged from 100 to 1 $\mu\text{g/L}$. Moreover, they found that the concentration levels of erythromycin, ofloxacin, and sulfamethoxazole in effluent samples were greater than those in influent samples, which can be explained by the deconjugation processes that may occur during their contact with activated sludge [36,37].

The interaction between microplastics (MPs) and pharmaceutical residues is an issue of increasing concern in various environmental compartments. Indeed, MPs can change the effect of pharmaceutical distribution and their transport through the sorbent and sorbate pair [38]. Microplastics coated with pharmaceutical residues have been transported across marine, freshwater, and terrestrial ecosystems [39]. The MPs with these contaminants pollute pristine ecosystems, leading to ingestion by marine and aquatic organisms, which can be lethal to marine life [40]. Data on the adsorption of pharmaceutical residues on the MPs surface are quintessential for risk and environmental assessment. Several studies showed that the desorption rates of polyethylene MPs increased in the order of propranolol, sulfamethoxazole, and sertraline, which were associated with the increment of the adsorption capacity and the hydrophobicity [21]. In addition, Lin et al. [41] revealed that marine and warm-blooded organisms are at higher toxicity exposure to atorvastatin, amlodipine, and tetracycline even at a lower concentration due to their chronic degradation and metabolites, which is in contrast to organisms that are cold-blooded.

In general, the reuse of wastewater (WW) for the irrigation of vegetable crops is widely applied all over the world [42]. In addition, pharmaceuticals can be obtained through the consumption of plants, vegetables, fruit, fish, and meat [42]. Some studies carried out by Christou et al. [42] show that different concentrations of pharmaceutical residues exist in plants (tomato) successively by sulfamethoxazole SMX (0.98 mg/kg) followed by trimethoprim TMP (0.62 mg/kg) and diclofenac DIC (0.35 mg/kg). However, in the first year of the study, DIC was not strongly detected. However, DIC showed the highest concentration (11.63 mg/kg) throughout the study, followed by SMX (5.26 mg/kg) and TMP (3.40 mg/kg). Very high concentrations of ciprofloxacin (31 mg/L), cetirizine (1.3–1.4 mg/L), and losartan (2.4–2.5 mg/L) were reported in the effluent of a treatment plant serving 90 bulk drug manufacturers in Patancheru, near Hyderabad, India. Enoxacin (150–300 $\mu\text{g/L}$), Citalopram

(770–840 µg/L), lomefloxacin (150–300 µg/L), enrofloxacin (780–900 µg/L), metoprolol (800–950 µg/L), ofloxacin (150–160 µg/L), norfloxacin (390–420 µg/L), and ranitidine (90–160 µg/L) were also found in this study. Clearly, this wastewater effluent is of great concern to local microorganisms and humans, where they are directly and indirectly exposed. The total release of ciprofloxacin (at 31 mg/L) into the environment is 44 kg per day. This release is equivalent to the total consumption of Sweden over five days (population of nine million). The evolution of drug-resistant bacteria is favored in these waters.

In fact, when pharmaceutical residues are thrown into the environment from untreated wastewater containing various toxic drugs, people will be directly exposed via the consumption of plants that are already irrigated or via the consumption of contaminated fish (Figure 1). As long as we have not found solutions or undergone advanced treatments for the elimination of dangerous pharmaceutical residues, man will always remain a victim of his own actions.

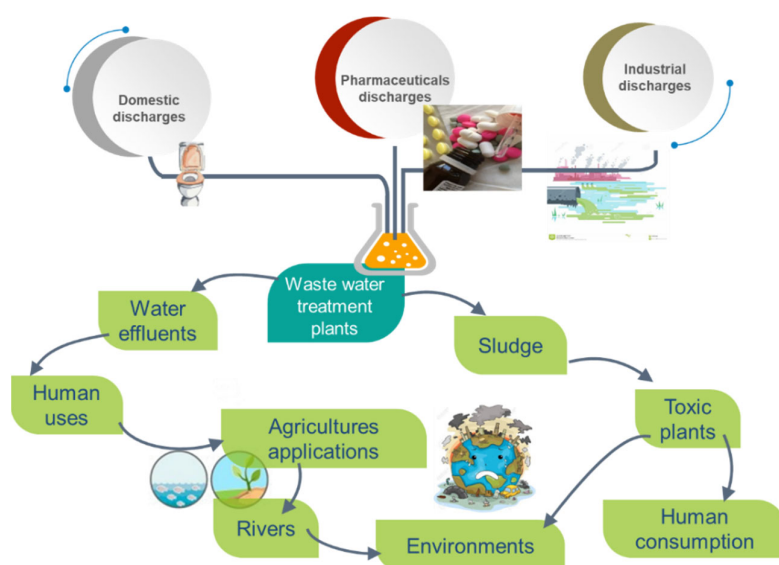


Figure 1. Sources of pharmaceutical contamination

Khan et al. [43] studied the abundance of antibiotics in the North of Pakistan in 19 sampling sites (river, dam, canal, sewage drain, etc.). They found high levels of antibiotics in a river in the close vicinity and downstream of Lahore city (10 million inhabitants). The highest concentration of antibiotics for foroxytetracycline, trimethoprim, and sulfamethoxazole was equal to 1100, 1700, and 2700 ng/L, respectively. They noted that the presence of antibiotics in surface water can be horizontally transferred to human-associated bacteria and thus contribute to antibiotic resistance proliferation.

4. Removal of Pharmaceuticals during Wastewater Treatment

4.1. Conventional Treatments

Conventional wastewater treatment consists of a combination of physical, chemical, and biological processes and operations to remove solids, organic matter, and, sometimes, nutrients from wastewater. General terms are used to describe different degrees of treatment in order of increasing treatment level; preliminary, primary, secondary, and tertiary and/or advanced wastewater treatment. In some countries, disinfection to remove pathogens sometimes follows the last treatment step [44]. It has been shown that pharmaceuticals can be removed only partially, as these wastewater treatment plants are not designed for full removal [1]. Depending on the composition of wastewaters, preliminary treatments with activated sludge systems or classic membrane bioreactors may be needed [45]. However, membrane fouling comprises a significant obstacle to their broad application [46]. Pharmaceutical com-

pounds are characterized by their limits of elimination by volatilization because of their low vapor pressure and pKa values between 3 and 10. Some drugs, such as ibuprofen, diclofenac, and carbamazepine, include extremities vulnerable to biodegradation and sorption. According to the review of Petrie et al. [47], diclofenac is removed by $\leq 50\%$, and any carbamazepine removal is low. From the study carried out by Tauxe-Wuersch et al. [48], in Switzerland, they noted the difficulties faced in the removal of different drugs such as ibuprofen, mefenamic acid, and diclofenac with biological and physico-chemical treatments. Additionally, this work reported that there was a difference in the elimination rates within wet and dry seasons. The removal of ibuprofen and ketoprofen was inhibited during winter in comparison to that during the dry period. This can be explained by the difference in the residence time of treated water in treatment plants depending on the rainfall. In fact, the flow rate was three times higher in winter than in the dry period. In addition, Lindqvist et al. [49] found ibuprofen, naproxen, ketoprofen, diclofenac, and bezafibrate in seven different sewage water treatment plants in Finland. Despite their effort to remove these pharmaceutical products, they detected them again in the rivers of discharge of sewage water treatment. In fact, in the river of Aurajoki (AUJ), they found low concentrations of all studied pharmaceuticals, but in the river of Seinajoki (SEJ, tributary of Kyronjoki, KYJ), they found a very low concentration, which was explained by the dilution of water up to five times. In the Kokemäenjoki river (KOJ), located in the South West of Finland, they found only IBU, NPX, and DIC, which was explained by dilution and also degradation and adsorption processes. The highest removal rate was attributed to ibuprofen with 92% and the lowest one to diclofenac with 26%. In the same context, Metcalfe et al. [50] found analgesic/anti-inflammatory drugs such as ibuprofen and naproxen, as well as the metabolite of acetylsalicylic acid, salicylic acid, in final effluents at $\mu\text{g/L}$ levels from 14 sewage treatment plants from the provinces of Manitoba, British Columbia, Quebec, Alberta, Ontario in Canada. The most important parameter for drug degradation is the sludge retention time (sludge age). When the sludge age is 10 to 15 days, partial biodegradation is observed, but after only four days, biodegradation of pharmaceuticals is almost zero [51]. The sludge age required for degradation of aspirin, ibuprofen, bezafibrate, and sulfamethoxazole is 2 to 5 days [52], although, for iopromide, roxithromycin, and diclofenac, 5 to 15 days are required for significant degradation [53]. Some products such as carbamazepine and diazepam remain unmodified even after >20 days [54]. Hydraulic retention times >27 days and sludge retention times >35 days have led to high removal of estrogens from water. From the results of the above-cited studies, it can be concluded that conventional WWTP settings, which have been performed to reduce the contamination of water, did not lead to a desirable quality of water. Indeed, pharmaceutical residues were not totally removed by these processes, and they are increasingly dangerous for humans and the environment. It is of interest to explore the technological and scientific gaps in wastewater treatment by the conventional techniques with the specific study. The review paper published by Grandclement et al. [55] reported that micropollutant removal appears to be compound- and process-dependent in all investigated processes. This paper also reported that even though some hybrid processes show promising micropollutant removal, further studies are needed to optimize these water treatment processes, in particular in terms of technical and economic competitiveness.

Conventional drinking water plants feature multiphase treatments, including clarification, filtration, and coagulation/flocculation steps [1]. Not one of these operations have shown an efficient removal of pharmaceutical products among the sixteen different medicines considered in this review [56]. When considering sewage water, Kooijman et al. [56] demonstrated the ineffectiveness of the coagulation–flocculation process for the elimination of pharmaceutical products. However, the use of iron (III) chloride as a flocculant product showed no significant removal for diclofenac, carbamazepine, bezafibrate, and clofibric acid from water [53]. Stackelberg et al. [57] observed low removal of sulfamethoxazole and acetaminophen up to 25%. According to Choi et al. [58], coagulation was shown to be effective for the removal of seven tetracycline classes of antibiotics (TAs), and the addition of poly-aluminium chloride (PACl) allowed authors to remove 43–94% of TAs at the optimum

conditions from the synthetic water. Overall conventional water and wastewater treatment processes are unable to reliably remove some recalcitrant pharmaceuticals, and it is necessary to introduce additional advanced treatment technologies prior to discharge into the environment.

Among the emerging treatment options, combined adsorption and AOPs are the most promising methods for the efficient removal of pharmaceutical residues. The combined adsorption—AOPs systems are discussed, which hold great promise to provide international alternatives for the manifold WWT process to mitigate pharmaceutical residues and meet acceptable limitations.

4.2. Biological Removal of the Pharmaceuticals

Bacteria occupy a dominant place in the biosphere; through their various metabolic capabilities, they support the metabolic cycles that are fundamental to all life on Earth [59]. Researchers are investigating the potential of different bacteria to degrade pharmaceuticals and personal care products (PPCPs) into eco-friendly monomers, which could be an alternative emerging way to eliminate pharmaceutical residues from the ecosystem [60]. Mainly related to the bacterial populations concerned, technologies that use sludge (aerobic, activated, or granular) have been highly efficient in the treatment of municipal wastewater [61]. A study evaluating the efficiency removal of pharmaceutical products such as atorvastatin, caffeine, paracetamol, xylazine, trimethoprim, sulfamethoxazole, naproxen, fluoxetine, diclofenac, ibuprofen, clarithromycin, carbamazepine, atenolol, azithromycin, erythromycin, ketoprofen, metoprolol, erythromycin, ciprofloxacin, valsartan, simvastatin, and losartan, using activated sludge in the laboratory, at concentrations ranging from 13.2 ng/L to 51.8 µg/L in Latvia in municipal wastewater highlighted that biostimulation through the addition of nutrients to the sludge showed biodegradation of these pharmaceutical contaminants by Nitrospirae, Actinobacteria, Verrucomicrobia, Firmicutes, Acidobacteria, Proteobacteria, Chloroflexi, and Bacteroidetes. As well, some genera and species involved in removal processes of pharmaceutical compounds such as metoprolol, venlafaxine, fluoxetine, alprenolol, propranolol, bisoprolol, salbutamol, norfluoxetine, gemfibrozil, and 17β-estradiol have demonstrated a 90% or higher removal efficiency [62]. Another study improved the efficiency of using a Gram-positive bacterium, designated as strain B1 (2015b) for the degradation of ibuprofen and naproxen, after six days for 20 mg/L of concentration and 35 days for 6 mg/L, respectively [63].

The biodegradation of PPCPs could be a potential solution to eradicate this residue. This process is carried out by micro-organisms, which are more likely to decompose this pharmaceutical waste into biomass, methane, carbon dioxide, water, and various inorganic compounds, while the enzymes of organisms play a vital role. Pharmaceutical removal by biodegradation depends on what configuration is needed. The reactor configurations can be as simple as a sand column, WWTPs, and constructed wetlands, sequencing batch reactors, membrane bioreactors, which have been studied by many researchers [64]. Environmental parameters, including temperature, sunlight, atmospheric humidity, and ultraviolet rays, have also been shown to influence biodegradation [65–67].

4.3. Electrocoagulation Process

Electrocoagulation is a treatment process in which cations are formed by metal electrodes in an electrical field [68,69]. It produces coagulants using metal electrodes that are more likely to encounter pharmaceutical products with several advantages, including sludge minimization, automatic treatment, and efficient and low operating costs [69,70]. The removal efficiency of the three most consumed pharmaceutical products such as carbamazepine (70%), diclofenac (90%), and amoxicillin (77%) was investigated by En-sano et al. [71] for a density of 0.5 mA/cm², an initial concentration of 10 mg/L, and a hydraulic retention time HRT of 38 h. Oxytetracycline, an antibiotic drug, was analyzed by Nariyan et al. [72]. The optimum current density was 20 mA/cm² for both anodes: iron and aluminum had a removal efficiency of 93.2% and 87.75%, respectively. The initial

concentration on removal efficiency was also studied: increasing the initial concentration of oxytetracycline hydrochloride up to 200 mg/L did not have a significant impact on its removal. The pH, Eh, and dissolved oxygen of all samples were measured during the experiments: with both anode–cathode combinations, pH was seen to increase considerably, while Eh and dissolved oxygen decreased substantially. Furthermore, the total removal of ciprofloxacin using electrocoagulation process was achieved at a density of 15 mA.cm⁻², pH 7.5, initial CIP concentration of 60 mg.L⁻¹, electrolyte dose of 0.07 M NaCl, and inter-electrode distance 1.58 cm within the equilibrium time of 20 min [71,73].

4.4. Sorption Process for the Removal of Pharmaceutical Products

The adsorption process by solid adsorbents shows potential as one of the most efficient for the treatment of a wide range of waters and wastewaters [1] that contain pharmaceutical products. In fact, there are excellent studies of carbon materials used to remove pharmaceutical pollutants, which is a financially attractive alternative for wastewater treatment.

Different types of adsorbents are classified into natural and synthetic adsorbents. Natural adsorbents include charcoal, clays, clay minerals, zeolites, and ores. These natural materials, in many cases, are relatively low-cost and abundantly available and have significant potential to modify and ultimately improve their adsorption capacities. Synthetic adsorbents are adsorbents prepared from agricultural products and waste, household waste, industrial waste, sewage sludge, and polymeric adsorbents. Each adsorbent has its own characteristics such as porosity, pore structure and the nature of its adsorbent surfaces. Many wastes used include fruit waste, coconuts, date nuts, used tires, bark and other tannin-rich materials, sawdust, rice husk, petroleum waste, fertilizer waste, fly ash, sugar industry waste, blast furnace slag, chitosan and seafood processing waste, and algae, peat, clays, red mud, zeolites, sediment and soil, ores, etc. [74].

The current application of advanced materials for the removal of PPCPs from wastewater can be viewed from three main perspectives: activated carbon (AC), clays, and biochar. Other more recent materials have also been reported, such as molecular imprinted polymers (MIPs), thermo-responsive gel, and magnetic nanoparticles, though comparatively, they still lack development and supporting case studies.

4.4.1. Activated Carbon

Removal of naproxen has been determined by different adsorbent materials and has shown different results. A compilation of pharmaceutical residue counts and removal efficiencies from literature is provided in Table 2. The more efficient adsorbent used was waste apricot plants from Malatya as activated carbon using a batch adsorption process. In fact, almost total elimination was found when the temperature increased to 50 °C for 100 mg/L [75]. In addition, the use of green synthesis of silver-reduced graphene (Ag-RGO) showed a good performance for the removal of naproxen NPX for 92.62% [76] for a quantity of adsorbent of 20.2 mg at pH of 4.5 and temperature of 24.25 °C. At the same condition of pH and temperature, the green synthesis of copper nanoparticles (CuNPs), as adsorbent materials, indicated an elimination of 86.9% after 60 min of experience for 10 mg of CuNPs. [77].

As well, activated carbon cloths can be exploited for the removal of ibuprofen according to Guedidi et al. [78]. This adsorbent was provided by Kuraray Chemical Co. Ltd. (Japan). They analyzed the removal of these drugs by distilled water and observed that the efficiency of elimination depends on the decrease of pH.

Since the research carried out for diclofenac DIC drugs, more effective adsorption has been achieved using an olive waste cake as activated carbon [79]. For a Ph = 4.5, Husein et al. [77] noted that a 91.4% of removal in 60 min by using green-synthesized copper nanoparticles (Cu NPs) as the adsorbent for a maximum capacity was 36 mg/g. The smallest percentage of elimination noted for a pH = 2, dose of *Cyclamen persicum* tubers CTAC = 0.7 g and a concentration of diclofenac 70

mg/L was 81% for removal after 120 min of contact time [2]. For antibiotic drugs, amoxicillin was totally removed from hospital wastewater and aqueous solutions by using magnetic adsorption prepared from olive kernel MA-OK situated in the southern regions of Iran produced from palm [80] for a maximum concentration of adsorbent and AMX 0.5 g/L, 200 mg/L, respectively, at a contact time of 90 min and pH of 6 [80]. For a better understanding of the in-depth mechanistics of the removal of pharmaceutical compounds by adsorption, Mansouri et al. [8] reported that there is no difference in the adsorption sites and kinetics for IBP and amoxicillin (AMX), but IBU is more adsorbed than AMX whatever the nature of the adsorbent. Authors have demonstrated that there is a relationship between the removal of IBP and the adsorption of ionic species present in the wastewater as opposed to AMX. Hasan et al. [81] studied the adsorption of two typical PPCPs such as naproxen and clofibric acid onto the metal-organic framework (MOFs), functionalized with aminomethanesulfonic acid (AMSA) and ethylenediamine (ED) as acidic and basic groups, respectively. They concluded that the highest efficiency for adsorption rate and adsorption capacity was obtained with basic ED-(MOFs). They explained such behavior by an acid-base interaction between the PPCPs and the adsorbents. They showed also that the effect of pH on the adsorption of naproxen supports this acid-base interaction.

4.4.2. Clays

However, clay minerals could be inexpensive and widely available materials for the removal of pharmaceuticals [82]. For clay materials, the most common types (illite, kaolinite, vermiculite, montmorillonite, bentonite, and sepiolite) have already been used for the removal of a variety of organic micro-pollutants. Montmorillonite is the most promising adsorbent for further investigations aimed at testing the practicability of a clay-based adsorbent for the removal of pharmaceuticals compounds [82]. The use of natural clay (montmorillonite (Mt), vermiculite (VER), bentonite (B), kaolinite (K)) and modified clay-based sorbents commercial acid-activated montmorillonites K10 and K30, and two carbonaceous-mineral nanocomposites (MtG5%T, BAIG3%C) for the removal of ibuprofen, diclofenac, ketoprofen, carbamazepine, bisphenol A, and triclosan, showed that vermiculite was the best adsorbent for the removal of all drugs. For the modified clay minerals, the best results were achieved for carbonaceous bentonite, and the two acids activated montmorillonites K10 and K30 [83]. Furthermore, the adsorption of gemfibrozil, mefenamic acid, and NPX using two different clays materials, exfoliated vermiculite and LECA, showed that both adsorbents were able to remove drugs from the aqueous medium, while vermiculite presented a high adsorption capacity up to 70% [84].

4.4.3. Biochar

Biochar has been used as an adsorbent of pharmaceutical compounds by Patel et al. [1]. They demonstrated that many factors affect pharmaceutical adsorption on biochar that are common to most sorbents: pH, temperature, feedstock, preparation conditions, presence of ions, humic acid, pharmaceutical structures, and functional groups present both in the biochar's surface and within its solid structure. Biochar-based materials have been used by Peiris et al. [85] for the removal of antibiotic sulfonamides and tetracyclines in aquatic environments. They showed that in contrast to active carbon (AC), biochar is considered a successful adsorbent; even with low surface area, it can have excellent potential as an adsorbent due to its ability to swell in water leaving more room for adsorbents [86]. Therefore, the adsorption of pharmaceuticals onto AC often results in both high removal efficiencies and capacities without generating toxic products. Hydrophobic pharmaceuticals tend to reach equilibrium with AC faster than hydrophilic compounds [1].

Table 2. Removal of pharmaceutical products by adsorption process.

Operation process	Drugs	Adsorption Process	Scale	Matrix	Experience Time (min)	Reactor Volume (mL)	pH	T(°C)	BET (m ² /g)	Capacity (mg/g)	Significant Findings	References
Batch adsorption	Ibuprofen Naproxen Diclofenac	Green-synthesized copper nanoparticles (Cu NPs)	Lab-scale	Wastewater	60	1000	4,5	24,85		33.9 33.9 36	The percentage of removal of IBU for about 74.4%, for DIC about 91.4% and NPX about 86.9%.	[77]
	Naproxen	Ag-RGO Nano-composite film	Lab-scale	Aqueous solution	3	50	4.5	24,85		229.25	92.62% of removal.	[76]
		AC from gooseberry seed-shells GB-GP-AgNs	Lab-scale	Water treatment plants	15	50	4.40		1328 645	154.98	61.99% of removal.	[87]
	Ibuprofen Amoxicillin	OP: Physical activation of the carbonized precursor using CO ₂	Lab-scale	Aqueous solution	60	100	9.5		1055	86.2	IBU is more adsorbed than AMX.	[8]
		OC: Chemical activation of the raw precursor using phosphoric acid					5.6	25	1106	78.8		
		OPox: Oxidation of OP in a saturated solution of ammonium persulfate in 4 N sulfuric acid					3.4		903	75.4		
	Diclofenac	Cyclamen persicum tubers activated carbon (CTAC)	Lab-scale	Aqueous solution	120	50	6	15	Zinc chloride activated: 880.936 Physical	Zinc chloride activated: 606.78 Physical	Elimination of 81% when DIC concentration was 70 mg/L and 0.7 g CTAC.	[2]

4.5. Removal of Different Pharmaceuticals by Advanced Oxidation Processes

Klavarioti et al. [29] describe advanced oxidation processes (AOPs) as aqueous phase oxidation methods. These AOPs are characterized by the use of high energy and the generation of hydroxyl radical ($^{\circ}\text{OH}$) as a very strong oxidant [7,89–91]. Researchers have repeatedly recognized that AOPs effectively degrade pharmaceuticals in wastewater and other aquatic systems. Photochemical, ozone-based ($\text{O}_3/\text{H}_2\text{O}_2$, O_3/UV), and photo-Fenton processes are generally more effective than ozonation alone due to the photon-initiated carbon–halogen bond cleavage and increased generation of hydroxyl free radicals [92]. In addition, UV or visible irradiation can generate reactive excited states of pharmaceuticals. The main problem associated with AOPs is the generation of toxic oxidation products that can remain in the sanitized water [93]. The literature outlined various types of heterogeneous photocatalysts, mechanisms, synthesis methods of the photocatalyst, the nature of the pharmaceutical compound, and photocatalytic reactor designs and their operating parameters, as well as the effect of the water matrices on the degradation [94,95].

The removal of paracetamol and acetaminophen ACE, as NSAID products, was mentioned by many studies [96–98]. Borràs-Ferris et al. [99] and Gomez-Avilés et al. [96] used two totally different photocatalytic processes for the elimination of acetaminophen ACE. In fact, the photo-electrocatalytic (PEC) degradation of ACE using TiO_2 nanotubes as photocatalysts demonstrated that the photodegradation of ACE was quicker at $\text{pH} = 3$, and a higher degree of mineralization was achieved [99]. In comparison, analyzing by photocatalysis using mixed Ti–Zr metal–organic frameworks under solar irradiation showed total removal of ACE, and high reusability of the photocatalyst had been noted that facilitated the utilization of this photocatalyst in real wastewater treatment [96]. Among analgesics, paracetamol was mentioned in Table 3 for a full degradation at $\text{pH} 9$ [98]. However, using photo-degradation for paracetamol resulted in 98% of removal under solar irradiation, using ferrioxalate for 2 mg/L as a concentration for 5 min of treatment once in an aqueous solution [97]. According to Jallouli et al. [100], using TiO_2 heterogeneous photocatalysis with UV-LEDs was efficient to remove IBU from pharmaceutical industry wastewater and from ultrapure water in natural pH (between 5 to 5.3) and less efficient in treating the wastewater from the municipal WWTPs. In real urban wastewater, they found a percentage between 89.83% and 100% of degradation after 40 min of treatment. Monteoliva-Garcia et al. [101] used light-driven AOPs, which is a good treatment process for three different pharmaceuticals products: ibuprofen, carbamazepine, and ciprofloxacin in real urban wastewater. They demonstrated a removal of 80.4% to 100% of carbamazepine, an antidepressant drug, after 40 min of treatment in real urban wastewater, also from 89.83% to 100% for ibuprofen and a total removal for ciprofloxacin. He et al. [102] also noted the efficiency of the photocatalysis process over photolysis, which was faster and characterized by a higher elimination of pharmaceutical products in wastewater: 74% removal of carbamazepine and 100% removal of both propranolol and DIC. For the other NSAIDs, Calza et al. [103] also studied aqueous solution by TiO_2 photocatalyst. They showed a total degradation and mineralization of DIC after 2 h of irradiation. Moreover, for NPX pharmaceutical compounds, Jallouli et al. [104] proved that their removal in ultrapure water by a photocatalytic process is more efficient than photolysis.

In fact, the TiO_2 -UV process results in higher removals of NPX with 98% and chemical oxygen demand COD of 25%. However, for photolysis at pH initial 6.5, the COD was 83% and 11% after 3 h, whereas Méndez-Arriaga et al. [23] showed the opposite in aqueous solution of 0.8 mmol/L; from their analysis, they noted that 3 h of photolysis process treatment resulted in 90% removal of NPX with just 5% of mineralization, but under the TiO_2 photocatalytic process, only 40% of removal and more than 20% mineralization resulted. As for antibiotics, many studies were observed in Table 3, [97,101,105–112]; they all agree on the efficiency of the photocatalytic process for the removal of different antibiotics drugs such as Ciprofloxacin CIP, which was completely removed from urban wastewater even before 20

min of treatment when they added Fe^{2+} and TiO_2 as catalysts in the wastewater treatment plants [101]. Additionally, this drug was eliminated under UVA light by combining two catalysts: TiO_2 and ZnO [109]. In their study, they have shown the efficiency of this combination by removal of $300 \mu\text{g L}^{-1}$ of CIP from ultra-pure water in less than 6 min. In addition to that, Elmolla and Chaudhuri [107] noted that the removal of antibiotics drugs, amoxicillin, ampicillin, and cloxacillin, under UVA irradiation and zinc oxide was observed when the pH of solution achieved 11. For amoxicillin AMX, it was also analyzed by two other methods, which are identified by Chen et al. [106]. They observed that AMX was completely removed after 90 min of treatment using carbon quantum dots modified potassium titanate nanotubes ($\text{CQDs}/\text{K}_2\text{Ti}_6\text{O}_{13}$) under UV irradiation (between 365 and 385 nm), and Tran et al. [110] reported a percentage of elimination of AMX and metronidazole of more than 70% after 120 min of treatment by UV/ TiO_2 photocatalysis at pH medium.

Molinari et al. [113] showed the importance of the photocatalyst process, mainly in the removal of furosemide and ranitidine drugs. In fact, in darkness and without photo-reaction, the percentages of rejection were between 10% and 60% for furosemide and between 5% and 30% for ranitidine, but a decrease to 0 was observed in the presence of light, photocatalyst, and oxygen. Despite the high cost of this process, many researchers are adapting these methods because of their effectiveness in the removal of most pharmaceutical drugs: antibiotics, analgesics, NSAIDs, anticancer, beta-blockers, antiseptics, etc. (Table 3). Calza et al. [103] identified the efficiency of the removal of two anticancer drugs, methotrexate and doxorubicin, in ultrapure water, reaching 100% using the UVA/ TiO_2 system. De la Cruz et al. [114] reported the removal of propranolol in ultrapure water in 240 up to 81% at the solar plant and 94% at the laboratory. From these different studies, we can observe the performance of photocatalysis in degrading pharmaceuticals that is significant. This technique is also characterized by utilizing TiO_2 , which is inexpensive, with low toxicity and high stability to light illumination, as well as its capacity to be regenerated several times without significantly losing its activity [115].

The antibiotic cloxacillin was also almost completely removed from a synthetic pharmaceutical wastewater using the combined TiO_2 /photo-Fenton reaction [116]. In addition, the use of a UV-A-LED-photo-Fenton reaction for the removal of antipyrine by Davididou et al. [117] showed a total degradation after 2.5 min and a 93% of mineralization after 60 min. Bautitz and Nogueira [105] have shown the efficiency of the photo-Fenton process for the degradation of tetracycline (TC) in WWTP effluent and surface water (Table 3). They have shown that total removal of TC drug was achieved after 1 min under black light radiation in the presence of $\text{Fe}(\text{NO}_3)_3$ for a concentration of 5.5 mg/L, while solar light irradiation favors ferrioxalate for a 2 mg/L of concentration.

In addition to the different methods of AOPs, ozone treatment enhances the removal of all drugs, including carbamazepine, where removals up to 96% are observed. Ozone is a powerful oxidizing agent ($E^0 = 2.07 \text{ V}$), capable of acting both directly and indirectly. The direct use of ozone without catalyst or irradiation is ozonation, while the additional use of a catalyst or photoactivation is considered AOP [1]. The removal of drugs such as antibiotics, estrogens, and neutral pharmaceuticals has been treated with Almomani et al. [118] in different types of water for the same pH = 8 and a temperature of 20°C . For a synthetic wastewater, they found more than 90% of removal for all pharmaceutical products in 2 min with concentration of ozone of 5.5 mg/L. Regarding wastewater, surface water, and wastewater treatment plants, WWTPs, the same percentage of more than 90% removal for antibiotics, estrogens, and neutral pharmaceuticals was achieved with ozone doses of 2.05, 1.11, and 1.30 mg $\text{O}_3/\text{mg DOC}$, respectively. Moreover, the simple use of ozone for water treatment shows good results, which were confirmed by Dantas et al. [119]. They noted that a total removal of Bezafibrate BZF drugs in the aqueous solution with the initial concentration of 0.5 mmol/L could be reached just after 10 min of treatment using the dose of 0.73 mmol/L of ozone (Table 3). However, degradation almost never results in complete mineralization. In addition, the oxidation of endocrine-disrupting compounds EDCs with comparable chemical structures such as Bisphenol A, 17β -Estradiol, and 17α -Ethinyl Estradiol

have been studied by Alum et al. [120]. They reported that, when using ozone at the concentration of 30 mmol/L, 99% transformation would be expected in less than 2 s. However, a residual estrogenic response could still be present because of the oxidation byproducts. They showed a transformation after 10 min. Carballa et al. [121] were interested in the effect of an oxidative pre-treatment with ozone, dose of 20 mg O₃/g TSS, on the removal of pharmaceutical and personal care products (PPCPs) during the anaerobic digestion of sewage sludge. They found an almost total elimination of all PPCPs of 99%, except for carbamazepine, which was only up to 60% removed under thermophilic conditions. Therefore, they concluded that ozonation could represent an economically feasible solution to improve sludge stabilization. Therefore, non-steroidal anti-inflammatory drugs such as indomethacin were removed by Zhao et al. [122] after just 7 min with the lowest dose of ozone.

Concerning the antineoplastic drug 5-fluorouracil, Koltsakidou et al. [123] also studied its degradation under solar irradiation. In fact, the results showed that the ferri-oxalate system was more efficient for this degradation and mineralization.

5. Various Methods for the Removal of Pharmaceuticals from Waters

The removal of pharmaceuticals depends on different water treatment processes that result in different efficiencies. Wastewater treatment plants are not designed to completely remove pharmaceuticals [1]. Adsorption has advantages over other methods because of its simple design that can involve low investment in terms of both initial cost and space required [124]. Adsorption processing for water remediation includes low capital investment, applicability at low adsorbate concentrations, suitability for batch or continuous processing, and the ability to reuse and regenerate adsorbents. Adsorption is a low consuming energy process that can be very efficient and lead to a removal of up to 90%, but it has a mild operation condition. With the Fenton process, it is possible to treat large volumes of wastewaters (need of large electrodes or cell stacks). The greatest advantage of photocatalysis lies in the use of the semiconductor TiO₂, which is non-hazardous, eco-friendly, inexpensive, and stable [94]. Indeed, in a quick and very high percentage of organic matter, degradation can be reached and can be more remarkable under sunlight irradiation and using in situ cathodic production of H₂O₂. However, this process presents many disadvantages such as the need for acidic conditions with a pH value near to 3.0. Thus, a neutralization is requested after the treatment, leading to the production of a large amount of sludge. Special attention should be paid to the formation of halogenated byproducts. According to Patel et al. [1], an advanced oxidation process can lead to a high degradation of pharmaceuticals, but it is difficult to apply on a wide scale of WWTPs due to the oxidative byproducts and high operation cost. A common problem to all AOPs is their high cost, mainly because of the high demand for electrical energy (Figure 2).

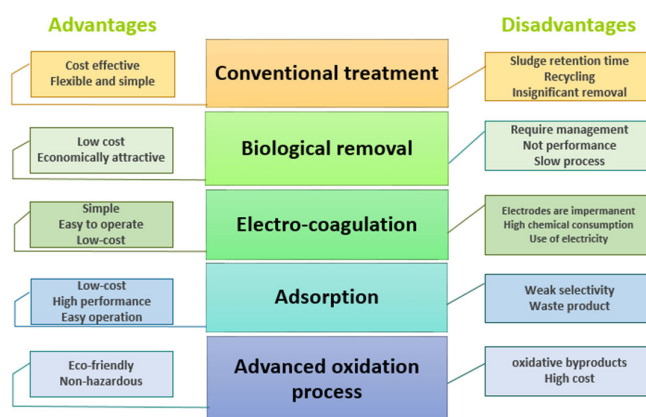


Figure 2. Advantages and disadvantages of different treatment process for the removals of pharmaceuticals.

Table 3. Removal of different pharmaceutical products by AOPs.

Operation process	Drugs	AOPs	Scale	Matrix	Experiment Duration (min)	Reactor Volume (mL)	Significant Findings	References
Photocatalysis	Acetaminophen	Mixed Ti-Zr metal-organic-frameworks	Lab-scale	Aqueous solution	180	150	90% of removal for ACE.	[96]
		TiO ₂ nanotubes photo catalysts	Lab-scale	Aqueous solution	120	12	The maximum conversion value for elimination was reached at pH = 3	[99]
	Paracetamol	TiO ₂ nanoparticles and TiO ₂ / under UV and sunlight irradiation	Lab-scale	Ultrapure water	150	1500	More than 90% of degradation pH optimum = 9	[98]
	Aspirin	TiO ₂ -based nanosheets	Lab-scale	Aqueous solution	210	30	100% of degradation 87.8% after 120 min	[125]
	Ibuprofen	TiO ₂ / UV-LED	Lab-scale	Ultrapure water, municipal wastewater, pharmaceutical industry wastewater	30	250	42% of removal for ultrapure water, 18% degradation for municipal wastewater and only 9% removal for PIWW	[100]
	Diclofenac	TiO ₂ suspensions	Lab-scale	Aqueous solution	120	50	100% of degradation	[103]
	Azithromycin Trimethoprim Ofloxacin Sulfamethoxazole	TiO ₂ / UVA-LEDs	Lab-scale	Secondary urban wastewater	60	150	Total degradation	[126]
	Metronidazole Amoxicillin	UV/TiO ₂	Lab-scale	Aqueous solution	120	1000	More than 70% of degradation	[110]
	Metronidazole	UV/TiO ₂	Lab-scale	Water matrix	30	1000	Degradation of MNZ decreased in the presence of H ₂ PO ₄ ⁻ , Fe ³⁺ , and humic acid (HA)	[111]

Ciprofloxacin	TiO ₂ /UVA ZnO/ UVA	Lab-scale	Ultra-pure water	6	50	Efficiency of degradation of CIP for two catalysts	[109]
Amoxicillin	Carbon quantum dots modified K ₂ Ti ₆ O ₁₃ nanotubes/ UVA	Lab-scale	Deionized water	90	50	Completely removal of AMX.	[106]
Amoxicillin Ampicillin Cloxacillin	UV/ZnO	Lab-scale	Aqueous solution	180	500	Total degradation for pH = 11.	[107]
Penicillin G	Ti ³⁺ self-doped TiO ₂	Lab-scale	MQ-water	120	50	98.3% elimination of penicillin G.	[108]
Furosemide Ranitidine Ofloxacin Phenazone Naproxen Carbamazepine Clo-fibric acid	TiO ₂	Lab-scale	Aqueous solution	900	200	Degradation of all pharmaceutical products.	[113]
Carboplatin	TiO ₂ /UV	Lab-scale	Aqueous solution	30	250	100% of degradation	[127]
Ifosfamide Cyclophosphamide	Pt-doped TiO ₂ TiO ₂	Lab-scale	Aqueous solution	240	50	92% removal for cyclophosphamide and 95% removal for ifosfamide.	[128]
Cytarabine	TiO ₂ / solar light	Lab-scale	Aqueous solution	360	100	Cytarabine was degraded in all experimental conditions.	[123]
Methotrexate Doxorubicin	TiO ₂ Degussa P25	Lab-scale	Ultrapure water	60 15	5	60% of removal for methotrexate 43% of removal for doxorubicin	[129]
Chlorhexidine digluconate	TiO ₂	Technical scale	Aqueous solution	60	100	99% of removal.	[130]
Carbamazepine Gabapentin Lamotrigine Oxcarbazepine	ZnO and TiO ₂ under UVA radiation	Lab-scale	Wastewater treatment plants	30	100	ZnO shows a higher degradation of pharmaceutical products than TiO ₂	[131]

	Venlafaxine Bisoprolol Celiprolol Talinolol Bezafibrate Tramadol Candesartan Eprosartan Irbesartan Valsartan							
Photolysis and photocatalysis	Propranolol Carbamazepine Diclofenac	TiO ₂ /solar light	Lab-scale	Wastewater effluent	5760	500	100% for propranolol, 100% for diclofenac; 76 ± 3% for carbamazepine	[102]
	Naproxen	Direct photolysis and TiO ₂ /UV	Lab-scale	Aqueous solution	180	120	83% after photolysis 98% after photo catalysis	[104]
		Direct photolysis/TiO ₂ /UV	Lab-scale	Aqueous solution	180	30	90% after photolysis 40% after photo catalysis	[23]
	Propranolol	Direct photolysis	Technical-scale	Ultrapure water	240	10000	71% of removal	[114]
			Lab-scale				77% of removal	
		TiO ₂	Technical-scale			1000	81% of removal	
			Lab-scale				94% of removal	
Photo-Fenton and photocatalysis	Oxolinic acid	TiO ₂	Lab-scale	Ultrapure water	30	100	TiO ₂ photocatalysis can be an efficient methods and rapid way for the elimination of oxolinic acid.	[132]
	Ibuprofen Carbamazepine	Photo-assisted H ₂ O ₂ / UV AOP	Lab-scale	Real urban wastewater	40 20	700	89.83 and 100% degradation for IBU 80.14 to 100% for carbamazepine	[101]

Photo-Fenton	Ciprofloxacin						100% removal for CIP	
	Antipyrine	UV-A-LED-photo Fenton reaction	Lab-scale	Aqueous solution	2.5	150	100% of degradation after 2.5 min. 93% of mineralization at 60 min.	[117]
	Cloxacillin	TiO ₂ / photo-Fenton process	Lab-scale	Synthetic pharmaceutical wastewater	240	150	Total degradation for antibiotic.	[116]
	Tetracycline	Fe(NO ₃) ₃ / solar and black light irradiation	Lab-scale	STP effluents	1.5	500	Total degradation of TC.	[105]
	Amoxicillin Bezafibrate Paracetamol	H ₂ O ₂ / solar and black light irradiation	Lab-scale	Aqueous solution	1	800	With FeOx 84% removal for amoxicillin or 62% was observed using Fe(NO ₃) ₃ ; 98% of removal for bezafibrate and paracetamol in the presence of Fe(NO ₃) ₃ .	[97]
Ozonation	5-fluorouracil	(Fe ³⁺ /H ₂ O ₂)/ ([Fe(C ₂ O ₄) ₃] ³⁻ /H ₂ O ₂ , Fe ³⁺ /S ₂ O ₈ ²⁻)	Lab-scale	Ultrapure water	20–60	100	In this study, it was found that the ferrioxalate system was more efficient for the degradation and mineralization of 5- fluorouracil.	[133]
	Antibiotics, steroid hormone, lipid regulator, antineoplastic, non-steroidal anti-inflammatory drug, and psychostimulant	Dose of ozone	Lab-scale	Synthetic wastewater, surface water, and the effluent of wastewater treatment plant	1	2000	The optimum dose of ozone was found to be yielding of 118.1, 222.3, and 222.4 mg/h, respectively, for synthetic waste water, surface water, and effluent of wastewater treatment plants. Ozonation experiments were carried out at 20 °C and at a pH of 8. This experience eliminated >99.9% of removal for most of the studied pharmaceuticals. The increased toxicity for aqueous solutions of acidic pharmaceuticals at a specific ozone dose of 2.24 mg O ₃ /mg DOC was due to formation of more toxic byproducts.	[118]

Indomethacin	Ozone and hydroxyl radicals	Lab-scale	Ultrapure water	7	300	This drug was eliminated within 7 min under the lowest ozone dose, but TOC removal was only 50% even under the highest ozone dose used in the experiments	[122]
Amoxicillin	medium-high frequency ultrasonic irradiation and/or ozonation	Lab-scale	Aqueous solution	90	250	The highest removal was achieved at 575 kHz ultrasonic frequency (>99%) with the highest pseudo first order reaction rate constant 0.04 min at pH 10.	[134]
Bezafibrate	Dose of ozone	Lab-scale	Aqueous solution	10	800	Total degradation after 10 min with a dose of ozone = 0.73 mmol/L	[119]
Bisphenol A 17 β -Estradiol, 17 α -Ethinyl Estradiol	Ozone	Lab-scale	Aqueous solution	10	40	Total removal for drugs and a rapid transformation in 10 min.	[120]
Pharmaceutical and personal care products (PPCPs)	Ozone	lab-scale	Aqueous solution	120	680	99% of elimination for all pharmaceuticals products.	[121]

6. AOPs/Adsorption as a Promising Alternative Treatment Technique

Many studies have shown the negative effects of PPCPs on the environment that we have mentioned before (3), essentially the endocrine-disrupting effects and the risk of the spread of antibiotic resistance [135]. According to the OECD [136], many countries have imposed rules to prevent the risk of developing drugs in the environment. For example, the United States has national regulations on the disposal of hazardous pharmaceutical waste in the health sector, and Germany has developed an environmental checklist for veterinarians and farmers with the aim of reducing the use and release of veterinary pharmaceuticals to the environment. Additionally, Korea uses suspect and non-target screening to identify and prioritize pharmaceuticals for water quality monitoring. In the same order, Australia has a national pharmaceutical collection and disposal program.

In this review, we show clearly that one singular method such as conventional treatment, physical treatment methods such as coagulation and adsorption, or advanced oxidation ones, including a combination of oxidizing agents (such as H_2O_2 and O_3), irradiation (such as ultraviolet light or ultrasound), and catalysts (such as Fe^{2+}), cannot remove them sufficiently. Thus, a combination of two or more processes is required to secure the total elimination of drugs in water.

The simultaneous application of ozonation and adsorption for the removal of imidazole, reported by Patel et al. [1], shows that 90–100% of degradation was achieved by ozonation and 10–20 % of mineralization. The presence of an adsorbent further reduces toxicity by 30%. Catalytic ozonation associated with adsorption can be effective for the removal of pharmaceuticals. In fact, ozonation degraded the drug products and the adsorbent can remove any remaining pharmaceutical and degradation byproducts. Additionally, Mojiri et al. [137] show that the application of a combined process of ozone and adsorption (cross-linked chitosan/bentonite) for the treatment of solutions containing acetaminophen and amoxicillin was efficiently removed by 84.8% and 82.7%, with an initial concentration of ozone of 0.17 and 0.16 mg/L, respectively (Table 4). Combined photo-Fenton and biological treatment were over 95% efficient, of which 33% corresponds to the solar photochemical process and 62% to the biological treatment [138]. Additionally, Sulfamethoxazole was successfully removed using both catalytic ozonation and adsorption on modified powdered activated carbon ($\text{Fe}_2\text{O}_3/\text{CeO}_2$ -loaded activated carbon) at 2 g/L, applied for only 50 min [139]. Sui et al. [140] studied the removal of 13 pharmaceutical and personal care products (PPCPs) by sequential ultraviolet and ozonation process in a full-scale wastewater treatment plant (Table 4). Authors showed that most of the target PPCPs were effectively removed, and the median removal efficiencies of individual PPCPs, ranging from 13% to 89%, were dependent on their reaction rate constants with molecular ozone. Moreover, Salgado et al. [141] studied the removal of eighteen drugs that have a biological removal rate in a full-scale activated sludge plant combined with UV photolysis. They showed that up to 75% of removal was usually found for 17 of the 18 most commonly detected PPCPs, with the only exception being for diclofenac, which has often shown negative values for the rate of biological elimination in activated sludge and has been mainly degraded by UV photolysis. In fact, in treatment water, there are different possibilities of combining advanced oxidation processes such as photo-Fenton/ozonation and photocatalysis/ozonation [142,143]. At the end of the treatment, the combined processes could generate transformation products more persistent and more toxic than the original pharmaceutical products. The combined processes AOPs/adsorption provided almost complete removal of pollution. Therefore, adsorption can remove low-molecular organic products issued from AOPs to achieve more cost-effective and advanced treatment. Thus, integration of AOP and adsorption has been proposed by many researchers to solve the shortcomings experienced when these two technologies are applied separately [144]. From this review, we can highlight that among the combined processes reported, the combination of photocatalysis and adsorption seems more attractive and has been presented as the most effective solution for the removal of pharmaceutical compounds and their byproducts from water.

Many studies have shown the efficiency of combination process, such as [145–147]. In fact, Brienza et al. [145] used methods of combination micelle-clay sorption to solar photo-Fenton in different pharmaceutical products in almost 13 drugs: Sulfamethazine, Caffeine, Tamoxifen, Ketoprofen, Sulfamethoxazole, Mepanypirim Diclofenac, Chlortianidin, Amoxicillin, Venlafaxine, Fenofibric acid, Carbamazepine, and Atenolol. They took the GAC from Aquacarb (Chemivor Carbon Company, city country), sand of Fontainebleau from PROLABO (particle size 150–210 μm , France), and montmorillonite from Wyoming Namontmorillonite SW γ -2 (grain size 0.8–1.5 mm, Montmorillonite Minerals Society, Columbia, MO). The lowest percentage of removal was tamosifen with 37.71%, contrary to others that were almost completely degraded. In Table 4, Rahmani et al. [147] used a combination of electrooxidation–ozonation for the antibiotic ciprofloxacin. This combination shows high performance for elimination about 90% in just 150 min.

Looking for the performance of the combination processes for adsorption/photocatalysis, both Lin et al. [148] and Wang et al. [146] used TiO₂ nanofibers combined with BN nanosheets and BiOCl_xly nanospheres, respectively. Lin et al. [148] found a higher degradation for ibuprofen. Additionally, Wang et al. [146] studied two different drugs, acetaminophen and hydroxyphenylactic acid (p-HPA). They resulted in a total removal for p-HPA and an 80% elimination for acetaminophen.

In fact, when pharmaceutical products become very harmful and our groundwater is at risk of contamination, we must become involved, like Lhotsky et al. [149]. They noted the presence of pharmaceutical plants for more than 80 years in the Czech Republic. For these reasons, they took the three principal dangerous drugs, benzene, toluene, and chlorobenzene, found in the site. They resulted from a higher elimination of these products after the treatment combination of UV/H₂O₂ for a 99% of removal.

Table 4. Removal of different drugs by combined processes.

Operation Process	Drugs	Combining Process	Scale	Matrix	Experience Time (Min)	Reactor Volume (mL)	Significant Findings	References
Ozone oxidation combined to adsorption	Acetaminophen	Ozone gas diffusion	Technical scale	Aqueous solution	25	2100	84.8% of removal	[137]
	Amoxicillin						82.7% of removal	
	Acetaminophen	Cross-linked chitosan/bentonite			25	200	Total removal of two drugs	
	Sulfamethoxazole	PAC and Fe ₂ O ₃ /CeO ₂ loaded activated carbon MOPAC	Lab-scale	Aqueous solution	30	100	Sulfamethoxazole was highly removed by combining adsorption activated carbon MOPAC	[139]
		Ozone			5	250	with ozonation at pH = 3.5.	
Photocatalysis Combined to adsorption	Ciprofloxacin	Graphitized mesoporous carbon	Lab-scale	Aqueous solution	10	100	Totally mineralized in 1.5 h.	[112]
		TiO ₂			20	200		
UV/O ₃ process combined to adsorption	Bizafibrate, clofibric acid, carbamazepine	UV and ozonation	Technical-scale	WWTPs	40	6	DF, TP, CP, and CBZ were removed about 80%. SP, MA, CA, PNN, and	[140]

	ine, caffeine, chloramphenicol, N,Ndiethyl-meta-tolamide, diclofenac, gemfibrozil, mefenamic acid, metoprolol, propranolol, sulpiride, trimethoprim						MTP are efficiently removed.	
Photolysis combined to adsorption	Diclofenac, Etacofenamate, Ibuprofen, ketoprofen, fluoxetine, clorazepate, hydroxyzine, indapamide, analapril, captopril, atenolol, cloridric-acid, ampicillin	Sludge adsorption	Technical-scale	Wastewater treatment plant	2 weeks	600 m ³	Incomplete removal of diclofenac. Removal of pharmaceuticals by adsorption was about 33% and UV was 22%.	[141]
UV radiation with hydrogen peroxide	benzene, toluene and chlorobenzene	UV/H ₂ O ₂ with aeration	Technical-scale	Ultrapure water	4 months	1000	High efficiency of both techniques for the removal of drugs. Removal efficiency ranging from 72% to 99%.	[149]
Electrooxidation-ozonation	Ciprofloxacin	Ti/PbO ₂	Technical-scale	Aqueous solution	90	280	90% of removal	[147]
Photo-Fenton combined to adsorption	Sulfamethazine Caffeine, Tamoxifen Ketoprofen Sulfamethoxazole	GAC/photo-Fenton	Lab-scale Technical-scale	Biological domestic wastewater treatment plant	120	6000	87.47% of removal 93.64% of removal 37.91% of removal 100% of removal 99.98% of removal 100% of removal 96.67% of removal 100% of removal	[145]

	Mepanypirim						100% of removal	
	Diclofenac						100% of removal	
	Chlo-tianidin						100% of removal	
	Amoxicillin						99.97% of removal	
	Venlafaxine						100% of removal	
	Fenofibric acid							
	Carbamazepine							
	Atenolol							
Photocatalysis combined to adsorption	Ibuprofen	TiO ₂ /boron nitride (BN) nanocomposites	Lab-scale	Aqueous solution	90	100	Efficiency of the combination for the removal of ibuprofen	[148]
	Acetaminophen and hydroxyphenylacetic acid (p-HPA)	BiOCl ₃ nano-spheres	Lab-scale	Aqueous solution	180	50	100% removal of p-HPA and 80% removal of acetaminophen.	[146]
Persulfate oxidation process combined to adsorption	sulfadimethoxine (SDM), sulfamonomethoxine (SMM), and sulfachloropyridazine (SCP)	MIL-101(Cr)	Lab-scale	Deep-water	90	1000	The adsorption capacity of MIL-101(Cr) decreased with the increase of oxidation times. The maximum adsorption capacities to SDM, SMM, and SCP were 588, 196, and 196 mg/g, respectively, by Langmuir at 25 °C	[150]
Ozonation and sonolysis	Diclofenac, Sulfamethoxazole, Carbamazepine	Ozonation and ultrasound (O3/US)	Lab-scale	Wastewater	120	8000	The remove efficiency yielding from 80% to 84%	[151]

7. Conclusions, Future Perspectives, and Challenges

The large-scale use of hospital, household, and industrial wastewaters has led to widespread contamination of water by different hazardous drugs, increasing concern for human health and the environment. Various analyses have been tried to reduce the presence of drugs in water to save the environment and the human body. For the removal of pharmaceutical products from water, many methods were taken into consideration, such as adsorption and advanced oxidation processes. In this review, we demonstrated that the application of one technology to treat pharmaceutical wastewaters seems insufficient for the total removal of PPCPs from WWTPs before discharge. In fact, a trace

of these PPCPs has also been found in rivers and lakes. An advanced oxidation process has been developed and constructed to show promising potential as a future generation for the treatment of water. The combination of adsorption and AOP processes can be considered an excellent way to completely remove pharmaceutical products such as antibiotics, NSAIDs, and analgesics, even at trace concentrations. A variety of techniques have been taken into account in this review to reduce the toxicity of PPCPs in water on humans via fresh drinkable water or food as well as on the environment (lakes and rivers).

This review also highlights the combination of the different treatment methods to achieve a high percentage of PPCPs removal that reaches up to 100% in a short operation time. In the case of coupling AOPs to adsorption, a number of low-cost and local materials such as clay, activated carbon, and olive waste can be used as adsorbents. Moreover, the operation costs and sustainability of this kind of process have to be optimized, notably by using renewable energy, i.e., solar light instead of artificial illumination.

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Nomenclature

AC:	activated carbon
ACE:	acetaminophen
AMX:	amoxicillin
AOPs:	advanced oxidation process
AUJ:	Aurajok
AZT:	azithromycin
B:	bentonite
BF:	Bezafibrate
CA:	Clofibric acid
CBZ:	carbamezapine
CF:	Caffeine
CIP:	Ciproflaxacin
COD:	Chemical oxygen demand
CP:	Chloramphenicol
CTAC:	Cyclamen persicum tubers based activated carbon
CTC :	Chloitetacycline-HCl
CuNPs:	Copper nanoparticles
DEET:	N,N-diethyl-meta-tolamide
DIC:	Diclofenac
DMC:	Democlocycline-HCl

DXC:	Doxycycline-hyclate
EDCs:	Endocrine disruption compounds
GAC:	Granular activated carbon
Gf :	Gemfibrozil
IBU:	Ibuprofen
K:	kaolinite
Kyj:	kyronjoki
KOJ :	Kokemäenjoki
MA:	Mefenamic acid
MCC:	Meclocycline-sulfosalicylate
MDD:	major depressive disorder
MNC:	Minocycline-HCl
MNZ:	metronidazole
MT:	Montmorillonite
MTP:	Metoprolol
MPs:	Microplastics
NPX:	Naproxen
NSAIDs:	Non-Steroidal anti-inflammatory drugs
OCD:	obsessive-compulsive disorder
OFX:	ofloxacin
OTC:	Oxytetracycline-HCl
PACl:	Poly-aluminum chloride
PEC:	Photo-electrocatalytic
PMDD:	premenstrual dysphoric disorder
PPCPs:	Pharmaceuticals and personal care products
PPN:	Propanolol
SEJ:	Seinajoki
SMX:	Sulfamethoxazole
SP:	Sulpiride
TAs:	tetracycline classes of antibiotics
TC:	tetracycline
TMP:	trimethoprim
UK:	United Kingdom
US:	United States
UVA:	ultraviolet A
VER:	vermiculite
WW:	waste water
WWT:	waste water treatment
WWTP:	waste water treatment plants

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