Occurrence and Elimination of Pharmaceuticals During Conventional Wastewater Treatment

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Abstract Pharmaceuticals have an important role in the treatment and prevention of disease in both humans and animals. Since they are designed either to be highly active or interact with receptors in humans and animals or to be toxic for many infectious organisms, they may also have unintended effects on animals and microorganisms in the environment. Therefore, the occurrence of pharmaceutical compounds in the environment and their potential effects on human and environmental health has become an active subject matter of actual research.

There are several possible sources and routes for pharmaceuticals to reach the environment, but wastewater treatment plants have been identified as the main point of their collection and subsequent release into the environment, via both effluent wastewater and sludge. Conventional systems that use an activated sludge process are still widely employed for wastewater treatment, mostly because they produce effluents that meet required quality standards (suitable for disposal or recycling purposes), at reasonable operating and maintenance costs. However,

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this type of treatment has been shown to have limited capability of removing pharmaceuticals from wastewater. The following chapter reviews the literature data on the occurrence of these microcontaminants in wastewater influent, effluent, and sludge, and on their removal during conventional wastewater treatment.

Keywords Pharmaceuticals • Removal • Sludge • Wastewater

**Contents**

Abbreviations

HRT   Hydraulic retention time
NSAIDs Nonsteroidal anti-inflammatory drugs
SRT   Solid retention time
WWTP   Wastewater treatment plant

1 Introduction

Pharmaceuticals are a large and diverse group of compounds designed to prevent, cure, and treat disease, and improve health. Hundreds of tons of pharmaceuticals are dispensed and consumed annually worldwide. The usage and consumption are increasing consistently due to the discoveries of new drugs, the expanding population, and the inverting age structure in the general population, as well as due to expiration of patents with resulting availability of less expensive generics [1]. After intake, these pharmaceutically active compounds undergo metabolic processes in organisms. Significant fractions of the parent compound are excreted in unmetabolized form or as metabolites (active or inactive) into raw sewage and wastewater treatment systems. Municipal sewage treatment plant effluents are discharged to water bodies or reused for irrigation, and biosolids produced are reused in agriculture as soil amendment or disposed to landfill. Thus body metabolization and excretion followed by wastewater treatment are considered to be the primary pathway of pharmaceuticals to the environment. Disposal of drug leftovers to sewage and trash is another source of entry, but its relative significance is unknown with respect to the overall levels of pharmaceuticals in the environment [2].

Continual improvements in analytical equipment and methodologies enable the determination of pharmaceuticals at lower concentration levels in different environmental matrices. Pharmaceuticals and their metabolites in surface water and aquatic sediment were subject of numerous studies concerning pharmaceuticals in the environment [3–5]. Several studies investigated the occurrence and distribution of pharmaceuticals in soil irrigated with reclaimed water [6–8] and soil that received biosolids from urban sewage treatment plants [9, 10]. These studies indicated that the applied wastewater treatments are not efficient enough to remove these micropollutants from wastewater and sludge, and as a result they find their way into the environment (Fig. 1). Once they enter the environment, pharmaceutically active compounds can produce subtle effects on aquatic and terrestrial organisms, especially on the former since they are exposed to long-term continuous influx of wastewater effluents. Several studies investigated and reported on it [11–13]. No evidence exists linking the presence of pharmaceuticals in the environment to human health risks; still complex mixtures may have long-term unseen effects, especially on tissues other than those on which the pharmaceuticals were designed to act.

Therefore, the occurrence of pharmaceutical compounds in the environment and their potential effects on human and environmental health, as well as the extent to which they can be eliminated during wastewater treatment, have become active subject matter of actual research. Since the concern about the discharge of pharmaceuticals (and other emerging contaminants, as well) into wastewater is relatively recent, it is not strange that they are not yet covered by the currently existing regulation.
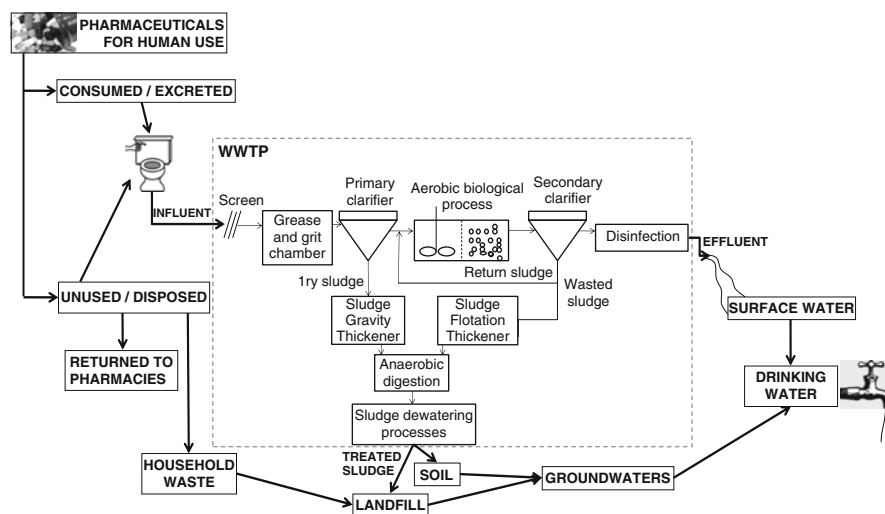
Fig. 1 Routes of release of pharmaceuticals for human use to the environment with a schematic diagram of a conventional WWTP

2 Activated Sludge Process for Treatment of Wastewater

Wastewater treatment systems that use activated sludge processes have been employed extensively throughout the world, mostly because they produce effluents that meet required quality standards (suitable for disposal or recycling purposes), at reasonable operating and maintenance costs. Figure 1 shows a schematic diagram of a conventional wastewater treatment. All design processes include preliminary treatment consisting of bar screen, grit chamber, and oil and grease removal unit [14], typically followed by primary gravity settling tank, in all but some of the smaller treatment facilities. The primary-treated wastewater enters into a biological treatment process—usually an aerobic suspended growth process—where mixed liquor (i.e., microorganisms responsible for the treatment, along with biodegradable and nonbiodegradable suspended, colloidal, and soluble organic and inorganic matter) is maintained in liquid suspension by appropriate mixing methods. During the aeration period, adsorption, flocculation, and oxidation of organic matter occur. After enough time for appropriate biochemical reactions, mixed liquor is transferred to a settling reactor (clarifier) to allow gravity separation of the suspended solids (in form of floc particles) from the treated wastewater. Settled solids are then returned to the biological reactor (i.e., return activated sludge) to maintain a concentrated biomass for wastewater treatment. Microorganisms are continuously synthesized in the process; thus some of suspended solids must be wasted from the system in order to maintain a selected biomass concentration in the system. Wasting is performed by diverting a portion of the solids from the biological reactor to solid-handling processes. The most common practice is to waste sludge from the return sludge line because return activated sludge is more concentrated and requires smaller waste sludge pumps. The waste sludge can be discharged to the primary sedimentation tanks for co-thickening, to thickening tanks, or to other sludge-thickening facilities, in order to increase the solid content of sludge by removing a portion of the liquid fraction. Through the subsequent processes such as digestion, dewatering, drying, and combustion, the water and organic content is considerably reduced, and the processed solids are suitable for reuse or final disposal. To achieve better effluent water quality, further treatment steps - tertiary treatment - can be added to the above outlined generla process, e.g. activated carbon adsorption, additioanl nutrient removal etc.

3 Occurrence of Pharmaceuticals During Conventional Wastewater Treatment

3.1 Occurrence of Pharmaceuticals in Wastewater Influent and Effluent

More than 10,000 prescription and over-the-counter pharmaceuticals are registered and approved for usage today, with around 1,300 unique active ingredients (Orange

book, FDA). This is a versatile group of compounds that differ in the mode of action, chemical structure, physicochemical properties, and metabolism. They are typically classified using the Anatomical Therapeutic Chemical Classification System (ATC system) according to their therapeutic application and chemical structure. Because of the volume of prescription, the toxicity, and the evidence for presence in the environment, nonsteroidal anti-inflammatory drugs (NSAIDs), antibiotics, beta-blockers, antiepileptics, blood lipid-lowering agents, antidepressants, hormones, and antihistamines were the most studied pharmaceutical groups [15].

Even though a number of research publications have been focused on the occurrence, fate, and effects of pharmaceuticals in the environment, we have data on the occurrence of only 10% of the registered active compounds, and very little information on their effects in the environment. There is even less information regarding the occurrence and fate of the transformation/degradation products (active or not) of pharmaceuticals. Both the qualitative and the quantitative analysis of pharmaceuticals in the environmental matrices are definitely a starting point for the establishment of new regulations for the environmental risk assessment of pharmaceutical products.

The pharmaceuticals find their way to the environment primarily via the discharge of raw and treated sewage from residential users or medical facilities. Through the excretion via urine and feces, extensively metabolized drugs are released into the environment. But the topically applied pharmaceuticals (when washed off) along with the expired and unused ones (when disposed directly to trash or sewage) pose a direct risk to the environment because they enter sewage in their unmetabolized and powerful form [2]. Even though the production of drugs is governed by rigorous regulations, pharmaceutically active substances are frequently released with the waste from drug manufacturing plants [16–18].

The occurrence of the pharmaceutical compounds in wastewater treatment plants has been investigated in several countries around the world (Austria, Canada, England, Germany, Greece, Spain, Switzerland, USA, etc). More than 150 pharmaceuticals belonging to different therapeutic groups have been detected in concentration ranging up to the μg/L level in sewage water. Their environmental occurrence naturally depends on the rate of production, the dosage and frequency of administration and usage, the metabolism and environmental persistence, as well as the removal efficiency of wastewater treatment plants (WWTPs). Figures 2 and 3 show the occurrence of the selected, most investigated pharmaceuticals in wastewater influent and effluent, as found in the literature.

NSAIDs are the most used class of drugs for the treatment of acute pain and inflammation. They are administered both orally and topically and available as prescription and over-the-counter (nonprescription) drugs. High consumption and way of administration of NSAIDs result in elevated concentration reported in the effluent from WWTPs. Among the most studied NSAIDs during wastewater treatments are ibuprofen, diclofenac, naproxen, ketoprofen, and mefenamic acid [19]. The compounds usually detected in the highest concentrations in the influent of WWTPs are ibuprofen, naproxen, and ketoprofen (in range of some μg/L)
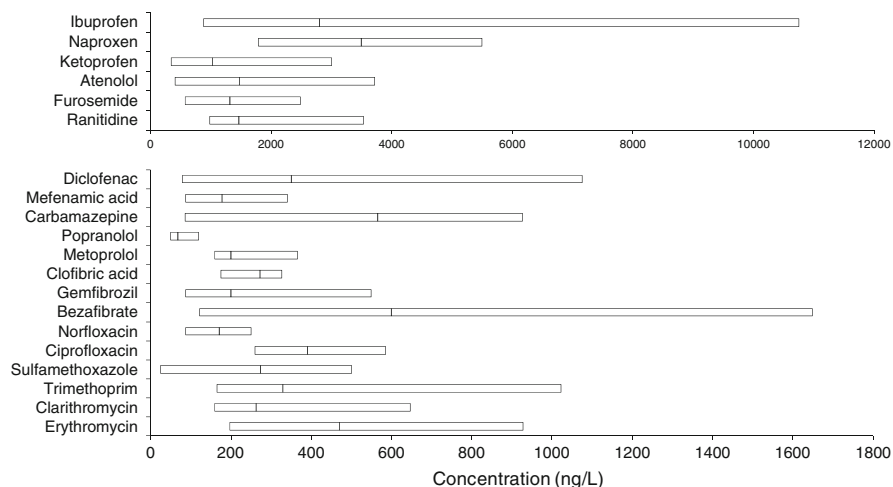
Fig. 2 Concentrations of the pharmaceuticals in wastewater influent (25th, median, and 75th percentile, for the values found in the literature)
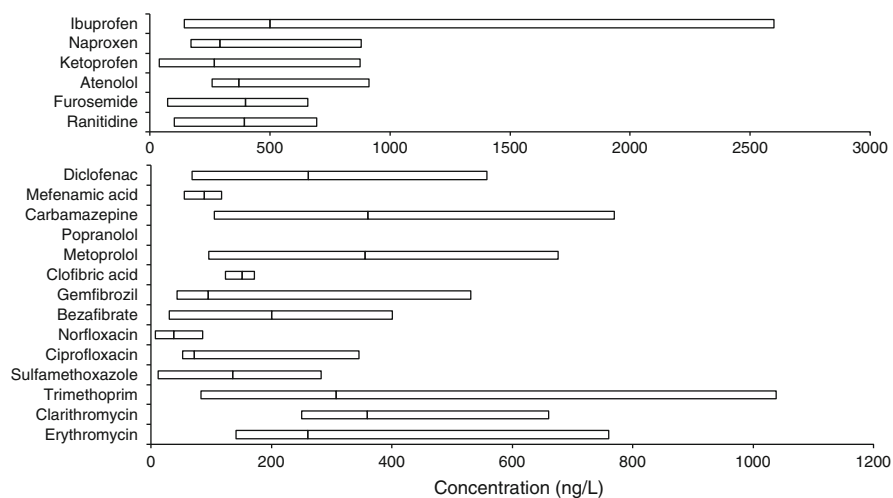
Fig. 3 Concentrations of the pharmaceuticals in wastewater effluent (25th, median, and 75th percentile, for the values found in the literature)

[20–22]. Even though the concentrations of these compounds are markedly lowered at the effluent, they are far from negligible. Heberer et al. [23] identified diclofenac as one of the most important pharmaceuticals in the water cycle, with low µg/L concentrations in both row and treated wastewater (3.0 and 2.5 µg/L at the influent and effluent, respectively).

Beta-blockers are another very important class of prescription drugs. They are very effective in treating cardiovascular diseases. As NSAIDs, beta-blockers are not highly persistent, but they are present in the environmental due to their high volume of use. Due to same mode of action of beta-blockers, it has been found that the mixture of beta-blockers showed concentration addition indicating a mutual specific nontarget effect on algae [24]. These compounds are generally found in aqueous phase because of their low sorption affinity and elevated biodegradability [25]. Atenolol, metoprolol, and propranolol have been frequently identified in wastewaters, where atenolol was detected in the highest concentrations, in some cases ranging up to 1 µg/L [26–28]. As a result of the incomplete removal during conventional wastewater treatment, these compounds were also found in surface waters in the ng/L to low mg/L range ([29, 30]; Ternes et al. 1998; [27]).

Lipid-lowering drugs, with statins and fibrates particularly, are used in the treatment and prevention of cardiovascular disease. In the last decade, statins became the drug of choice to lower cholesterol levels and their usage is increasing. According to the National Center for Health Statistics of USA [32], from 1988–1994 to 2003–2006, the use of statin drugs by adults aged 45 years and over increased almost tenfold, from 2 to 22%. Among lipid-lowering drugs and pharmaceuticals, in general, clofibric acid is one of the most frequently detected in the environment and one of the most persistent drugs with an estimated persistence in the environment of 21 years [15]. It has been detected in the ng/L range concentrations in influent, without big difference in the concentrations at the effluent. Many analogues of clofibrate, such as gemfibrozil, bezafibrate, and fenofibrate, were detected in the samples of sewage plants in concentrations up to low µg/L at the influent [20, 27, 33]. Among statins, atorvastatin, mevastatine, and prevastatine were detected in various environmental matrices including raw and treated wastewater as well as surface water near the points of discharge [20, 30, 34–36].

Antibiotics are destined to treat diseases and infection caused by bacteria. They are among the most frequently prescribed drugs for humans and animals in modern medicine. Beta-lactams, macrolides, sulfonamides, fluoroquinolones, and tetracyclines are the most important antibiotic groups used in both human and veterinary medicine. High global consumption of up to 200,000 tons per year [37] and high percentage of antibiotics that may be excreted without undergoing metabolism (up to 90%) result in their widespread presence in the environment [38]. Unmetabolized pharmaceutically active forms of antibiotics concentrated in raw sludge may promote the development of bacterial resistance. Bacteria in raw sludge are more resistant than bacteria elsewhere [39]. Many active antibiotic substances were found in raw sewage matrices, including both aqueous and solid phase. Beta-lactams are among the most prescribed antibiotics. Despite their high usage, they readily undergo hydrolysis, and thus have been detected in very low concentrations in treated wastewater, or not at all detected [40]. Sulfonamides, fluoroquinolone, and macrolide antibiotics show the highest persistence and are frequently detected in wastewater and surface waters [38]. Sulfamethoxazole is one of the most detected sulfonamides [41–45] that was reported with various concentrations and up to ca. 8µg/L (in raw influent in China) [46]. Sulfamethoxazole

is often administered in combination with trimethoprim, and commonly analyzed together [47]. Trimethoprim exhibits high persistence with little removal being effected by WWTPs, and thus is ubiquitously detected in ranges from very low ng/L to 1 µg/L in wastewater influent and effluent [41, 48]. Fluoroquinolone antibiotics ciprofloxacin and norfloxacin have been frequently detected in various streams in low µg/L [22, 41, 49, 50]. Even though it is greatly reduced during treatment, ciprofloxacin was found to be present in effluent wastewater at average concentration from 0.1 to 0.6 µg/L [48, 51, 52]. The class of tetracyclines, widely used broad-spectrum antibiotics, with chlortetracycline, oxytetracycline, and tetracycline as mostly used, was detected in raw and treated sewage in many studies in the ng/L [53] to µg/L concentrations [54]. Tetracyclines and fluoroquinolones form stable complexes with particulates and metal cations, showing the capacity to be more abundant in the sewage sludge [55, 56]. Some of the most prescribed antibiotics— macrolides clarithromycin, azithromycin, roxithromycin, and dehydro-erythromy-cin—were found in various environmental matrices in a variety of concentrations from very low ng/L to few µg/L [57–59]. High effluent concentrations were reported for dehydro-erythromycin, i.e., up to 2.5 µg/L [51, 54, 60]. In the final US EPA report CCL-3 from September 2009, erythromycin was one of three pharmaceuticals included as priority drinking water contaminant, based on health effects and occurrence in environmental waters [61].

According to the National Center for Health Statistics of USA [32], the usage of *antidiabetic drugs* by adults aged 45 years and over increased about 50%, from 7% in 1988–1994 to 11% in 2003–2006, as a consequence of an increase in the detection of antidiabetics in the environment over time. Still, only few data are reported on the occurrence and fate of antidiabetics. Glyburide (also glibenclamide) was found to be ubiquitous in both aqueous and solid phase of sewage treatment [20, 30, 62].

Histamine H2-receptor antagonists are used in the treatment of peptic ulcer and gastro-esophageal reflux disease. Certain preparations of these drugs are available OTC in various countries. Among H2-receptor antagonists, cimetidine and raniti-dine have been frequently detected in wastewater and sludge. As for all the other pharmaceuticals, the reported concentration varies from very low ng/L to a few µg/L [20, 21, 63].

While antiepileptic carbamazepine is one of the most studied and detected pharmaceuticals in the environment, there is not much information on the occurrence and fate of other of psychoactive drugs in WWTPs. Carbamazepine is one of the most widely prescribed and very important drug for the treatment of epilepsy, trigeminal neuralgia, and some psychiatric diseases (e.g., bipolar affective disorders) [64, 65]. In humans, following oral administration, it is metabolized to pharmaco-logically active carbamazepine-10,11-epoxide, which is further hydrolyzed to inactive carbamazepine-10, 11-trans-dihydrodiol, and conjugated products which are finally excreted in urine. Carbamazepine is almost completely transformed by metabolism with less than 5% of a dose excreted unchanged [66]. Still, glucuronide conjugates of carbamazepine can presumably be cleaved during wastewater treatment, so its environmental concentrations increase [27]. In fact, carbamazepine and its metabolites have been detected in both wastewaters and biosolids [67].

Carbamazepine is heavily or not degraded during wastewater treatment and many studies have found it ubiquitous in various environment matrices (groundwater, river, soil) [34, 62, 68–71]. The concentrations of carbamazepine vary from one plant to another, and they are usually around hundreds ng/L, and in some cases also few µg/L [27, 72].

3.2 Occurrence of Pharmaceuticals in Sewage Sludge

Sludge, originating from the wastewater treatment processes, is the semisolid residue generated during the primary (physical and/or chemical), the secondary (biological), and the tertiary (often nutrient removal) treatment. In the last years the quantities of sludge have been increasing in EU because of the implementation of the Directive 91/271/EEC on urban wastewater treatment. There was nearly nine million tons of dry matter produced in 2005 in EU Member states. Similar regulation in USA was introduced by US EPA regulations 40 Code of Federal Regulations Part 503 (40 CFR 503) that established the minimum national standards for the use and disposal of domestic sludge. By this regulation, sludge was classified into two different microbiological types according to the extent of pathogen removal achieved by the sludge treatment process, i.e., Class A (usage without end-use restrictions) and Class B (controlled/limited disposal). The amount of sludge generated in 2006 was estimated to be more than eight million tons of which 50% were land applied [73].

Due to the physical–chemical processes involved in the treatment, the sludge tends to concentrate heavy metals and poorly biodegradable trace organic compounds as well as potentially pathogenic organisms (viruses, bacteria, etc.) present in waste waters. Sludge is, however, rich in nutrients such as nitrogen and phosphorous and contains valuable organic matter that is useful when soils are depleted or subject to erosion. It has been used in agriculture over a long time. In EU, since 1986, the utilization of sewage sludge has been ruled by the EU Directive (86/278/EEC), which encouraged the use of sludge regulating its use with respect to the quality of sludge, the soil on which it is to be used, the loading rate, and the crops that may be grown on treated land. None of the regulations cover the question of pharmaceuticals and other emerging pollutants that may be transported to soil after land application of biosolids, having the potential to enter surface water, leach into groundwater, or be accumulated by vegetation or other living organisms.

Most of the studies on the fate of pharmaceuticals in WWTPs focused only on the aqueous phase, and concentrations of the compounds in sludge were rarely determined mainly due to the demanding efforts required in the analysis in this difficult matrix. Out of 117 publications studied by Miege et al. [19], only 15 reported the concentrations of pharmaceuticals in sludge and 1 in suspended solid, and none of these papers reported the removal obtained taking into account both aqueous and solid phases of WWTPs. Still, the screening of sewage sludge showed that these micropollutants are very present in this medium [74–77]. High aqueous-phase removal rates for some compounds would suggest very good removal of

these compounds during the wastewater treatment. But only a certain percent of the total mass of input is really lost (i.e., biodegradaded) during the treatment. The rest accumulates in sludge or ends up discharged with the effluent. As shown in Fig. 4, sorption of some pharmaceuticals analyzed in the study of Jelic et al. [20]
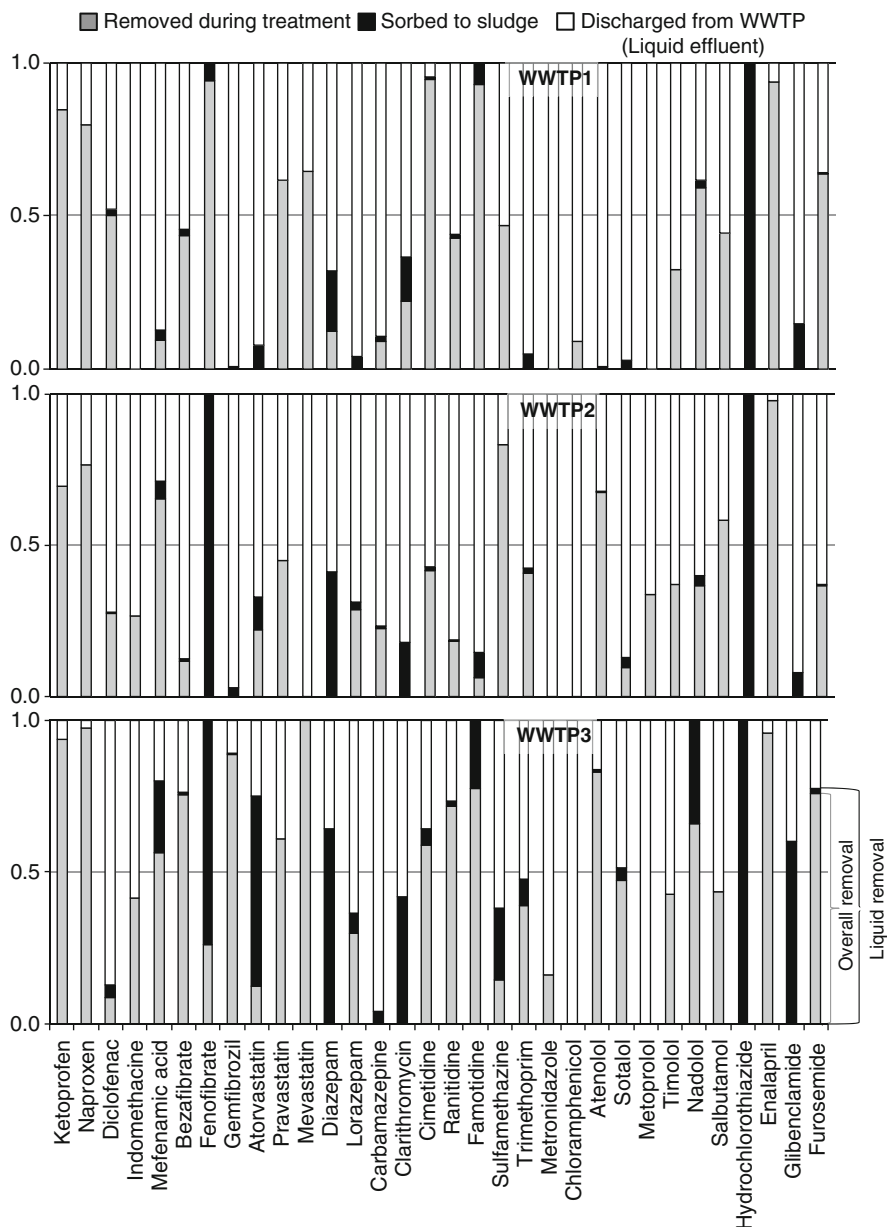

Fig. 4 Normalized mass loads of the selected pharmaceuticals entering three studied WWTPs, i.e., fraction discharged with effluent, sorbed to sludge, and removed during treatment

(e.g., atorvastatin, clarithromycin) contributed to the elimination from the aqueous phase with more than 20% related to the amount of these compounds at the influent. In the figure, term *liquid removal* indicates a difference in the loads of pharmaceuticals between influent and effluent wastewater, and *overall removal*, a difference in the loads that enter (i.e., influent) and exit (including both effluent and sludge loads) the plants. The difference between overall and liquid removal is the fraction that sorbed to sludge matter.This example clearly indicates the importance of the analysis of sludge when studying wastewater treatment performances.

The sorption behavior of pharmaceuticals can be very complex and difficult to assess. These compounds can absorb onto bacterial lipid structure and fat fraction of the sewage sludge through hydrophobic interactions (e.g., aliphatic and aromatic groups), adsorb onto often negatively charged polysaccharide structures on the outside of bacterial cells through electrostatic interactions (e.g., amino groups), and/or they can bind chemically to bacterial proteins and nucleic acids [78]. Also the mechanisms other than hydrophobic partitioning, such as hydrogen bonding, ionic interactions, and surface complexation, play a significant role in the sorption of pharmaceuticals in sludge. Therefore, also the compounds with low $LogK_{ow}$ and $LogK_d$ values may easily sorb onto sludge. Despite their negative K_{ow}, fluoroquinolones have a high tendency for sorption because of their zwitterionic character ($pK_{aCOOH} = 5.9 - 6.4$, $pK_{aNH2} = 7.7 - 10.2$) [49]. These antibiotics were reported to be present in the highest concentration in sewage sludge samples from various WWTPs [50, 74, 79]. Also tetracycline and sulfonamides exhibit strong sorption onto sludge particles, higher than expected based on their hydrophobicity.

In general, data on the occurrence of pharmaceuticals in sludge are sparse, where the group of antibiotics was mostly analyzed and found to be the most abundant. Kinney et al. [7] measured erythromycin-H_2O, sulfamethoxazole, and trimethoprim in microgram per kilogram concentrations in nine different biosolids. Out of the 72 pharmaceuticals and personal care products targeted in the study of EPA in its 2001
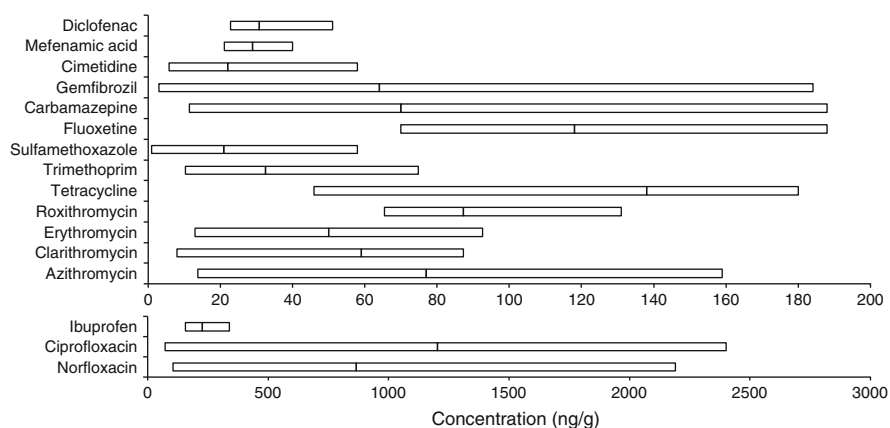
Fig. 5 Concentrations of the pharmaceuticals in sludge (25th, median, and 75th percentile, for the values found in the literature)

National Sewage Sludge Survey, 38 (54%) were detected at concentrations ranging from the low ng/g to the μg/g range. All the analyzed antibiotics constituted about 29% of the total mass of pharmaceuticals per sample [76]. Only few studies reported data on the occurrence of anti-inflammatories and some other therapeutic classes (psychoactive drugs, lipid-lowering drugs, etc.) [20, 79–82]. Figure 5 summarizes some literature data on the occurrence of several pharmaceuticals in sewage sludge in various WWTPs.

4 Removal of Pharmaceuticals During Conventional Wastewater Treatment

Municipal wastewater treatment plants were basically designed to remove pathogens and organic and inorganic suspended and flocculated matter. Even though the new treatment technologies have been developed to deal with health and environmental concerns associated with findings of nowadays research, the progress was not as enhanced as the one of the analytical detection capabilities and the pharmaceutical residues remain in the output of WWTPs. When speaking about pharmaceuticals, the term *removal* refers to the conversion of a pharmaceutical to a compound different than the analyzed one (i.e., the parent compound). Thus, it accounts for all the losses of a parent compound produced by different mechanisms of chemical and physical transformation, biodegradation, and sorption to solid matter. All these processes (mainly biodegradation, sorption, and photodegradation) are limited in some way for the following reasons: (a) pharmaceuticals are designed to be biologically stable; (b) the sorption depends on the type and properties of the suspended solids (sludge); (c) and even though they are photoactive, because many of them have aromatic rings, heteroatoms, and other functional groups that could be susceptible to photodegradation; they may also give the products of environmental concern.

Removal, as difference in the loads between influent and effluent, has negative values in some cases. The explanation for this could be found in sampling protocols [83], not only because they could be inadequate, but because of the nature of disposal of pharmaceuticals. The fact is that the substances arrive in a small number of wastewater packets to the influent of WWTP, in unpredictable amounts and time intervals; thus the influent loads, especially, are easily systematically underestimated.

Even though the analysis of effluent and sludge yields more certain results, because they come from stabilization processes, the sampling in general may result in underestimated and even negative removals. Furthermore, the negative removal can be explained by the formation of unmeasured products of human metabolism and/or transformation products (e.g., glucuronide conjugate, methylates, and glycinates) that passing through the plant convert back to the parent compounds. This can be considered as a reasonable assumption since the metabolites and some derivates of pharmaceuticals are well known (e.g., hydroxy and epoxy-derivatives of carbamazepine, 4-trans-hydroxy and 3-cis-hydroxy derivatives of glibenclamide,

ortho- and parahydroxylated derivatives of atorvastatin, etc.) [67, 84, 85]. During complex metabolic processes in human body and biochemical in wastewater treatment, various scenarios of transformation from parent compound to metabolite and derivatives and vice versa can occur. Generally speaking, metabolites tend to increase the water solubility of the parent compound. Two different strategies are followed to achieve that objective: chemical modification of the parent molecule through addition of polar groups like OH, COOH, etc.; alternatively, the parent structures can be linked reversibly to polar highly soluble biological molecules, such as glucuronic acid, forming the so-called conjugates. Metabolites can be just as active as their parent compounds. Therefore, the occurrence of metabolites and transformation products and pathways should be included in the future studies in order to obtain accurate information on the removal of pharmaceuticals during treatment and to determine treatment plant capabilities.

The extent to which one compound can be removed during wastewater treatment is influenced by chemical and biological properties of the compound, but also of wastewater characteristics, operational conditions, and treatment technology used. Therefore, as shown in the following examples, high variations in elimination may be expected, and no clear and definitive conclusion can be made on the removal of any particular compound, and even less on the fate of a therapeutic group. Some operating parameters such as hydraulic retention time (HRT), solid retention time (SRT), redox conditions, and temperature may affect removal of pharmaceuticals during conventional treatment [127]. Of all the operating parameters, SRT is the most critical parameter for activated sludge design as SRT affects the treatment process performance, aeration tank volume, sludge production, and oxygen requirements. It has been proved that longer SRT, especially, influences and improves the elimination of most of the pharmaceuticals during sewage treatment [43, 68, 86]. WWTPs with high SRTs allow the enrichment of slowly growing bacteria and consequently the establishment of a more diverse biocoenosis with broader physiological capabilities (e.g., nitrification or the capability for certain elimination pathways) than WWTPs with low SRTs [68].

NSAIDs have been the most studied group in terms of both occurrence and removal during wastewater treatment. As noted, the pharmaceuticals are grouped according to the therapeutic applications; thus high variations in removal rates were observed within the group due to the differences in chemical properties. While ibuprofen and naproxen are generally removed with very high efficiency, diclofenac is only barely removable during conventional treatment. The removal rates of ibuprofen and naproxen are commonly higher than 75% and 50%, respectively [87–92]. Diclofenac shows rather low and very inconsistent removal rates, between 0 and 90% [88, 89, 91, 92]. Its persistence is attributed to the presence of chlorine group in the molecule. Some studies on removal during wastewater treatment showed no influence of SRT on the removal of diclofenac [68, 93, 94]. The removal of ibuprofen, ketoprofen, indomethacin, acetaminophen, and mefenamic acid is reported to be very high (>80%) or even complete for SRT typical for nutrient removal (10 < SRT < 20 days) [88, 90, 94].

Beta-blockers were reported to be only partially eliminated by conventional biological treatment [128, 26, 27, 31]). The data on their removal are very inconsistent and the removal rates vary from less than 10% up to 95% depending on the treatment. Maurer et al. proved that the elimination of beta-blockers in WWTPs depends on the HRT, which could be a good explanation for the variable removal reported in the literature. The highest average elimination rates can be observed for atenolol and sotalol (around 60%). But for the same compounds low removals were reported as well. Maurer et al. [95] and Wick et al. [96] reported removal rates lower than 30% for sotalol, and Castiglioni et al. [87] reported a removal of 10% for atenolol during the winter months. In the same study, atenolol achieved better elimination in summer (i.e., 55%) due to a higher microbial activity [87]. In most cases, metoprolol showed very low removal rates, i.e., 10–30% [26, 31, 97]. The occurrence and microbial cleavage of conjugates are well known to influence the mass balance in WWTPs [98–100]. The microbial cleavage of conjugates of metoprolol could be responsible for an underestimation of its removal efficiency. For propranolol as well, various removal rates, mostly moderately low [96, 101], were observed. This compound is by far the most lipophilic beta-blocker and the only one with a bioaccumulation potential. Sludge–water partition coefficients were found to be less than 100 L/kg_{ss} for sotalol and atenolol, and 343 L/kg_{ss} for propanolol [95]. For $K_{d,s}$ values less than 500 L/kg_{ss} the removal by sorption in a WWTP with a typical sludge production of 0.2 g_{ss}/L is less than 10% [102] and hence does not significantly contribute to the removal of beta-blockers in activated sludge units [96]. Therefore, the partial removal of beta-blockers can be assumed to be due to biotransformation.

No significant to medium removal was reported for all the *lipid regulators*. Zorita et al. [22] reported a medium removal of 61% during primary and biological treatment, where during the latter one no removal was observed. Lower removal rates were reported by some other authors, <35% [87, 103, 104]. No or low removal of clofibric acid was observed in different WWTPS of Berlin [105]. Winkler et al. [106] found no evidence for biotic degradation of clofibric acid. Radjenovic et al. [36] showed that clofibric acid may be removed more efficiently with MBR (72–86%) compared to the activated sludge process (of 26–51%). The removal rates of fibrates bezafibrate, fenofibrate, and gemfibrozil vary between 30 and 90% [88, 94, 107]. Various removal rates during biological treatment in ten WWTPs in Spain were reported in the studies of Jelic et al. [20] and Gros et al. [30]. It was found that sorption to sludge particulate contributes to the removal values with ca. 20% [20].

Results from various studies showed that *anticonvulsant carbamazepine* is recalcitrant to biological treatment and it is not removed during either conventional wastewater treatment or membrane bioreactor treatments [34, 62, 69, 71, 91, 108]. Physicochemical processes such as coagulation-flocculation and flotation did not give better results concerning its degradation [109–111]. It was constantly found at higher concentrations at the effluent of WWTPs. Knowing that the activated sludge has glucuronidase activity, which allows the cleavage of the glucorinic acid moiety in WWTP [112], rational explanation for the increase in concentration is conversion

of CBZ glucorinides and other conjugated metabolites to the parent compound by enzymatic processes in a WWTP. No influence of SRT on the removal of CBZ during conventional wastewater treatment was noticed [68, 93]. Except for carbamazepine, information on the occurrence and fate of other psychoactive drugs in WWTPs is very scarce. This is probably because of the low therapeutic dose resulting generally in low concentrations in the environment [63, 113, 114]. Conventional treatment achieves a removal lower than 10% in case of diazepam [72]. Zorita et al. [22] reported very high removal efficiency in case of fluoxetine and its active metabolite norfluoxetine. Still, the lowest observed effect concentration of fluoxetine for zooplankton and benthic organisms is close to the maximal measured WWTP effluent concentrations [115]. Low effluent concentrations can be due to the fact that fluoxetine rapidly passes to solid phase where it appears to be very persistent [116, 117]. Additionally, it was found that it has a high bioaccumulation potential when detected in wild fish [118].

The removal of several other drugs such as the *histamine H2-receptor antagonists* cimetidine, famotidine, and ranitidine varied from low to very high. Radjenovic et al. [36] reported rather poor and unstable removal of histamines during conventional treatment (15–60%). Castiglioni et al. [87] found that the removal of ranitidine depends on season, and showed 39% removal in winter and 84% in summer. High removal of ranitidine during activate sludge treatment (89%) was observed in a study of Kasprzyk-Hordern et al. [21].

Antibiotics cover a broad range of chemical classes, and it is very difficult to characterize their behavior during activated sludge process due to varying removal efficiencies reported from studies undertaken worldwide. Due to their limited biodegradability and sorption properties, sulfonamides and trimethoprim appear to be only partially removed by conventional wastewater treatment. The removal of these antibiotics has been reported to vary significantly [41–44, 97, 119]. The explanation could be found in different operational parameters such as HRT, SRT, and temperature and also in the fact that sulfonamides are easily transformed from their parent compounds to their metabolites and vice versa; thus the removal efficiencies may be easily or underestimated or overestimated. In case of trimethoprim, only minor removal was noticed during primary and biological treatment, but the advanced treatment [43] and nitrification organisms appear to be capable of degrading trimethorpim [120, 121]. This suggests an important role for aerobic conditions for the biotransformation of trimethoprim. Consistent with this, removal efficiency of trimethoprim appears to be enhanced by long SRT during biological treatment, which is conducive to nitrification [122]. Also macrolide antibiotics are often incompletely removed during biological wastewater treatment. Studies from different conventional WWTPs have revealed that the removal of macrolides varied from high but negative values, to around 50% [43, 88]. Karthikeyan and Meyer [59] found that 43 to 99% of erythromycin was removed by activated sludge process and aerated lagoons. In the study of Kobayashi et al. [123], 50% of clarithromycin and azithromycin were removed from three conventional WWTPs. Gobel et al. [43] proposed gradual release of the macrolides (e.g., clarithromycin) from feces particles during biological treatment as an explanation for the possible negative

removal rates for these antibiotics. Sorption of macrolides to wastewater biomass is attributed to hydrophobic interactions (high partitioning coefficient). But knowing that the surface of activated sludge is predominantly negatively charged , and under typical wastewater conditions, the basic dimethylamino group (pKa > 8.9) is protonated, sorption could occur due to cation exchange interaction as well [124]. Greater adsorption of azithromycin to biomass compared to clarithromycin has been reported [123]. Varying removal was reported for fluoroquinolone antibiotics, as well. [125] found that norfloxacin and ciprofloxacin were removed with 78% and 80%, respectively, where around 40% was removed during the biological treatment. Similar removal was reported by Zorita et al. [22] during secondary and tertiary treatment. The predominant removal mechanism of fluoroquinolones has been suggested to be adsorption to sludge and/or flocs rather than biodegradation [22, 49, 122, 125]. Ciprofloxacin and norfloxacin sorbed to sludge independently of changes in pH during wastewater treatment, and more than 70% of the total amount of these compounds passing through the plant was ultimately found in the digested sludge [125]. These findings indicated sludge as the main reservoir of fluoroquinolones that may potentially release the antibiotics into the environment when applied to agricultural land. Karthikeyan and Meyer [59] reported removal efficiency of 68% for tetracycline, and Yang et al. [45] have reported removals of 78 and 67% for chlortetracycline and doxycycline, respectively, during activated sludge processes. Also some tetracyclines have significant potential for absorption onto solids due to a combination of non-hydrophobic mechanisms, such as ionic interactions, metal complexation, hydrogen bond formation, or polarization [126]. Their removal is not so affected by HRT, but SRT appears to significantly influence the removal during biological treatment [53].

5   Conclusion

Various studies showed that even though the conventional WWTPs meet the regulatory requirements for wastewater treatment (Directive 91/271/EEC), they are only moderately effective in removing pharmaceuticals. The removal of pharmaceuticals will naturally depend on their chemical and biological properties, but also on wastewater characteristics, operational conditions, and treatment technology used. Thus, high variations in removal may be expected, and no clear and definitive conclusion can be made on the removal of any particular compound. Of all the operating parameters, the solid retention time (SRT) is the most critical parameter for activated sludge process and it has been proved that longer SRT improves the elimination of most of the pharmaceuticals during sewage treatment. Estimation of removal rates may be underestimated due to at least three factors: removal efficiency was calculated from the mean concentration values; the metabolites and transformation products of pharmaceuticals and their amounts were not defined; and the time-proportional sampling may not be perfectly suitable for pharmaceutical analysis, especially on influent. Still, the fact is that a number of

pharmaceuticals were detected in effluent wastewater and sludge samples. These pharmaceuticals cover a wide range of physical-chemical properties and biological activities. Although the chronic toxicity effects of such a mixture are unknown and thus the risk that it could pose to the environment could not be fully assessed, their presence must not be ignored. More information on quality, quantity, and toxicity of pharmaceuticals and their metabolites is definitely needed especially when attempting to reuse wastewater and dispose sludge to agricultural areas and landfills.

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