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Review

The occurrence and fate of anti-inflammatory and analgesic pharmaceuticals in sewage and fresh water: Treatability by conventional and non-conventional processes

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ABSTRACT

The presence of pharmaceutical (PhAC) residues in the environment is an emerging issue due to their continuous and uncontrolled release (via excretion from medical care) to the water environment and detrimental effects on aquatic organisms at low concentrations. A large fraction of PhAC pollution in water is composed of anti-inflammatory (AI) and analgesic (AN) drugs, which are rapidly excreted in urine. The present review is aimed to emphasize the occurrence of AI/AN wastes in sewage and fresh water bodies, their impacts on non-target organisms, and conversion or elimination by chemical, biochemical and physical treatment methods. The first part of the study is devoted to a critical review of most common AI/AN drugs and the relative efficiency of some selected sewage and drinking water treatment operations for their elimination/separation from aqueous systems. The second part focuses on pilot- or lab-scale applications of various advanced oxidation processes that are promising solutions to the ultimate degradation and/or conversion of such medical residues in effluents of drinking water treatment plants (DWTPs) and wastewater treatment plants (WWTPs) to less harmful and non-toxic products.

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1. Introduction

A significant portion of pharmaceutically active compounds (PhACs) are excreted as unchanged or metabolites, which after disposal to municipal sewage systems find their way to the aquatic environment and groundwater aquifers [1,2]. Although excretion (from human and animal medical care) is the major source of water and soil pollution by PhACs, other sources such as emission from production sites, manufacture spill accidents, direct disposal of surplus drugs in households, underground leakage from sewage infrastructures, therapeutic treatment of livestock on fields, and effluents from farms are of significance, as well [1,3–7]. Most pharmaceuticals are designed to target specific metabolic pathways in humans and domestic animals; but their action on non-target organisms may become detrimental even at very low concentrations [8–11]. This is justified by the level of their acute toxicity in surface water (in $\mu g\,L^{-1}$), which signifies their potential for biological activity and for adverse health effects in drinking water [12,13].

Although the exact fate and effect of medical substances in the water environment is not easy to predict, anticipated exposure routes are as schematized in Fig. 1 [14]. In accordance, the occurrence or fate of PhACs residues in water is categorized in three pathways: (i) ultimate mineralization (as aspirin); (ii) partial biodegradation (i.e. partly retained in sediment); (iii) conversion to more hydrophilic but persistent metabolites (i.e. end up in receiving water bodies).

2. Anti-inflammatory and analgesic drugs

A significant portion of pharmaceutical wastes in wastewater is composed of anti-inflammatory (AI) and analgesic drugs (AN), which are used as pain relievers and inflammation reducers, respectively [15]. Both groups of chemicals are extensively used without prescription with an estimated annual consumption of several hundred tons in developed countries [8]. A simplified classification of ANs and AIs and variation of their consumption by years and country (European) are given in Table 1.1 and Table 1.2, respectively.

As a consequence of their outstanding contribution to total quantity of pharmaceutical pollution in water, the present study is aimed to present a thorough and critical review of the most common and commercially available AN and AI chemicals, their

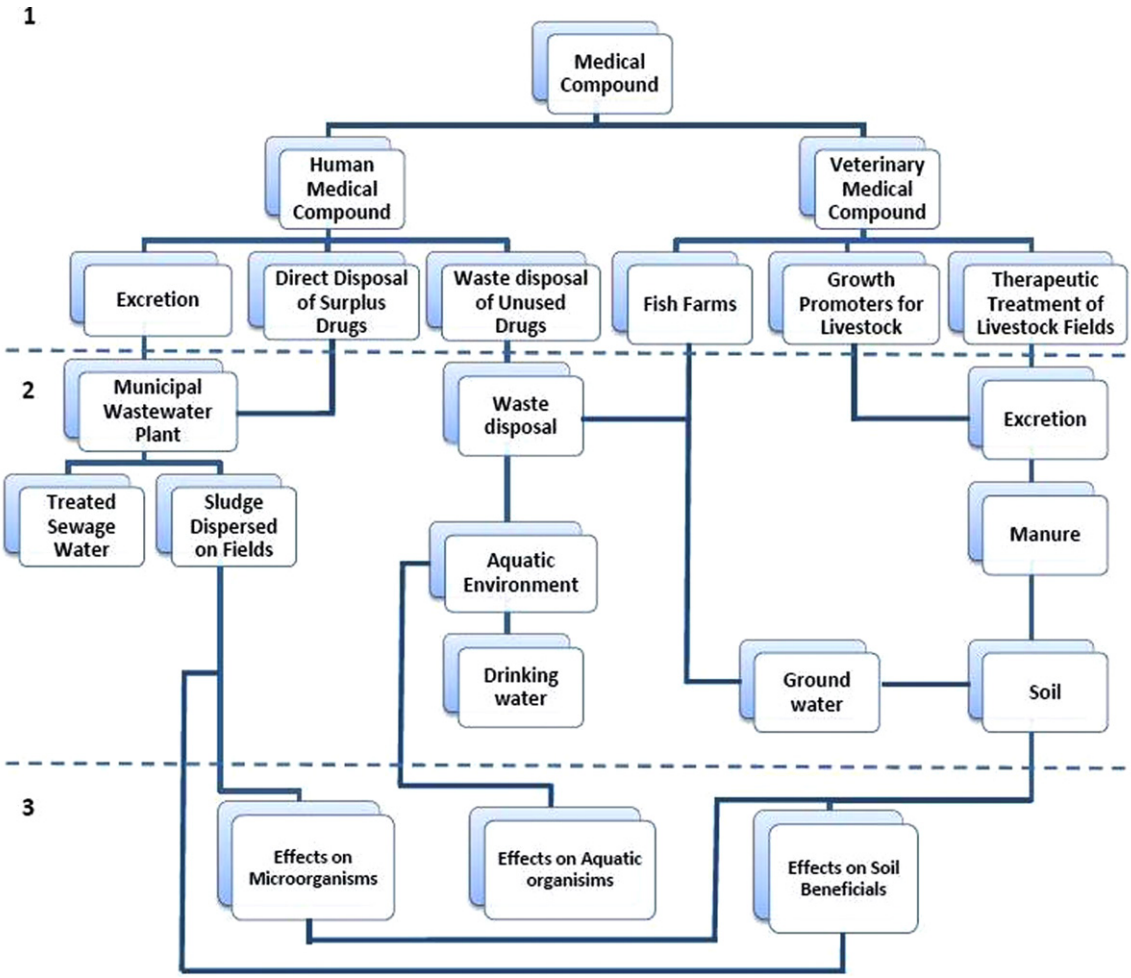

Fig. 1. Occurence and environmental effects of pharmaceutical wastes (1 – exposure, 2 – fate, and 3 – effects) [1,14].

Table 1.1
Classification of analgesic and anti-inflammatory drugs [16].

Analgesics (ANs)	Anti-inflammatories (AIs)
Opiates and opioids	Pyrazolones
Morphines	Phenylbutazone
Pethidine	Acetic acid derivatives
Pentazocine	Indomethacin
Dextropropoxyphene	Sulindac
Acetysalicyclic acids and derivatives	Diclofenac
Paracetamol	Oxicans
	Piroxicam
	Propionic acid derivatives
	Ibuprofen
	Naproxen
	Ketoprofen
	Fenoprofen
	Fenemates
	Mefenamic acid
	Tolfenamic acid

occurrence and fate in the water environment and their treatability in sewage and drinking water treatment plants. The second part of the study brings an overview and interpretation of the literature on the degradability of such chemicals in water and/or in effluents of water/wastewater treatment plants by advanced oxidation processes.

2.1. Anti-inflammatory (AI) drugs

The following sub-sections present basic information on the outstanding properties and environmental behavior of some common AIs. A summary of the discussed properties and toxicities if available are provided in Table 2.1.

2.1.1. Diclofenac (DCF)

DCF (2-[2,6-dichlorophenyl)-amino]benzeneacetic acid is a highly consumed AI and very commonly used in ambulatory care [24]. It is readily metabolized to hydroxylated (4′-hdroxy-DCF; 4′5-dihydroxy-DCF; 3′-hydroxy-DCF; 5′-hydroxy-DCF) or methoxylated derivatives (3′-hydroxy-4′-methoxy DCF) and further conjugated to glucuronides [24–26]. The presence of these metabolites in sewage treatment plant effluents signifies their potential to transfer to surface waters and threaten aquatic life forms. DCF has the highest acute aquatic toxicity within the class of ANs and AIs [15] and microorganisms that usually comprise of lotic biofilms are inhibited by concentrations around 100 $\mu g\,L^{-1}$ [27]. Moreover, ingestion of DCF by birds while scavenging on livestock results in death shortly after exposure [26]. The presence of 1 $\mu g\,L^{-1}$ DCF has been reported to damage the liver and kidney cell functions in fish [28].

Table 1.2
Relative consumption of some ANs and AIs.

Compound	Consumption ($t\,year^{-1}$)	Country
DCF	4.5	Switzerland, 2004 [15]
	1	Finland, 2002 [17]
	86	Germany, 2001 [18]
	26	England, 2000 [19]
	4.4	Australia, 1998 [20]
IBP	162	England, 2000 [12]
	25	Switzerland, 2004 [15]
	70	Finland, 2002 [17]
	345	Germany, 2001 [18]
	14.2	Australia, 1998 [20]
NPX	35	England, 2000 [18]
	6.7	Finland, 2002 [17]
	22.8	Australia, 1998 [20]
KTF	1.4	Finland, 2002 [17]
	0.25	Switzerland, 2002 [21]
MEF	17	Switzerland, 2002 [21]
PCT	403	England, 2000 [12]
	95	Switzerland, 2004 [15]
	622	Germany, 2001 [18]
	621	Germany, 2001 [22]
ASA	78	England, 2000 [12]
	896	Germany, 2001 [18]
	836	Germany, 2001 [23]

2.1.2. Ibuprofen (IBP)

IBP is commercially available as 2-(4-isobutylphenyl) propionic acid, and used widely in the treatment of rheumatic disorders, muscular pain and fever [29,30]. It is a non-steroidal, antipyretic (lowering elevated body temperatures without impairing consciousness) drug that is recognized with a huge global consumption rate [31]. IBP is rapidly excreted in form of various conjugates, e.g. hydroxy-IBP, carboxy-IBP, and carboxy-hydratropic acid [30,31], which not only have high acute toxicity, but are also suspected of endocrine disrupting activity in human and wildlife [31].

2.1.3. Naproxen (NPX)

NPX (6-methoxy-α-methyl-2-naphthalene acetic acid) is a non-steroidal anti-inflammatory drug widely used in mild-to-moderate pain relief and in treating osteoporosis, rheumatoid arthritis, menstruation and headaches [32]. The drug is additionally used in veterinary medicine in appreciable quantities [33]. Bioassay tests have shown that chronic toxicity of NPX is higher than its acute toxicity, and byproducts of photodegradation are more toxic than itself [34].

2.1.4. Ketoprofen (KTF)

KTF is a non-stereoidal anti inflammatory drug with analgesic and antipyretic effects and classified under acidic drugs because of the presence of a carboxylic group in its chemical structure [35]. The drug is metabolized mainly in conjugation with glucuronic acid (carboxylic acid), and excreted in the urine (85%) [36].

2.1.5. Mefenamic acid (MEF)

MEF is another non-steroidal anti-inflammatory drug classified under “anthropogenic” pharmaceuticals and personal care products [37]. It is a diphenylamine derivative, a pollutant class whose environmental relevance is of significance [38]. More than 50% of an ordinary dose of MEF is recovered in the urine mainly as conjugated metabolites [36].

2.2. Analgesic (AN) drugs

The following sub-sections cover the most outstanding properties and environmental behavior of some common ANs. A list of their physical/chemical characteristics and aquatic toxicity (if available) can be found in Table 2.1.

2.2.1. Paracetamol (PCT) or acetominophen (ACT)

PCT (European trade) or ACT (USA trade) is a mild analgesic that is commonly used in combinatory drugs for the relief of fever, headaches and some minor pains [39,40]. It is metabolized in the liver to the sulfate and glucuronide conjugates and excreted in the urine [41]. Hence, the source of PCT pollution in surface water is majorly sewage plant effluent [42], while that in soil and groundwater is caused by consumption of the drug for controlling brown tree snakes [43]. The most important side effect of PCT is impairment with the liver and kidneys via the formation of hepatoxic metabolites such as N-acetyl-p-benzoquinone imine [15,44].

2.2.2. Acetylsalicyclic acid or aspirin (ASA)

ASA is one of the most popular pain killers that is readily degraded to the more active salicyclic acid and two other metabo-

Table 2.1
Physical/chemical and aquatic toxicity parameters of some common ANs and AIs.

Drug	Molec. weight ($g\,m^{-1}$)	Vapor pressure (mm Hg)	Solubility ($mg\,L^{-1}$)	pK_a (20 °C)	$\log K_{ow}$	Henry's constant (at $m^3\,m^{-1}$)	EC_{50} ($mg\,L^{-1}$)	
							Daphnia	Algae
DCF	296.2 [17,48]	6.14×10^{-8} [50]	2.37 [48,50]	4.1–4.5 [50,52,53]	1.9–4.5 [50,54]	4.7×10^{-12} [54]	22–68 [47,55]	72 [47]
IBP	206.3 [48]	1.86×10^{-4} [50]	21 [48,50]	3.5–4.9 [17,52]	2.5–4.0 [47,50]	1.5×10^{-7} [54]	9–101 [47,55]	342 [47]
NPX	230.3 [17]	1.27×10^{-6} [23]	144 [23]	4.2–4.5 [17,53]	3.2–3.3 [52,53]	3.4×10^{-10} [54]	166.3 [47]	625 [47]
KTF	254.3 [17]	1.46×10^{-6} [23]	51 [23]	4.5 [35,53,54]	3.1 [35,53]	2.1×10^{-11} [54]	164 [55]	248 [55]
MEF	241.3 [35]	5.83×10^{-9} [23]	20 [51]	4.2 [35]	5.1 [35]	1.7×10^{-8} [51]	–	4.33 [23]
FNF	242.3 [35]	4.78×10^{-5} [23]	43.65 [23]	7.3 [35]	3.9 [35]	1.3×10^{-8} [23]	–	32 [23]
PCT	151.2 [49]	5.20×10^{-6} [50]	1400–2400 [50]	2.3 [50]	2.0 [50]	6.4×10^{-13} [23]	50 [46]	133 [56]
ASA	180.0 [11]	6.56×10^{-5} [23]	4600 [23]	3.5 [23]	1.2 [47]	1.9×10^{-9} [23]	88 [47]	107 [47]

lites (ortho-hydroxyhipuric acid and gentisic acid), all of which are easily eliminated in conventional sewage treatment operations [45]. It has been reported that water bodies containing ASA derivatives exhibit high toxicity to a wide range of aquatic organisms [46,47].

3. Occurrence and fate of ANs and AIs in the aquatic environment

World-wide investigations on contamination levels by anti-inflammatory drugs such as diclofenac (DCF), ibuprofen (IBP), ketoprofen (KTF), fenoprofen (FNF), mefenamic acid (MEF), indometacine and naproxen (NPX) have shown that individual concentrations are within $\mu g\,L^{-1}$ range in aquatic and surface water bodies, signifying the high proportion of municipal sewage effluents [1,7,31,57–59]. Hence, regardless of the efficiency of a wastewater treatment plant for PhACs removal from sewage, many of wasted AI/AN drugs and their metabolites are ultimately disposed into receiving water bodies. This is confirmed in Table 3.1, where a summary of regional variations in concentrations of ANs and AIs in influent and effluent of WWTPs and surface water is depicted. Note that in water, concentrations lie between 0.001 and 4.11 $\mu g\,L^{-1}$ [17,21,57,60], whereas in WWTP effluents the range is between 0.002 and 33.9 $\mu g\,L^{-1}$ [3,61,62]. Much lower levels in surface water than WWTP effluent is not only due to dilution effect, but also to the potential elimination by natural pathways such as hydrolysis, sorption, biodegradation and photolysis. However, there is also evidence that some PhAC residues (e.g. ANs/AIs) may leach into groundwater aquifers under recharge conditions, as they have been detected in ground water samples from water works downstream of municipal sewage treatment plants [1].

Research on the fate of anti-inflammatory and analgesic PhACs in receiving waters have shown that many of them and their metabolites undergo transformation via combinations of abiotic and biotic processes and direct or indirect photo-transformation [54,62,66]. The low volatility of these chemicals implies that their distribution in compartments of the environment is governed primarily by aqueous transport mechanisms, and by dispersal of the food chain. In surface waters, some of the residues may also undergo biotransformation, but the extent of conversion by abiotic reactions is still much larger [15].

Throughout the literature we reviewed, we found that hydrolysis is an insignificant pathway of elimination for environmentally relevant human drugs, and the majority of them is transformed by photo-and bio-degradation processes. We also found that those human drugs that are incapable of absorbing solar radiation (non-photolabile) are relatively biodegradable, and those that are poorly or partially biodegradable are photo-reactive. IBP was the only human drug (within those reviewed in this study) that is characterized by a high sorption coefficient; thus being transferred to the sediment as an additional elimination route [54]. Table 3.2 gives a brief summary of the literature on the major metabolic forms of some common ANs and AIs and their environmental fate by means of photo- and biodegradation processes.

4. Overview of ANs and AIs elimination in WWTPs

The removal of PhAC residues in municipal wastewater treatment plants is a major challenge in reducing the emission of micropollutants to the aqueous environment. As "the activated sludge process" (AcS) has been the most common unit operation in municipal WWTPs, the majority of research on treatability of PhACs in WWTPs is focused on this process and its relative efficiency.

The performance of AcS unit operations for AN and AI removal varies from "very poor" to "complete" break-down [67]. Although the mechanism is not clear, there is consensus on processes such as sorption, adsorption, sedimentation and biotransformation. Sorption occurs via hydrophobic or electrostatic interactions between the drugs and particulate matter or biomass. However, the process is ineffective for acidic drugs ($4.2 < pK_a < 4.9$) such as ASA, IBP, FNF, KTF, NPX and DCF that are highly hydrophilic and remain in the aqueous phase [18]. For such chemicals, biodegradation is expected to be a more potent elimination pathway in aerobic or anaerobic zones of the activated sludge. Nevertheless, common sewage treatment operations are found insufficient for complete or appreciable elimination of these pharmaceuticals from sewage water [42]. Some of them are reported to be released in a modified form after treatment in AcS units; such as for example IBP, which is largely (90%) transformed to its hydroxy and carboxy derivatives [18]. This is important because the metabolites may later be hydrolyzed and converted to the parent compound [68].

The efficiency of PhACs elimination in municipal WWTPs is also related to the seasonal conditions and design/operation of the secondary treatment plant (e.g. hydraulic retention time, sludge age) [15,18,21]. Accordingly, the efficiency is lower during winter months because of heavy rainfall and low water temperature, both of which lead to slower rates of biodegradation [31,58]. In addition, elimination of some chemicals like NPX, IBP and KTF sharply decreases at the end of October as a consequence of reduced atmospheric temperature (lower reaction rates) and increased health problems (cold, flue, rheumatic pains) that cause enhanced consumption of the drugs [54]. Such problems can be resolved by operation of the plant at longer hydraulic residence times for a period until the concentration of the drugs in the sewage becomes stable again. Another significant operation parameter in WWTPs is pH, the value of which is particularly critical for those pharmaceuticals characterized by increasing water-sludge partition coefficients with elevated acidity [69].

Table 4.1 summarizes total removal of some selected PhACs in various unit operations of municipal WWTPs in Europe. Note that almost complete elimination of IBP is possible by consecutive application of primary settling, activated sludge (AcS), and nitrification/denitrification (N/DeN) processes provided that the systems are operated at the most suitable conditions. Note also that com-

Table 3.1
Country-wise occurrence of ANs and AIs in surface water, and influents/effluents of WWTPs.

Drug	Surface water ($\mu g\,L^{-1}$)	WWTP influent ($\mu g\,L^{-1}$)	WWTP effluent ($\mu g\,L^{-1}$)	Country
DCF	0.020–0.150	–	0.100–0.700	Switzerland [63]
	–	–	0.25–5.45	France, Italy, Sweden [61]
	0.001–0.370	0.470–1.9	0.310–0.930	Switzerland [24]
	n.d–1.03	3.02	2.51	Germany [1]
	–	0.105–4.11	0.035–1.95	France [62]
	0.005–0.49	–	0.005–1.59	Germany [3]
	0.272	2.33	1.561	Germany [59]
	–	2.59	1.97	South Korea [46]
	0.15	3.5	0.81	Germany [5]
	0.02	3.1	1.5	Austria [5]
	0.020–0150	1.4	0.95	Switzerland [5]
	0.001–0.069	–	–	Germany [64], Italy [65]
IBP	0.010–0.400	–	0.100–1.5	Switzerland [61]
	–	–	0.02–7.11	France, Italy, Sweden [61]
	–	–	0.061–0.115	Romania [11]
	n.d–0.201	0.17–83.5	0.002–95	Italy [65], France [62]
	0.05–0.28	5.533	0.05–3.35	Germany [3], Germany [59]
	0.002–0.146	0.03	0.07	Germany [64], South Korea [46]
NPX	0.022–0.107	–	–	USA [57]
	0.010–0.400	–	0.100–3.5	Switzerland [63]
	0.001–0.032	–	0.29–5.22	Germany, France, Italy [64], Sweden [61]
	n.d–0.037	1.79–611	0.17–33.9	France [62], Italy [65], USA [57]
	n.d	0.732	0.261	Germany [59]
KTF	n.d–0.005	–	n.d–0.200	Switzerland [63]
	n.d–0.007	0.08–5.7	0.04–1.62	Italy [65], France [62]
	0.329	0.321	0.141–1.62	Germany, France, Italy [59], Sweden [61]
MFA	–	0.14–3.20	0.09–2.40	France [62]
	–	1.6–3.2	0.8–2.3	Switzerland [21]
PCT	n.d	5.53–292	n.d–0,001	France [5], USA [57]
		0.07	0.06	South Korea [46]
	0.005–0.066	–	0.140–1.480	Germany [2,64]
ASA	–	–	0.028–0.037	Romania [11]
	<0.05	–	0.05–1.51	Germany [3]
FNF	0.002–0.054	–	n.d–0.28	France, Sweden [61], Germany [64], Italy [65]

bined AcS and N/DeN followed by physicochemical treatment is very effective in getting complete elimination of KTF and NPX.

4.1. Relative fates of ANs and AIs in WWTPs

DCF as one of the most important PhAC in the water cycle is eliminated by 0–75%, and 21–50% of it occurs in AcS plants operated at very different anoxic-to-oxic ratios [2,18,78]. The relatively low efficiency is due to low biodegradability of the drug arising from the presence of –Cl and N–H functional groups that inhibit the rate of growth of sewage bacteria. However, considerable enhancement in biodegradability was reported by operating the plant at a sludge retention time of eight days or more [18].

IBP is the most efficiently eliminated PhAC (60–100%) in WWTPs, with 12–45% removal in primary sedimentation tanks [21,51,54]. The large variation in the efficiency is due to differences in the applied hydraulic retention times. Further elimination of the drug (>90%) is possible by extending the AcS system to allow nitrification and denitrification processes [51]. In general, the mechanism of IBP elimination involves transformation of the parent drug to its hydroxyl and carboxyl derivatives followed by rapid degradation of the latter. The hydroxyl derivative is, however, much more stable and may later be hydrolyzed to yield the parent compound again [18,79].

NPX is significantly removed (50–80%) in AcS units operated with N/DeN and further eliminated by sand filtration (SF) of the effluent [78]. In some cases, however, the WWTP effluent is found to contain a higher concentration of the parent drug than the influent, which is attributed to the presence of large concentrations of hydrolysable metabolites in the sewage system [17]. Elimination of NPX in AcS plants may be considerably improved by operating them at hydraulic retention times longer than 12 h [51].

The efficiency of WWTPs to remove KTF is very sensitive to external perturbations as rain, and the average range reported for conventional systems using primary settling, physicochemical and activated sludge processes is 15–98% [17,21]. Maximum elimination occurs during primary sedimentation of coagulation/flocculation effluent [21] and biotransformation starts only

Table 3.2
Metabolic forms and natural degradation pathways of AIs and ANs in water.

Drug	Metabolic forms in water	Environmental fate
DCF	4′-Hdroxy DCF, 4′5-dihydroxy DCF, 3′-hydroxy DCF, 5′-hydroxy DCF, 3′ hydroxy-4′-methoxy DCF [24]	Partial biodegradation [36] Photodegradation [54]
IBP	2-[4-(2-Hydroxyl-2methylpropyl)phenyl] propionic acid, 2-[4-(2-carboxypropyl) phenyl]propionic acid, carboxy-hydratropic acid (carboxy-HA) [7,24,25,27]	Biodegradation [31,54] Sedimentation
NPX	NPX, 6-O-desmethylated metabolite, DM-naproxen [70]	Biodegradation [54] Photodegradation [71]
KTF	2-(3-Benzoylphenyl)-propanoic acid, 2-[3-(3hydroxybenzoyl)phenyl]-propanoic acid, 2-[3-(4hydroxy benzoyl) phenyl]-propanoic acid, 2-[3(hydroxy(phenyl) methyl)phenyl]-propanoic acid [72]	Partial biodegradation [46] Photodegradation [71]
MEF	Alkali-labile ester glucuronides [73]	Partial biodegradation [36]
PAC	Sulfate conjugates, paracetamol cysteine, mercapturate [7]	Biodegradation [72]
ACA	ACA, salicyclic acid, ortho-hydroxy-hippuric acid, gentisic acid [7]	Biodegradation [7]

Table 4.1
Region-wise wastewater treatment operations for the elimination of ANs and AIs.

Drug	WWTP influent ($\mu g\,L^{-1}$)	WWTP effluent ($\mu g\,L^{-1}$)	Removal (%)	Unit operations	Region
DCF	3.02	2.51	17	Conventional WWTP [74]	Berlin (Germany)
			23–60	AcS, P removal [17]	Aura, Tampere, Harjavalta (Finland)
			9–25	AcS/N/DeN/phosphate removal [17]	Helsinki, Seinajoki, Turku (Finland)
	0.6–0.8	0.01–0.2	75	1° Settling, AcS [75]	Rio de Janeiro (Brazil)
		0.68–5.45		1° settling, AcS [43]	France, Italy, Greece[a]
	0.11	0.9	18	AcS, disinfection [76]	Baltimore (USA)
IBP		0.05–7.11		1° Settling, AcS [43]	France, Italy, Greece[a]
			78–100	AcS/phosphate removal [17]	Aura, Tampere, Harjavalta (Finland)
			92–99	AcS/N/DeN/phosphate removal [17]	Helsinki, Seinajoki, Turku, Finland
		0.37–3.4		1° Settling, AcS, 2°settling [42]	Frankfurt (Germany)
			60–70	1° settling, AcS, 2° [60]	Galicia (Spain)
			86	1° Settling, AcS/N/DeN, 2° settling [77]	S. England
	0.2–0.4	0.01–0.2	75	1° Settling, AcS [75]	Rio de Janeiro (Brazil)
			62–79	AcS, ppt with $FeCl_3$ [21]	on Lake Geneva (W. Switzerland)
NPX		0.081–0.106		1° Settling, AcS, 2° settling [57]	Ontario (Canada)
		1.12–5.22		1° settling, AcS [43]	France, Italy, Greece[a]
			55–98	AcS/phosphate removal [17]	Aura, Tampere, Harjavalta (Finland)
			69–94	AcS/N/DeN/phosphate removal [17]	Helsinki, Seinajoki, Turku (Finland)
		0.3–0.52		1° Settling, AcS, 2° settling [42]	Frankfurt (Germany)
	0.4–0.6	0.01–0.2	78	1° Settling, AcS [75]	Rio de Janeiro (Brazil)
			50–80	AcS/N/DeN, sand filtration [78]	Kloten/Opfikon (Switzerland)
KTF		n.d–1.62		1° Settling, AcS [43]	France, Italy, Greece[a]
			51–100	AcS/phosphate removal [17]	Aura, Tampere, Harjavalta(Finland)
			63–98	AcS/N/DeN/phosphate removal [17]	Helsinki, Seinajoki, Turku (Finland)
			15–72	AcS, ppt with $FeCl_3$ [21]	on Lake Geneva (W. Switzerland)
			69	1° settling, AcS [75]	Rio de Janeiro (Brazil)
MEF			91	1° Settling, AcS/N/DeN, 2° settling [77]	S. England
			28–74	1° Settling, AcS, ppt with $FeCl_3$, 2° settling [21]	on Lake Geneva, W. Switzerland
			19–69	AcS, ppt with $FeCl_3$ [21]	on Lake Geneva (W. Switzerland)
ASA		0.22–1.5		1° Settling, AcS, 2° settling [42]	Frankfurt (Germany)
FNF		n.d–0.28		1° Settling, AcS [43]	France, Italy, Greece[a]
PCT			91	1° Settling, AcS/N/DeN, 2° settling [77]	S. England
	0.96	n.d	>99	AcS, disinfection [76]	Baltimore (USA)
			98	1° Settling, AcS, 2° settling [42]	Frankfurt (Germany)

[a] Data from WWTPs in Chatillon-sur Chalarone and Pierre Benite (France), Iraklio (Greece), Latina, Rome and Naples (Italy).

after 28 days of sludge retention time in the activated sludge reactor [59].

The data on the elimination of MEF by standard WWTP operations are controversial. Some researchers reported that the drug is stable and remains nearly at the same concentration in the plant influent, effluent and downstream [80]; while others found that physicochemical and bio-treatment operations may remove 21–36% and 30–50% of the drug, respectively [21].

PCT is relatively stable in activated sludge processes [79], but 99% elimination is possible if AcS treatment is applied after preliminary and final clarification and is extended to N/DeN [42,81]. On the other hand, some researchers have observed almost complete removal of PCT residues in non-conventional lagoon treatment operations operated with hydraulic detention times of 16.5–48 days [82].

ASA is completely biodegradable in laboratory test systems, but removed by 80–98% in full-scale WWTPs, where considerable fraction of the metabolites is also eliminated [42,57,83]. Most important of all, the effluent containing trace quantities of the primary derivative-salicyclic acid is non-toxic to aquatic organisms [17].

4.2. Elimination of AIs and ANs in WWTPs integrated with advanced processes

Integration of WWTPs with advanced treatment processes is a promising strategy for rendering complete elimination of PhAC residues, provided that the most proper treatment units or combinations thereof are applied. Relative effectiveness of some basic or advanced processes such as sand filtration (SF), ozonation, UV irradiation and activated carbon adsorption (ACA) applied to AcS treatment effluent after sedimentation are summarized in Table 4.2.

Among all advanced processes tested, ozonation was found the most effective for complete disappearance of most ANs and AIs in secondary clarification effluent [52,86]. The reactivity of these chemicals with ozone is related to the functional groups in their structure as well as the operating conditions. Some researchers reported that lab-scale treatment of AcS effluent with 3 $mg\,L^{-1}$ O_3 for 27 min destroys more than 68–99% of NPX, 54–99% of MEF and 52–93% of KTF residues [52,86]. The degradation of IBP and FNF under the same conditions was highly variable or poor, mainly because of low concentrations of the drugs in AcS effluent and the unfavorable structural properties that lowered their reactivity with ozone. An example to such properties is the presence of a carboxylic group attached to an aromatic ring, which due to the e-withdrawing character depresses the reactions of ozone with the ring carbons. On the other hand, the presence of e-donating functional groups such as –OH facilitates the attack of ozone to aromatic rings, which explains the high degradability of phenolic PhACs by ozonation. In addition, the reactivity of sulfidic groups with ozone is much larger than that of protonated amino groups [88], explaining why DCF is efficiently degraded in neutral pH but not so in acidic solutions. Substantial elimination of NPX by ozonation is also a matter of structural character such as a naphthalene moiety, which is highly reactive with molecular ozone ($k = 3.0 \times 10^4\,M\,s^{-1}$). Hence, a lower but moderate degree of MEF elimination can be explained by the opposing effects of an e-withdrawing (benzoic acid) and an e-donating group in its structure (dimethylbenzene) [85].

The above discussion highlights the importance of the operation pH on the efficiency of ozonation on the elimination of AI/AN chemicals in WWTP effluents. If a compound is not reactive with ozone,

Table 4.2
Relative fractions of ANs and AIs removal in conventional and tertiary treatment units of WWTPs.

Process/condition	Removal (%)							
	DCF	IBP	NPX	KTF	MEF	PCT	ASA	FNF
1° Settling [21][a]	–	12–45	–	3–12	4–16	–	–	–
Coag($FeCl_3$)/Floc/Settling [21][a]	–	–	–	5–36	21–36	–	–	–
AcS [42,21,75,84][a]	21–50	20–43	–	8	30–50	–	80–98	–
Bio-membrane (of pretreated eff) [42,60,84]	23–87	>90	36–99	50–99	75	99	–	–
SF (of AcS eff) [85]		30–96	0–48	–	0–99	–	–	42
Ozonation (of ACs eff) [86,85,87][a]	96	0.75–62	68–99	52–93	54–99	–	85–95	1–16
UV irradiation (250 kJ cm^{-2}) [87][a]	29	–	–	–	–	–	–	–

[a] Pilot scale.

such as IBP ($k = 9.1\ M\ s^{-1}$), it is likely to react strongly with OH radicals ($OH^{\bullet}$), which are highly abundant when the process is carried out at alkaline pH. This is why ozonation at acidic or neutral pH is ineffective for compounds that react slowly with ozone, but that at highly alkaline pH is very effective as in the case of IBP, which reacts strongly with $OH^{\bullet}$ ($k = 7.4 \times 10^9\ M\ s^{-1}$). Thus, the observed variability of IBP elimination in Table 4.2 by ozonation of sewage treatment plant effluents is the consequence of variations in the operation pH.

5. Overview of AN and AI elimination in drinking water treatment plants (DWTPs)

The main purpose of DWTP in the past was to remove natural organic matter, hardness and microorganisms from the target source. As the presence PhACs in drinking water has lately been a significant health concern, elimination of such pollution has now become a major challenge, particularly if the source is effluent-dominated surface water. Fortunately, a conventional coagulation process (CG), which is a counterpart of most DWTPs can effectively remove pharmaceuticals with $\log K_{ow} > 5$ [89]. On the other hand, CG is effective for negatively charged anti-inflammatory drugs only if the coagulant is made of trivalent cations that can easily neutralize the charge on the parent drug [90]. Positively charged ionic drugs are more easily eliminated by adsorption (ADS) on particles and by flocks that form upon electrostatic interactions [53]. However, sand filtration (SF), which is also a common unit process in DWTPs, renders no significant removal of AN and AI residues due to the low sorption properties and high persistence of most PhACs in water [15]. It is reported that a rapid sand filter designed to remove excess flocks after sedimentation can eliminate an additional 10% of DCF, IBP, NPX and KTP [53]. Oxidative degradation of PhACs in disinfection units of DWTPs such as chlorination, ozonation, and UV irradiation is limited by the functional groups and reactivity of the drugs with the oxidant. For example, DCF and NPX can be almost totally eliminated by chlorination, while IBP is only transformed to a variety of intermediate products [91]. DCF and NPX are also eliminated considerably by ozonation (>95%) owing to the amine functional groups in their structure [92–94], while IBP is not unless the reaction is run at acidic pH to promote the generation of OH radicals, which are by far more reactive than ozone. Unfortunately, the intensity of UV irradiation applied commonly in disinfection units of DWTPs is too low to render photo-transformation of even the UV-absorbing PhACs [95]. It was found that complete elimination of some PhAC resides (e.g. DCF) by UV treatment is possible only under extensive irradiation at pH 6–8 and at an intensity that is at least 25-fold larger than that applied in DWTPs [87].

Finally, advanced treatment of DWTP effluent in granular activated carbon units (GAC) has been found very effective, particularly for the elimination of non-ionic and hydrophobic pharmaceuticals with high K_{ow} [89,92,96,97]. The elimination of PhAC residues containing carboxyl groups (e.g., DCF, IBP and NPX) is less effective in GAC units due to deprotonation of the acidic functional group [95,98]. Relative fractions of PhAC elimination in some unit operations of DWTPs are summarized in Table 5.1.

6. Advanced oxidation processes (AOPs) as viable options for destroying PhAC residues in WWTP and DWTP effluents

AOPs are based on the in situ generation of very powerful oxidizing agents as the hydroxyl radical, which is highly reactive with a wide range of organic compounds regardless of their concentration [100]. Unlike many other oxidizing species, $OH^{\bullet}$ is nonselective and readily attacks most organic compounds to convert them to less complex and less harmful intermediates. At sufficient contact time and proper operation conditions, AOPs may mineralize all organic carbon to CO_2, which is the most stable end product of chemical oxidation.

The most important advantage of AOPs over chemical/biological processes is that they are environmental-friendly or "green" as they neither transfer pollutants from one phase to the other as in chemical precipitation, adsorption and volatilization; nor produce

Table 5.1
The fate of most common ANs/AIs in unit processes of DWTPs (1–4); elimination in effluents or fresh water surface by photolysis (5).

Process/Condition	Fate or removal (%)			
COMPOUND	DCF	IBF	NPX	PCT
1. Coagulation (CG)				
$Fe_2(SO_4)_3$ [48]	66	<20		
$Al_2(SO_4)_3$ [48]		<20		
2. Sand filtration (SF) (of CG effluent) [53]	10	10	10	
3. GAC [95,97]	39	16	52	72–93
4. Disinfection (DIS)				
Cl_2 (3–3.8 mg L^{-1}) [94]	80–95	0	80–95	
O_3 (1.2–1.5 mg L^{-1}) [53,92]	>99	92	75	
5. Photolysis (surface water)				
Solar	4			
254 nm (0.4 kJ m^{-2}) [35,99]	97–100		29	

Table 6.1
Most common AOPs for water and wastewater treatment [104].

Advanced oxidation processes	
Photochemical	Other
UV oxidation	Ozonation
UV/H_2O_2	Fenton
UV/O_3	Ultrasound (US)
$UV/H_2O_2/O_3$	US/H_2O_2, US/O_3
UV/ultrasound	Electrochemical oxidation
Photo-Fenton	Supercritical water oxidation
Photocatalysis	Ionizing radiation
Sono-photocatalysis	Electron-beam irradiation
Vacuum UV	Wet-air oxidation
Microwave	Pulsed Plasma

massive amounts of hazardous sludge as in bio-chemical processes [101]. Application of single or combined AOPs before or after bio-treatment operations may considerably decrease the concentration of PhAC residues in effluents of DWTPs and WWTPs via mineralization of organic carbon and enhancement of biodegradability, respectively. Note that AOPs are further important for the destruction of multi-resistant bacteria that may develop in wastewater bodies containing very low concentrations of PhACs [102,103].

The most common AOPs developed for water and wastewater remediation are listed in Table 6.1. Some of these processes are commercially available, e.g. UV photolysis, which has more than 3000 applications in Europe and a large number in the US [104]. Others such as Fenton's, super-critical oxidation, ionizing radiation and combinations of H_2O_2, O_3 and UV have all been used at full scale. The only AOPs that have no full scale applications so far for water remediation are photocatalysis and ultrasound.

Klavariotti et al. have recently published an extensive review on the degradability of a wide range of PhACs and some endocrine disrupting compounds in water by various AOPs [105]. The following sections, cover a more concise review of the literature on AOPs applied to sufficiently low concentrations of AI and AN chemicals (DCF, IBP, NPX, KTF, FNF and PCT), with emphasis on process details and relative efficiencies. A summary of the discussion is also given in Table 6.2.

6.1. Ozonation

Ozonation has already been discussed in previous sections as an advanced treatment option that demonstrated high effectiveness in DWTP and WWTP effluents for destroying PhAC residues. The mechanism of destruction for phenolic PhACs (e.g. PCT, NPX) is based on ionic/radical reactions with byproducts such as hydroquinone, 1,2,4-trihydroxybenzene, 2-hydroxy-4-(N-acetyl) and aminophenol [43,121]. It is important to note that the degradability of such drugs increases with increasing pH, due to higher reactivity of phenol with hydroxyl radicals than with molecular ozone [113,122]. For most pharmaceuticals, the reactive species correspond to the predominant species in the pH range from 5 to 10 [52]. This is why DCF reacts particularly faster with ozone than most of other amine-containing PhACs that have quite low values of pK_a (<5) [52].

The most remarkable advantage of ozonation is that it increases the biodegradability of PhAC residues in water appreciably when applied as a pretreatment option [112]. The process is also effective for remediation of groundwater contaminated with low concentrations of AI and AN chemicals, but less so in fresh water and WWTP effluent, due to the reactivity of dissolved organic matter and background constituents with $OH^\bullet$ in the latter two [113]. Note also that ozonation is not effective for toxicity reduction and mineralization, except with the presence of H_2O_2, which may slightly increase TOC elimination, but not toxicity [43].

Since the rate of oxidation of water constituents by ozone is limited by the mass rate of gaseous O_3 transfer to solution, the efficiency of ozonation can easily be improved by promoting the rate of mass transfer and decomposition of ozone. A promising method for this is catalytic ozonation, which involves adsorption of the gas on a catalytic surface to initiate surface reactions. Most common catalysts used in water remediation by ozone are TiO_2 and activated carbon, both of which are reported to provide more than 90% AIs and ANs removal at optimized laboratory conditions [114,115].

6.2. Combined processes

Combined homogeneous AOPs such as UV/H_2O_2, O_3/UV, Fe^{2+}/H_2O_2 (Fenton) and $O_3/UV/H_2O_2$ are also promising options for enhancing the elimination and mineralization of PhAC residues in water. In all, the achievement is the outcome of excess $OH^\bullet$ production by photolysis (e.g. of H_2O_2) and/or hydrolysis (e.g. of FeO^{2+}) of the reagents. The following sub-sections cover basic information and research notes on the degradation of selected AN/AI chemicals by UV/H_2O_2, Fenton and UV-Fenton (photo-Fenton) processes.

6.2.1. UV/H_2O_2

UV/H_2O_2 is one of the most viable AOP technique via its potential for photolytic cleavage of all H_2O_2 to $OH^\bullet$ at a stoichiometric ratio of 1:2, provided that the light source has sufficient emission at 190–200 nm. The process is preferable to ozonation, because it is less sensitive to the nature and concentration of background species. Kim et al. have reported 90% degradation of a large number of AIs and ANs (e.g. KPF, FNF, MEF, PCT, NPX, DCF) in lab-scale operations using 9.32 kJ m^{-2} UV (medium pressure lamp), 7.8 mg L^{-1} H_2O_2 and drug concentration range of 3.0×10^{-6} to 120×10^{-6} mg L^{-1} [116]. The use of low pressure halogen light sources at the same light intensity was found to be less efficient [117] due to lower absorption capacity of H_2O_2 at 254 nm. It was also found that the addition of excess H_2O_2 did not contribute significantly to the reactions [118].

6.2.2. Fenton and UV/fenton

Fenton oxidation is recognized as the most effective pretreatment method for pharmaceutical wastewater due to its capacity for extensive detoxification and biodegradability enhancement [123,124]. The process is based on the production of $OH^\bullet$ from Fenton's reagent (Fe^{2+}/H_2O_2) at acidic pH, Fe^{2+} acting as the homogeneous catalyst. A further advantage of Fenton process is the formation of ferric-hydroxy complexes that promote coagulation of suspended solids after oxidation reactions [67]. A full-scale pharmaceutical wastewater treatment plant using Fenton process as primary treatment and sequencing batch-type AcS process as secondary is reported to provide 98% COD and 98% BOD_5 removal, which allowed complying with regional effluent discharge limits [125].

Combined operation of Fenton oxidation with UV irradiation, or the so-called "photo-Fenton process" inherently produces more $OH^\bullet$ and is therefore more effective than the dark method. A photo–Fenton process employed in a parabolic collector solar pilot plant (30 W m^{-2}) was found to provide partial degradation, mineralization and precipitation of DCF upon a considerable decrease in pH [113,119]. Enhanced precipitation by increased acidity is due to the weakly acidic character of the drug and the insolubility in protonated form. Mineralization of DCF is also related to its solubility equilibrium, as verified by the increase in dissolved organic carbon content (DOC) of the solution shortly after reaction (via the formation of soluble intermediates) [119]. In another study, it was also found that complete mineralization of the drug is possible using a 400-W low pressure Hg lamp (254 nm) and an activation energy of 16 kJ mol^{-1}, which signifies the role of energy-requiring reac-

Table 6.2
Efficiency of lab-scale AOPs for the degradation and mineralization of AI/AN chemicals.

Process System parameters, C_0, t	Degradation (mineralization) %						Source
Compound	DCF	IBP	NPX	PCT	KTF	FNF	
1. US							
20 kHz, 80 mg L^{-1}, 60 min	>55						[106]
213 kHz, 18.5 mg L^{-1}, 180 min		(16)					[107]
216 kHz, 50 mg L^{-1}, 60 min	87						[108]
300 kHz, 21 mg L^{-1}, 60 min		98 (8)					[109]
617 kHz, 50 mg L^{-1}, 60 min	>90						[108]
850 kHz, 50 mg L^{-1}, 60 min	24						[108]
861 kHz, 9.5 mg L^{-1}, 60 min	>90 (23)						[110]
574 kHz, 25 mg L^{-1}, 240 min				95			[56]
574 kHz, 25 mg L^{-1}, 480 min				100 (39)			[56]
574 kHz, 150 mg L^{-1}, 240 min				56			[56]
2. O_3/US and sonocatalysis							
20 kHz, 31 g h^{-1} O_3, 80 mg L^{-1}, 40 min	(35)						[106]
213 kHz, 1 g TiO_2 L^{-1}, 18.5 mg L^{-1}, 10 min		23					[107]
213 kHz, 20 mg Fe^{2+} L^{-1}, 19 mg L^{-1}, 15 min		45					[107]
861 kHz, 0.09 mg L^{-1} NPI[a], 9.5 mg L^{-1}, 90 min							[110]
300 kHz, Xe-lamp, 100 mg Fe^{2+} L^{-1}, 10 mg TiO_2 L^{-1}, 8 mg L^{-1}, 240 min		(92)					[109]
3. Ozonation and catalytic ozonation							
31 g O_3 h^{-1}, 80 mg L^{-1}, 40 min	(22)						[106]
36 g O_3 h^{-1}, 32 mg L^{-1}, 90 min	(32)						[111]
220 mg O_3 L^{-1}, 200 mg L^{-1}, 30 min	>99						[112]
20 mg O_3 L^{-1}, 30 mg L^{-1}, 120 min	(40)						[114]
5 mg O_3 L^{-1}, 0.23 mg L^{-1}			>9				[113]
38–40 mg O_3 L^{-1}, 15 mg L^{-1}, 120 min			(50)				[115]
38–40 mg O_3 L^{-1}, 1 g TiO_2 L^{-1}, 15 mg L^{-1}, 120 min			(62)				[115]
1 g O_3 h^{-1}, 55 mg Fe^{+2} L^{-1}, 157 mg L^{-1}, 240 min				(83)			[99]
1.54 g O_3 h^{-1}, 760 mg L^{-1}, 20 min				100			[43]
4. Photolysis (UV/H_2O_2)							
10 W – Lp-Hg lamp, 0.05 mg L^{-1} as TOC, 10 min	>90		>50	>60	> 90	> 70	[116]
17 W – Lp-Hg lamp, 61.2 mg H_2O_2 L^{-1}, 32 mg L^{-1}, 90 min	(39)						[111]
1 kW – Mp lamp (200–300 nm), 10 mg H_2O_2 L^{-1}, 1.0 mg L^{-1}			52				[117]
17 W – Lp-Hg lamp, 175 mg H_2O_2 L^{-1}, 150 mg L^{-1}, 90 min				(39)			[111]
Lp Hg lamp (254 nm), 700 mg H_2O_2 L^{-1}, 150 mg L^{-1}, 4 min				100 (40)			[43]
5. Dark and light fenton							
Fe^{2+}/H_2O_2 = 1:50, 1.03 mg L^{-1}			100				[118]
1 kW – Mp lamp (290–400 nm), 1.2 mg H_2O_2 L^{-1}, 6.66 mg L^{-1} Fe^{2+}, 179 mg L^{-1}, 120 min			80 (40)				[109]
30 Wm^{-2} solar UV (320–400 nm), Fe^{2+}/H_2O_2 = 1:100, 50 mg L^{-1}, 100 min	100 (100)						[119]
6. Photocatalysis							
30 W m^{-2} solar UV, 200 mg TiO_2 L^{-1}, 50 mg L^{-1}, 200 min	(100)						[119]
15 W – Lp Hg lamp, 800 mg TiO_2 L^{-1}, 302 mg L^{-1}, 80 min				>95			[120]
450 W – Xe Lamp, 1 g TiO_2 L^{-1}, 18.5 mg L^{-1}, 180 min		(88)					[107]

[a] Nanoparticles of super-paramagnetic iron.

tions in the overall degradation process other than radical chain reactions [118].

6.3. Photocatalysis

Photocatalytic reactions in the presence of photo-generated holes of semiconductors (oxides of Ti, Cu, Zn, etc.) have been thoroughly investigated during the last few decades for water remediation, particularly for eliminating recalcitrant compounds. The process is based on the excitation of semiconductor metal surfaces by near UV irradiation to generate active oxygen species on the crystals.

The electronic structure of most semiconductors is comprised of a highest (the valence band) and a lowest occupied band (the conductance band). Illumination of the surface of such materials by energies larger than the band-gap energy produces electron–hole pairs, h^+e^-, which either recombine to release heat or hit the catalyst surface to react with surface-adsorbed species [126]. The phenomenon is simplified in the following scheme for a surrogate semiconductor S-C:

$$\text{S-C} + h\upsilon \rightarrow e^- + h^+ \quad (1)$$

$$h^+ + H_2O \rightarrow OH^\bullet + H^+ \quad (2)$$

$$h^+ + OH^- \rightarrow OH^\bullet \quad (3)$$

The majority of research on photocatalytic decomposition of PhACs is carried out with TiO_2 and focused on the impact of initial solute concentration, semiconductor dose, pH and optimal solution temperature. The following discussion covers a critical review of the literature on TiO_2-catalyzed photo-decomposition of AI/AN chemicals in water.

The efficiency of TiO_2-based photocatalytic processes is closely related to the initial drug concentration and semiconductor dose. At small-to-moderate levels of TiO_2 (104–502 mg L^{-1}) the degradation depends only on the initial solute concentration, while at higher levels it varies proportionally with the amount of TiO_2 and the number of active sites on it [127,128]. The presence of excess TiO_2 reduces the extent of elimination; thus optimization of the catalyst dose is very important to avoid superfluous catalyst con-

centrations and ensure complete absorption of radiation photons [129].

Elimination of PCT from wastewater and drinking water samples by TiO_2-photocatalysis is highly efficient at pH 9.0 (no toxic byproduct formation) although the drug is poorly adsorbed in the dark due to its poor chelating ability with Ti [119,128]. At higher pH, degradation is less effective due to electrostatic repulsions between the catalyst surface and the phenolic moiety, which exists as phonolate [128]. It was also found that the extent of degradation is further reduced by high initial concentrations of the drug, which leads to a competition for active reaction sites and photons that lower the rate of oxidant generation [120].

The process was found highly effective for detoxifying and mineralizing very small concentrations of some drugs (e.g. DCF) by using low catalyst and low radiation doses [130]. At higher TiO_2 loadings and DCF concentrations, however, 20-min and 40-min treated samples were found to be more toxic than untreated ones, indicating relatively long life times of the intermediate products (e.g. hydroxyl- and bi-hydroxyl derivatives) [127].

6.4. Sonolysis

Generation of hydroxyl radicals in water by ultrasonic pressure waves is based on the formation, growth and violent implosion of cavitation bubbles to release very extreme local conditions (5000 K, 2000 atm) that lead to high energy chemistry [131,132]. The literature on sonochemical degradation of PhACs is limited with studies on DCF, IBP, PAC and some mixtures in synthetic or real WWTP effluents to assess the impact of operation parameters such as frequency, concentration, pH, dissolved gases, ultrasonic power, radical scavengers and solid catalysts. The following discussion covers a critical review of lab-scale studies on ultrasound-assisted elimination of some AI/AN chemicals in deionized water or in effluents of WWTPs.

Hartman et al. found that irradiation of a 90 mg L^{-1} synthetic DCF solution successively by 216, 617 and 850 kHz at 90 W for 1-h provides at least 87%, 90% and 24% degradation of the drug, respectively [108]. Reduced efficiency at high frequency ultrasound can be attributed to exceeding of the threshold frequency that is specific of the experimental system [133]. In accordance, sonication of DCF (C_0 = 30 μM) at 577, 861 and 1145 kHz showed that maximum degradation was obtained at 861 kHz and minimum at 1145 kHz [110]. The formation of hydroxylated derivatives, phenylacetic acid, dichloroaniline and dichlorophenol in the work of Hartman et al. (2008) during early sonolysis (30-min) was explained by the dominance of $OH^•$-mediated reactions in the degradation process, and that of carboxylic acid and HCl after extended sonication (60-min) by the mineralization of the intermediates.

Naddeo et al. have reported that optimum conditions for DCF elimination in urban wastewater treatment effluent (UWTP) by 20 kHz ultrasound (US) are low pH and air sparging, and the rate of $OH^•$-mediated degradation of the compound speeds up with increases in the initial concentration. The authors reported 15% biodegradability enhancement in sonicated UWTP effluent spiked with a mixture PhACs that contained DCF, amoxicillin and carbamazepine [134].

Comparison of ozonation and sonication for mineralization of DCF at optimal conditions showed that sonication was more effective (30% and 36%, respectively), and combination of the two was only slightly better (39%) [106]. The observed enhancement in combined US/O_3 application is due to increased rate of ozone mass transfer and excess $OH^•$ production by thermal decomposition of O_3 [135]. A simplified reaction scheme is as the following [135]:

$$O_3 + H_2O \rightarrow 2HOO^• \quad (4)$$

$$O_3 + HOO^• \rightarrow OH^• + 2O_2 \quad (5)$$

$$H_2O +))) \rightarrow H^• + OH^• \quad (6)$$

$$O_3 +))) \rightarrow O_2(g) + O(^3P)(g) \quad (7)$$

$$O(^3P)(g) + H_2O(g) \rightarrow 2OH^• \quad (8)$$

Finally, it was shown that sonochemical degradation and mineralization of DCF (C_0 = 30 μM) at 861 kHz was considerably accelerated by the addition of soluble and insoluble Fe-species such as Fenton's reagent and paramagnetic Fe-oxide nanoparticles [110]. The positive influence of solid particles was also highlighted by Hartmann et al, who attributed the effect to the larger surface area of asymmetric cavity bubbles that accelerated the rate of reaction at the gas-liquid interface [108].

Degradation of IBP by 300 kHz US in synthetic solutions showed that the rate of reaction is limited by the availability of $OH^•$ and increases with increased solute concentrations (2–21 mg L^{-1}), air sparging and acidity ($pH < pK_a$) [109]. It was also found that 30 min sonication at optimized conditions rendered complete IBP removal and 35% biodegradability enhancement. Hybrid advanced oxidation processes involving US provided more promising results in terms of full elimination and mineralization of IBP, as 92% TOC removal was obtained after combined TiO_2/Fe^{2+}/US (300 kHz) application for 4-h [136]. Similarly, the decomposition of IBP increased synergistically by combined TiO_2/US and Fe^{3+}/US (213 kHz) applications, while the increase in mineralization was synergistic only in Fe^{3+}/US combination and additive in that of TiO_2/US [107]. Larger efficiency of Fe^{3+}/US process for mineralization was attributed to the formation of photoreactive complexes between Fe^{3+} and carboxylic byproducts that formed after extended contact.

The literature on sonochemical degradation of PCT is limited to a single study, which showed that maximum yield was obtained by 240-min sonolysis of the drug (C_0 = 25 mg L^{-1}) at 574 kHz and 32-W providing complete conversion and 39% mineralization of the drug [56]. The authors reported that the fraction of degradation increased with reduced solute concentrations, enhanced power inputs and reduced quantities of $OH^•$ scavengers. The efficiency was further improved by the addition of an optimum dose of H_2O_2, which provided excess $OH^•$ upon decomposition in gaseous cavity bubbles.

7. Conclusions

The occurrence of pharmaceutical residues in water and their treatability in water and wastewater treatment plants have been of significant scientific and public concern during recent years, due to their uncontrolled discharge, relative persistence to biodegradation and the detrimental effects on non-target organisms. The study has covered a critical review of the literature on the presence, fate, environmental impacts and treatability of a major class of pharmaceuticals, namely anti-inflammatory (AI) and analgesic (AN) drugs, which being available without prescription are consumed in huge quantities in the northern hemisphere. A brief outline of the conclusions is the following:

1. AI/AN drugs are readily excreted with the urine and exist in sewage water as unchanged or in form of the metabolites. Influents of WWTPs may contain concentrations as high as 200–600 μg L^{-1} (e.g. NPX, PCT), which can only be reduced to 25–35 μg L^{-1} after treatment. The extent of treatability of AI/AN chemicals in conventional WWTPs is operation-dependent, but is expected to follows the order: MEF > IBP > NPX > KTF > ASA > PCT > DCF. On the other hand, the concentration of AI/AN residues in surface water bodies receiving WWTP effluents may range between 0.4 and 0.5 μg L^{-1} (e.g.

DCF, IBP, NPX), a range which may cause chronic toxicity in some aquatic organisms or undesired health effects in humans upon prolonged exposure.
2. The major natural degradation route for AI/AN residues in water is photolysis (e.g. DCF, NPX, KTF), and some may undergo slow biodegradation (e.g. IBP, NPX, PAC, ASA) that is only partially complete after several weeks. Adsorption on sediments is a minor route of elimination, but is significant for IBP.
3. Treatability of AN/AI residues in fresh water reservoirs varies with the type of process, the operation parameters and properties of the contaminant. Generally, the most effective unit process is disinfection by Cl_2 and O_3, which may destroy 95–100% of some residues (e.g. DCF, NPX), respectively.
4. Further treatment for complete destruction and mineralization is possible using advanced oxidation processes; however the attempts so far have remained in lab-scale studies only, and still require more research before applicability. The most effective AOP methods for ultimate mineralization of very low concentrations of AI/AN chemicals are combinations thereof such as sonolysis/sonocatalysis, ozonation/catalytic ozonation, photolysis and photo-Fenton processes.

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