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Trends in organic micropollutants removal in secondary treatment of sewage

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Abstract

Organic micropollutants (OMPs) comprise a wide group of substances highly consumed in modern societies. There has been a growing social and scientific interest on OMPs in wastewaters in the 21st century. This research paper has identified the evolution of the research trends in the period 2001-2017 on OMPs fate during secondary wastewater treatment. These trends have moved from a global perspective on the occurrence of OMPs in wastewaters to more specific research focussed on understanding their behaviour during advanced treatment processes. Based on a bibliometric analysis carried out using one of the leading scientific databases, pharmaceuticals have been identified as the main group of OMPs. An increasing number of publications have been released on the fate of pharmaceuticals in wastewater with a growing number of countries involved: from 38 publications belonging to 14 countries in first 5-year period analysed (2001-2005) up to 138 from 42 countries only in the last two years (2016-2017). The main operational conditions in wastewater treatment plants influencing the removal of OMPs, as well as the mechanisms involved depending on the physico-chemical characteristics of the substances are reviewed. The paper also considers the role of microbial populations, as well as technological and operational features in OMPs abatement. Finally, a specific section is dedicated to the metabolic and cometabolic biotransformations of some OMPs taking place under heterotrophic, nitrifying and anaerobic conditions, a more novel research trend explored more recently.

Keywords: advanced treatments, biotransformation, cometabolism, operational conditions, organic micropollutants, removal mechanisms

1. Introduction

The abatement of “emerging pollutants” is becoming a specific target in the conception of modern wastewater treatment schemes. In most cases the term used should be “pollutants of emerging concern”, since what is really new is the information recently obtained with the modern powerful analytical techniques which allow measuring concentrations of almost every compound consumed by our society at extremely low concentrations. Most of these pollutants are characterized by their occurrence at trace level, being consequently also referred to as micropollutants. Most of them have an organic nature, consequently called organic micropollutants (OMPs).

OMPs comprise a wide group of substances largely consumed in modern societies (Omil et al., 2010), including pharmaceuticals, endocrine disruptors (EDCs), personal care products (PCPs), biocides, brominated flame retardants (BFRs), pesticides and linear alkylbenzene sulphonates (LAS). In general, the production of these substances has been increasing during the last years even though the population trend in many developed countries is hardly stable or declining, which constitutes an indication of the progressive higher consumption per capita of pharmaceuticals, hormones, other therapeutic substances, cosmetics, etc. The aging of society plays a key role in such trend, but also other changes in social habits are relevant, as for example the access to contraception, which supposes an increasing consumption of the hormone 17 α-ethinylestradiol (EE2, the active ingredient of the contraceptive pill). The extensive use of antibiotics, new antiviral drugs or disinfectants is another example of the wide distribution of these substances in our society (Van der Aa et al., 2011).

Pharmacokinetics is the study of the time course of drug absorption, distribution, metabolism, and excretion from the body (usually into the water cycle). It is a key issue to estimate the concentration of pharmaceuticals and endocrine disruptors in wastewaters, together with their consumption and disposal patterns (Ortiz de Garcia et al., 2013; Besse et al., 2008; Kolpin et al., 2004). In fact, compounds with a low excretion rate, such as ibuprofen (IBP), diclofenac (DCF) or sulfamethoxazole (SMX), are usually present at noticeable concentrations in wastewaters due to their massive use (Kolpin et al., 2004). Other important factors to be considered are the diurnal occurrence patterns, which are correlated with the daily drug administration (Plósz et al., 2010) and with the climate conditions. In this sense, increases in the concentration of pharmaceuticals in wastewater were observed under dry weather conditions in combined sewer systems (Kasprzyk-Hordern et al., 2009). A seasonal influence on the concentrations of several pharmaceuticals, such as IBP and ketoprofen (KET) has been reported (Santos et al., 2009).

In wastewater treatment plants (WWTP), high variations in the inlet OMP concentrations can be found. This occurs in one installation along a period of time but especially when comparing data from different plants (Miège et al., 2009; Mussolf et al., 2009; Spongberg and Witter, 2008; Ellis, 2006; Carballa et al., 2004). The usual influent concentrations of OMPs in WWTPs are in the range of μg L^{-1} and ng L^{-1}. For example, some musk fragrances, such as galaxolide (HHCB), tonalide (AHTN) or celestolide (ADBI), widely used in the formulation of cosmetic products, have been found at concentrations ranging between 0.9-16.6 μg L^{-1} (Clara et al., 2011; Carballa et al., 2004). The anti-inflammatories IBP, naproxen (NPX) or DCF were found in a wider range, going from 12 ng L^{-1} to 84 μg L^{-1} (Gómez et al., 2007; Kim et al., 2007; Nakada et al., 2006; Vieno et al., 2005). Hormones are present in sewage at the lowest concentration ranges, usually below 50 ng L^{-1} (Belhaj et al., 2008; Carballa et al., 2004), as expected from the low medication drug doses prescribed.

1.1 Concerns of the society related to OMP emissions

The growing social interest in this topic is evidenced by the increasing number of news all around the world which can be found in different mass media. Since the concentrations of OMPs in water (wastewaters, surface waters, groundwater) are extremely low, especially when compared to conventional macropollutants, the reasons for such concern are not related to their chemical impact, but to other potential problems (toxicity, bioaccumulation and estrogenicity caused to the micro and macroorganisms exposed to these emissions). Adverse effects on fishes exposed to the anti-inflammatory diclofenac at 0.5-1 μg L^{-1} have been reported by Hoeger et al. (2005) and Triebskorn et al. (2004). Eguchi et al. (2004) studied the toxicity of different antibiotics such as erythromycin (ERY), oxytetracycline and tylosin on the green algae *Selenastrum capricornutum*. The endocrine disrupting effect of the estrogens 17 β-estradiol (E2) and the synthetic EE2 was observed in different organisms, including fishes (Parrott and Blunt, 2005; Hirai et al., 2006; Orlando et al., 2007).

As a consequence, the European Union decided in 2015 to include 7 OMPs in the “Watch List” of the Water Framework Directive (WFD) to discuss the future limits of discharge of these substances, namely 3 hormones (estrone, E1, E2 and EE2) and 4 pharmaceuticals (diclofenac and the macrolide antibiotics azithromycin, clarithromycin and ERY) due to their estrogenic, toxic or antibacterial resistance potential (Table 1). The aim of this legislative measure is to monitor and gather information regarding the potential risks related to the exposure to those OMPs in the aquatic environment.

Table 1. *European Union legislation in terms of organic micropollutants*

The Swiss Federal Office for the Environment (FOEN) can be highlighted as pioneer in developing a legal framework for OMP emissions in wastewater effluents. A new Water Protection Ordinance has been applied since 2015 in order to reduce the levels of micropollutants in their water bodies. The Swiss legislation is targeting the protection of sensitive waters and drinking water sources by limiting the OMP content in treated wastewater below 20% of the concentration present in the raw wastewater. The selection of the target OMPs has been carried out based in extensive research programmes carried out along the Swiss territory for a number of years (www.bafu.admin.ch). As a general rule, the substances which appeared most frequently and were not removed during biological treatment were selected. Each canton in Switzerland has to select 6 of a list of 12 substances for which WWTPs have to achieve removal efficiencies above 80% after upgrading to advanced treatment based on ozone or activated carbon. This list comprises the following compounds: amisulpride, carbamazepine, citalopram, clarithromycin, diclofenac, hydrochlorothiazide, metoprolol, venlafaxine, benzotriazole, candesartan, irbesartan and mecoprop.

1.2 Research trends compared to state of the art

In order to analyse the evolution of the scientific community focus concerning OMPs in wastewater, a bibliometric study has been carried out following the strategy: Source *Scopus (Title-abstract-keywords)*; Search *pharmaceuticals* and *wastewater*; period *from 2001 to 2017*. In general, the studies related to pharmaceuticals during wastewater treatment have been increasing exponentially in the last decades, moving from a limited perspective mainly oriented to the occurrence to a research with an increased level of detail and complexity, as will be demonstrated in the following paragraphs.

According to the scientific background, firstly the analytical methods were developed and optimized for the measurement of OMPs concentrations in different matrixes (from milliQ water to the complex mixed liquors existing in WWTPs) with the aim of assessing their occurrence in the different compartments and streams of WWTPs (Ternes et al., 2001; Buser et al., 1998; Hirsch et al., 1998; Huppert et al., 1998). These first studies reported a high variability in the removal efficiencies of OMPs in wastewater treatment using similar treatment schemes (Table 2), which was attributed to the differences in the environmental and operational conditions applied (hydraulic retention time, HRT; solid retention time, SRT, etc.). Consequently, the influence of those conditions on OMP removal was the main objective of many studies (Maeng et al., 2013; Gerrity et al., 2011). Most of efforts carried out to elucidate the behaviour of OMPs along WWTPs have focussed on the determination of the overall removal efficiencies achieved by different technologies (activated sludge, membrane reactors, postreatments, etc.) working under different operational conditions (Clara et al., 2005a; Reif et al., 2008) and only in few cases the removal mechanisms in each specific case were the subject of the research (Carballa et al., 2007; 2004; Alvarino 2014). Attention was especially paid to the sorption and/or biotransformation of OMPs. In this sense, Ternes et al. (2004) reported a rapid method to measure the solid-water distribution coefficient to determine sorption of pharmaceuticals onto sludge, whereas Joss et al. (2005) studied sorption and biotransformation of different pharmaceuticals and musk fragrances taking place in biological reactors of WWTPs.

Table 2. *Overall ranges for removal efficiencies reported for selected OMPs in wastewater treatment (Behera et al., 2011; Lin et al., 2010; Gómez et al., 2007; Kupper et al., 2006; Nakada et al., 2006; Bester, 2005; de Mes et al., 2005; Carballa et al., 2004; Baronti el al., 2000; Stumpf et al.,1999; Ternes et al., 1998)*

Along the last years, the number of works following this approach has been increasing, with the aim of applying this knowledge to the design and development of innovative wastewater treatment technologies able to remove OMPs more efficiently. New technological approaches include hybrid reactors, the use of membranes, supports and/or adsorbents (Escolà-Casas et al., 2015; Falås et al., 2013), post-treatment with activated carbon or ozone (Kovalova et al., 2013; Margot et al., 2013), etc. These new treatment strategies are conceived for including modifications in the existing plants (not only related with their physical configuration but also their way of operation) and also for constructing new installations. In both scenarios, the formulation of a conceptual design to maximise OMPs removal requires a detailed knowledge about key mechanisms involved in their transformation, being the analysis of the processes at macroscopic level not sufficient. This was the starting point for more specific studies such as those addressing primary and secondary metabolism, metabolic pathways and even enzymatic activities.

The aim of the present review is to obtain a clear picture of the main issues involved in this challenging topic, focussing on the evolution observed along the first 17 years of this century, based on an extensive bibliometric study. This period matches with the time passed from the adoption of the WFD (October 2000) up to the final inclusion of the first group of pharmaceutical OMPs in the "Watch List" (2015). Besides, the last two years 2016-2017 can be an indicative of the impact of such decision. The article is structured according to the time evolution of the main topics identified in Fig. 1: i) occurrence and fate; ii) influence of operational conditions applied in WWTPs; iii) identification of removal mechanisms; iv) technological concepts addressing OMP removal and v) metabolism/cometabolism.

***Fig. 1** Evolution of research trends dealing with OMPs in WWTPs*

2. Occurrence and fate

Fig 2A shows the number of publications along the period 2001-2017 for different groups of OMPs. A clear growing trend can be observed for all categories. In the case of pharmaceuticals, PCPs and BFRs, around 70% of publications were released in the last 7 years. Somewhat lower values (50-60%) were found for the rest of compounds. In the case of pesticides and biocides, the relative number of publications in the period 2001-2005 was already significant, indicating that the concern on those persistent organic pollutants started earlier than those related to pharmaceuticals and personal care products. The number of works containing the terms "wastewater" and the specific group of OMP were: 4663 with "pharmaceutical", 1002 with "PCP", 1170 with "EDC", 1183 with "pesticide", 320 with "biocide", 172 with "LAS" and finally 92 "BFR" (Figure 2A). Thus, among these 7 categories, half of the scientific interest was focussed on pharmaceuticals along the entire 17 years considered.

***Fig. 2** Scientific papers published along 2001-2017: A) types of OMPs in wastewater; B) selected pharmaceuticals and estrogens in wastewaters; C) fate of pharmaceuticals in wastewaters*

(Source: Scopus; General Search: GS; Specific Search: SS. Full spelling of terms was used in the search).

Among the wide number of pharmaceuticals and EDCs reported, it is interesting to note that some specific substances are present in a growing number of articles, such as three specific pharmaceuticals (DCF, ERY and carbamazepine, CBZ) and three hormones (E1, E2, EE2), as shown in Fig. 2B. One of the factors explaining their consideration as representative OMPs is their inclusion in the European and/or Swiss legislation. According to the number of publications, those related to DCF, E2 and CBZ in wastewater represent the double compared to the other 3 compounds (around 1000 vs. 500, respectively). If their time evolution is analysed, DCF, ERY and CBZ show a stepwise increasing trend especially highlighted since 2011. In fact, around 70% of their respective publications were released in the last 7 years. In the case of ERY this trend could be related to the current concern about antimicrobial resistance derived from the discharge of antibiotics into the environment. Within the hormones, E2 received more attention compared to EE2 and E1, although EE2 has shown to be a more potent endocrine disruptor than the natural hormones with in vivo juvenile rainbow trout screening assays (Thorpe et al., 2003). For these EDCs, the interest in publication increased especially in period 2006-2010, while the figures related to the period 2011-2017 reveal a certain stabilization trend.

If the bibliometric search is refined from pharmaceuticals in “wastewater” to “fate of pharmaceuticals in wastewater”, which is related to a more technological approach, the number of studies decreases in one order of magnitude, as illustrated by Fig. 2C, with 578 works along the 17 years analysed. Although publications with a global perspective on the fate of pharmaceuticals in wastewater treatment are clearly the most abundant, other on more specific topics, such as the identification of the main removal mechanisms and the development of technologies targeting pharmaceutical removal have evidenced a growing trend (Fig. 2C). This is especially clear along the last two years, when the publications related to “fate” already achieved 52% of those corresponding to 2011-2015, and in the case of “removal mechanisms” an outstanding value of 111% was achieved. On the other hand, studies about the role of primary/secondary metabolism on pharmaceuticals biotransformation are very scarce, with only 6 articles found since 2006. Publications tackling the study of pharmaceutical removal mechanisms suppose a 9% of the total publications on the fate of pharmaceuticals in WWTPs, whereas only 1% deals with the primary/secondary metabolism responsible for pharmaceutical biotransformation.

The geographical involvement of the scientific community in the study of the fate of pharmaceuticals in wastewater has been changing over time. In Fig. 3 the total number of publications per country origin (PCO) for each period is shown. It represents the number of publications in which research groups from a given country were involved. The first works were concentrated in only 14 countries, with an outstanding productivity in the United States, Germany and Switzerland (Fig. 3A). In fact, the US has been leading the number of publications in all periods analysed. The number of countries involved in this research has been continuously increasing, achieving a total number of 42 in the last two years (2016-2017). China started to publish on this topic later in 2006, reaching the second position from 2011 onwards. A similar trend can be observed for Canada. Spain moved from a modest position in 2001-2005 to the top-4 in the following 12 years. Since the beginning, UK, France and Australia maintained a quite stable position in the ranking, while other countries as for example Switzerland left the topic in the last 7 years. Most probably, this was because the OMP presence in wastewaters has been incorporated into Swiss regulations moving the challenge to full-scale implementation. Besides, it is worth to note the increasing number of developing countries all around the world that have started focussing their attention on this issue in the last two years. India, Taiwan, Brazil and Pakistan are examples of this evolution.

In order to identify the main research trends in the different countries, Fig. 4 shows the previous search (Fig. 2C) refined with three selected research fields: removal mechanism, technology and co-metabolism. In the first case, Fig. 4A shows that groups from 23 countries have been involved in the assessment of removal mechanisms, being observed that 50% of the pie chart belongs to four countries: United States, China, Germany and Spain. In the case of technologies, Switzerland, Canada and Great Britain are also present in the first positions from a total of 29 countries involved (Fig. 4B). Few articles address the role of the cometabolic biotransformations taking place during the abatement of pharmaceuticals, belonging to research groups from the United States, followed by France, China, Spain and, more recently, Denmark (Fig. 4C).

The number of collaborations between research groups from different countries working on the fate of pharmaceuticals in wastewaters can be analysed from the ratio between the sum of publications per country origin (SPCO) in Fig. 3 and the sum of publications (SP) corresponding to a certain period (Fig. 2). The ratio SPCO/SP was of 1.21, 1.34, 1.33 and 1.41 going from the first (2001-2005) to the fourth (2016-2017) period considered, respectively. These numbers evidence the increasing trend in the collaborations between research groups from different countries on that topic.

Fig. 3 *Publications per country origin focussed on the fate of pharmaceuticals in wastewater in the period 2001-2017 classified by country (source: Scopus; GS: pharmaceutical, wastewater, fate; SS: period; country codes according to ISO 3166)*

Fig. 4 *Publications per country origin dealing with the different research fields focussed on fate of pharmaceuticals in wastewater in the period 2001-2017 classified by country*

(source: Scopus; GS: pharmaceutical, wastewater, fate; SS: research field; country codes according to ISO 3166)

3. Influence of operational conditions

There is not a unique classification of OMPs in function of their removal in WWTP due to the broad ranges of removal efficiencies reported for most of these compounds (Table 2). This different behaviour could be partially explained in terms of the different environmental and operational conditions applied in each case, such as HRT, SRT and redox conditions (Table 3). For instance, IBP is considered one of the most readily biodegradable OMPs in conventional biological treatments (Clara et al., 2005a; Carballa et al., 2004). However, IBP is a recalcitrant compound under anaerobic conditions (Alvarino et al., 2014).

Table 3. *Influence of SRT, HRT and temperature in the removal of OMPs (Fernandez-Fontaina et al., 2012; Reif et al., 2011; Suárez et al., 2010; Clara et al., 2005b; Tauxe-Wuersch et al.,2005)*

3.1 Hydraulic and sludge retention time

Maurer et al. (2007) observed that the removal efficiencies of some betablockers strongly correlated with the HRT. Clara et al. (2005a) reported a high dependence of the behaviour of the anti-inflammatory DCF, with removal efficiencies around 70% at long HRTs (13 d) which became negligible when a lower HRT was applied (1.2 d). Fernandez-Fontaina et al. (2012) reported an increase in the removal of ROX and FLX at higher HRTs, whereas no influence of the HRT was observed for IBP and NPX. These differences can be related to kinetic limitations, which are especially relevant in the case of the compounds with medium biodegradability.

The operation at high SRT allows the increase of the microbial diversity due to the development of slowly growing bacteria, as well as higher biomass concentrations and better acclimation to disturbances and toxic substances (Clara et al., 2005b). De la Torre et al. (2015) operated an IFAS-MBR (a membrane bioreactor which combines suspended and fixed biomass) at different SRTs (10 and 20 d). Higher removal efficiencies of pharmaceuticals were observed when operating at an SRT of 20 d. Surprisingly, a removal efficiency above 80% was reported for carbamazepine in the IFAS-MBR operated at an SRT of 20 d (De la Torre et al., 2015), which was related to the operation at low F/M ratios which induced the microorganisms to biotransform the recalcitrant compounds (Verlicchi et al., 2012). Suárez et al. (2012) reported a significant influence of the SRT on the removal of lipophilic compounds, such as estrogens or musk fragrances. For instance, EE2 removal increased 11% when the SRT was maintained above 20 d. For these compounds, a stronger influence of the SRT compared to the HRT was reported, based on the assumption that compounds with a low biological kinetic constant can be biologically transformed at high SRTs if they are mainly sorbed onto the sludge. Reif et al. (2011) compared the removal of OMPs in a MBR operated with a SRT of 6 and 20 d and observed a reduction in the discharge of acidic drugs and musk fragrances in the final effluent at the higher SRT. In fact, Clara et al. (2005b) identified that SRT > 10 d increased removals for several OMPs, such as hormones and ibuprofen. The enhancement in the removal of certain OMPs when the SRT is increased has been related to the presence of slowly growing nitrifiers (Miège et al., 2009; Göbel et al., 2007; Clara et al., 2005b), as occurs with ibuprofen, estrone or estradiol, whose removal has been correlated with the nitrification activity (Alvarino et al., 2016a).

3.2 Redox conditions

Redox conditions strongly influence the degree and route of OMP biotransformation. The OMP behaviour is mainly related to the chemical structure of the compound and the metabolic pathways promoted under each environment (Fig. 5 and 6). In general, OMPs are removed to a higher extent under aerobic conditions (Alvarino et al., 2018). For instance, a recalcitrant behaviour was reported by McAvoy et al. (2002) in the case of triclosan under anaerobic conditions, while it was a readily removed in aerobic processes. However, some pharmaceuticals, like SMX or NPX, were easily removed at negative redox conditions, with removal efficiencies above 99% for SMX during the anaerobic digestion of sludge (Carballa et al., 2007a). Comparing the aerobic and anoxic removal of OMPs, it was reported that most of the compounds were efficiently removed under aerobic conditions, whereas three compounds (ROX, CLA, and clindamycin (CLI)) were removed only under anoxic conditions (Burke et al., 2014). In general, the operation of biological reactors at different redox conditions results in an increased microbial diversity and a broader enzyme spectrum which enhances OMPs biotransformation (Suárez et al., 2012).

Fig. 5. *Biotransformable and recalcitrant moieties under anaerobic conditions*

Fig. 6. *Biotransformable and recalcitrant groups under aerobic conditions*

3.2.1 Anaerobic conditions

The presence of electron-withdrawing groups enhances the removal of OMPs by reductive biotransformation reactions (Banzhaf et al., 2012; Field, 2002), whereas the cyclic or heterocyclic groups or the halogens in the chemical structure difficult the removal under anaerobic conditions (Fig. 5, Dutta et al., 2014; Monsalvo et al., 2014; Musson et al., 2010; Adrian et al., 1994), as in the case of progesterone, DCF, CBZ or DZP. The substituted heterocycles are susceptible to be degraded under anaerobic conditions (Adrian et al., 1994). This was the case in the metabolic route proposed by

Alvarino et al. (2016b) for SMX removal in a pure anaerobic culture being the attack site in the substituted heterocycle 3-amino-5-methyl-isoxazole ring.

Under negative redox conditions, OMPs removal can occur by hydrogenation or hydroxylation reactions. The hydroxylation of the carbons present in the aromatic ring promotes the ring cleavage under anaerobic conditions. However, the hydroxylation can be interfered by some ring substitutions, as in the case of acetaminophen. Its low removal might be associated with the branched chain substitution in the aromatic ring (Musson et al., 2010). Carboxylic and hydroxyl functional groups promote the hydroxylation (Musson et al., 2010). For instance, metoprolol (MTP) is an OMP with a medium-high removal because its structure contains a hydroxyl moiety, in spite of the presence of an amine group that is recalcitrant under anaerobic conditions (Musson et al., 2010). Nonylphenol and the short-chain nonylphenol ethoxylates are the intermediate products of the anaerobic removal of the surfactant nonylphenol ethoxylates due to the sequential removal of ethoxyl groups (Lu et al., 2008, 2007). Falås et al. (2016) observed the demethylation and deionination of organic micropollutants with a recalcitrant behavior under aerobic conditions, such as diatrizoate or venlafaxine, in an anaerobic postreatment.

3.2.2 Aerobic conditions

Under aerobic conditions, Boethling et al. (1994) showed that the presence of heterocyclic N-containing aromatic rings hampers biodegradation (Fig. 6), which explains the stability of CBZ that contains three fused aromatic rings (Fernandez-Fontaina et al., 2016). The presence of chlorine atoms in the OMP structure generates an electron deficiency, thus the molecule is less susceptible to oxidative catabolism (Knackmuss, 1996; Keener and Arp, 1993). The micropollutants with electron donating functional groups, such as amines or hydroxyl groups, are more prone to be biotransformed by an electrophilic attack by oxygenase enzymes (Tadkaew et al., 2011). For instance, Müller et al. (2013) studied the biotransformation of SMX under aerobic conditions and 3-amino-5-methyl-isoxazole was the main stable metabolite detected, being the attack site in the amine. Jewell et al. (2016) observed the removal of TMP by demethylation to form the intermediate metabolite 4-desmethyl-TMP under aerobic conditions. This metabolite was not stable and quickly transformed to 2,4-diaminopyrimidine-5-carboxylic acid by hydroxylation and oxidation. Other authors showed another biotransformation pathway for TMP by ether cleavage (Quintana et al., 2005).

A wide range of polycyclic aromatic hydrocarbons, aryl ethers and aromatic ethers, such as naphthalene (NAP), diphenyl ether (DE) or anisole can be cometabolically degraded through O-dealkylation or hydroxylation by the ammonia monooxygenase (AMO) enzyme, produced by ammonium oxidizing bacteria (Chang et al., 1997), as well as the straight-chain hydrocarbons through hydroxylation (Hyman et al., 1988). Tadkaew et al. (2011) showed a high removal of micropollutants with an aromatic-aliphatic ether, such as gemfibrozil (98%) and verapamil (87%), that can be biotransformed by ether cleavage.

Dorival-Garcia et al. (2013) observed a medium removal of the quinolone antibiotics (14-40%) under aerobic conditions, while the biodegradation was negligible under anoxic environments. This difference can be related to the higher oxidation potential of the oxygen, compared to the nitrate (Sigg, 2000), since redox reactions occur in the order of the thermodynamic conditions, being oxygen the lowest unoccupied electron level (Stumm and Morgan, 1996). Due to that, the hydrolysis of primary and secondary amides can occur under both redox conditions, while the oxidation of tertiary amides is viable only under aerobic conditions (Helbling et al., 2010).

4. Identification of the OMP main removal mechanisms

Once the occurrence and fate of the OMPs are accurately determined in WWTPs, the next step consists in the understanding of the behaviour of these substances during biological treatment. Taking into account the three phases in which the OMPs can be present in a biological reactor (solid, liquid and gas streams), three main removal mechanisms can be distinguished: biotransformation, sorption, and volatilization (Pomiès et al., 2013; Joss et al., 2006). Volatilization and sorption consist in the transfer of OMPs between two compartments based on equilibrium mechanisms (liquid-gas, and liquid-solid, respectively), whereas biotransformation is the degradation of the parent OMP in the mixed liquor (Pomiès et al., 2013). In WWTPs, the fate and behaviour of OMPs strongly depend on the physicochemical properties of the compound (Boethling et al., 2007) and the type of treatment processes applied (physicochemical or biological).

Volatilisation depends on the physicochemical properties of the OMPs, such as the Henry law constant (H), as well as on the conditions of the process, such as the air flow, stirring or temperature. In WWTPs, two volatilization processes can be involved: stripping and surface volatilization. In general, the contribution of the volatilization to the overall removal of OMPs is negligible. Only for some compounds, such as the musk fragrance celestolide (ADBI), volatilization has to be taken into account in the mass balances. Suárez et al. (2012), who studied the removal of musk fragrances in a single-sludge nitrification-denitrification plant, observed that around 20-40% of the removal of ADBI was due to stripping, whereas Alvarino et al. (2014) determined a low contribution of volatilization (5-15%) in a CAS unit.

Sorption depends on the OMP lipophilic character or its tendency to be ionized or dissociated in aqueous phase (presence of amino or carboxyl groups, etc.), as well as on the physico-chemical characteristics of the sludge (organic compound fraction or particle size) (Verlicchi et al., 2013). Two mechanisms have to be taken into account (Sipma et al., 2010): absorption, that is associated to the hydrophobic interactions between the aliphatic and aromatic groups of a compound with the lipophilic cell membrane of the microorganisms and the fat fractions of the sludge, and adsorption, that refers to the electrostatic interactions of the positively charged groups of the OMPs with the negatively charged surfaces of the microorganisms (Verlicchi et al., 2013). The trend to be absorbed is usually related to the octanol-water coefficient (K_{ow}) (Suárez et al., 2008). Among OMPs characterized by a high Kow are the musk fragrances or fluoxetine (Alvarino et al., 2018; Horsing et al., 2011). In the case of the hydrophobic OMPs, the charge and the molecular size explain their adsorption into the negatively charged biomass (Wunder et al., 2011). This fact explains the higher adsorption of ERY (positively charged) compared to the SMX (negatively charged) (Wunder et al., 2011).

Biotransformation in WWTPs is related to the biochemical reactions induced by the presence of microorganisms in water, such as bacteria, which assimilate the pollutants as growth or maintenance substrates leading to their transformation (Tran et al., 2013; Yang et al., 2013). Although complete degradation (biomineralization) can be reached for some OMPs, for most of them the removal efficiencies achieved are only partial, being some compounds completely recalcitrant (Clara et al., 2004; Collado et al., 2014). The study of the metabolites generated as intermediate products is a very useful tool to understand the fate of OMPs in bioprocesses as well as the biochemical reactions and enzymes involved.

As previously studied in section 3.2, the degree of OMP biotransformation under the different redox conditions applied during wastewater treatment is very much influenced by the chemical structure of the compounds. Other parameters of the biological processes that play a key role on the OMP fate, include the biomass concentration and activity (heterotrophic aerobic/anoxic/anaerobic, nitrifying), as well as the operational conditions considered (HRT, SRT). Other influencing factors less considered in literature include the bioavailability of the substance to be biotransformed or the fraction of inert matter contained in the sludge. As an overall approach biotransformation is quantified by biological kinetic coefficients (k_{biol}). Normally the mass balances assume pseudo steady-state conditions, a continuous stirred tank reactor model pattern and pseudo-first-order kinetics (Joss et al., 2006; Ternes et al., 2006). The information obtained through this approach is interesting and very useful especially to compare the differences in biotransformation between OMPs. However, the high number of factors involved makes that k_{biol} only gives accurate biotransformation rates under the specific conditions studied, being difficult to extrapolate them to other configurations.

The influence of biomass concentration on the value of the kinetic coefficients can be illustrated by the following case study for the anti-inflammatory NPX (Alvarino et al., 2014). The k_{biol} coefficient was determined for this OMP in two reactors: an aerobic CAS unit and an anaerobic UASB reactor, treating the same influent. Although NPX was removed to a high extent in both systems, the calculated k_{biol} in the anaerobic system (1.1 L g_{VSS}^{-1} d^{-1}) was much lower than in the CAS unit (9 L g_{VSS}^{-1} d^{-1}), being this difference related to the biomass concentration (30 and 1.8 g_{VSS} L^{-1}, respectively).

5. Technological concepts for OMPs removal

In the case OMPs removal is aimed due to their possible toxicity and bioaccumulation potential, it should be specifically addressed when conceiving innovative processes. This is especially relevant for wastewaters containing higher amounts of OMPs, such as hospital wastewater (HW) with concentrations of pharmaceuticals 4-150 times higher compared to those present in municipal wastewater (Verlicchi et al., 2010).

Processes based on conventional activated sludge (CAS) for carbon and nutrient removal are the most extended technologies implemented in urban WWTPs. They consist of a biological reactor with suspended biomass (or a series of them) followed by a settler. Although these processes are able to readily remove certain OMPs, such as IBP, acetaminophen (PAR), acetylsalicylic acid (ASA), musk fragrances or bisphenol A (BPA), other compounds show a recalcitrant behaviour reaching the final effluents of the WWTPs and thus being discharged into the environment (Gabet-Giraud et al., 2010; Clara et al., 2005a; Carballa et al., 2004). Although there has been a huge development of innovative technologies (hybrid systems considering different redox conditions, biomass configurations, use of membranes, etc.) to address the challenges of achieving more sustainable wastewater treatment in accordance with the current regulations in developed countries (e.g. EU WFD), the removal of OMPs is usually not addressed specifically.

In the case of new technological developments targeting OMPs removal, most of the publications are focussed in MBR systems (Park et al., 2017; Reif et al., 2008; Abegglen et al., 2009; Clara et al., 2005), while only few papers considered for instance the anammox-based configurations (Kassotaki et al., 2018, Laureni et al., 2016; Alvarino et al., 2015; de Graaf et al., 2011). The first works dealing with OMP removal in MBRs compared to the conventional processes were published in 2005 (Clara et al., 2005a), while the first report of a hybrid process combining the use of supports and suspended biomass can be found in 2008. Three years later, in 2011 the first results were published concerning OMPs behaviour in an anammox-based process (de Graaf et al., 2011).

Among the most innovative technological options proposed for increasing OMP removal during secondary wastewater treatment, the following features can be summarised: i) the use of reactors operating at high biomass concentrations and long SRTs; ii) the use of different biomass conformations (biofilms, granular, flocculent); iii) the combination of several redox potentials; iv) the promotion of more specific bacterial populations and v) the addition of adsorbents directly into the mixed liquor of biological reactors. The innovative systems considered in this paper are based on the combination of these new technological options.

5.1 Technologies promoting higher biomass retention

5.1.1 Membrane bioreactors (MBRs)

MBRs are particularly relevant when available space is a serious limitation and water reclamation is an important issue. This technology has some advantages compared to the CAS process, such as the high-quality effluents produced, the low sludge production and the possibility to work at short HRTs (Ng et al., 2007; Stephenson et al., 2000).

Additionally, the use of membranes allows increasing the sludge concentration and the SRT applied so that the biomass growth is not restricted to the fast-growing and floc-forming microorganisms (Radjenović et al., 2009; Brepols et al., 2008).

Better OMP removal efficiencies in MBR compared to CAS units have been reported in different works (Radjenović et al., 2009; González et al., 2006; Kimura et al., 2005; Quintana et al., 2005). The particular operational conditions of MBRs have shown to enhance the removal of OMPs by sorption, such as in the case of tetracycline, ciprofloxacin (CIP) or ofloxacin (OFL), as well as by biotransformation due to the development of slower growing species (de la Torre et al., 2015; Kim et al., 2007). The consequent reduction of the F/M ratio could benefit biotransformation of the more recalcitrant compounds (De Wever et al., 2007; Clara et al., 2005a). Other authors showed comparable results in MBR and CAS systems if similar operational conditions were applied (Clara et al., 2005a; Joss et al., 2005). Reif et al. (2011) determined higher OMP removals in an MBR compared to a CAS when the SRT was 10 d, whereas the differences were not significant anymore when both systems were operated with an SRT of 20 d.

The role of OMP retention by the membrane due to size exclusion is only relevant in the case of nanofiltration or reverse osmosis. Xue et al. (2010) reported a removal of OMPs by sorption into the membrane body and/or on the cake layer. Even OMP retention by size exclusion in the cake layer has been observed (Terzic et al., 2005). Membranes produced with hydrophobic materials have shown significant sorption of OMPs (Jermann et al., 2009).

5.1.2 Biofilm reactors

Among the biofilm reactor concept, some alternatives combine suspended and attached biomass, allowing the achievement of high biomass concentrations and SRT compared to CAS systems. The use of supports allows the development of a broader spectrum of microorganisms that could be active in the biotransformation of some OMPs, due to the retention in the system of slow-growing bacteria. This is the case of nitrifiers that were promoted by the use of supports (Di Trapani et al., 2014). Falås et al. (2012) observed a higher removal rate per unit biomass in a biofilm compared to the suspended biomass for DCF, KET, mefenamic acid, gemfibrozil and clofibric acid. The formation of anoxic and anaerobic environments inside the biofilm promoted biotransformation routes under different redox conditions (Alvarino et al., 2017).

High removal efficiencies (> 80%) were achieved in moving bed MBRs (MBMBR) for IBP, NPX or ASA, mainly related to the presence of strong electron donating functional groups, such as hydroxyl groups, which enhance the removal of OMPs under aerobic conditions (Luo et al., 2014). This high removal could be related to the ability of the ammonia oxidizing bacteria to oxidize compounds with hydroxyl groups (Fernandez-Fontaina et al., 2012).

De la Torre et al. (2015) assessed the removal of OMPs in different reactors operating with suspended and attached biomasses. The best behaviour in terms of OMPs removal was achieved in the IFAS-MBR with average removal efficiencies above 65% due to the combination of both types of biomasses in high concentrations. On the other hand, low removals were observed in the system operated only with attached biomass due to the low biomass concentrations. Arya et al. (2016) reported that a submerged attached biofilter (SABF) was the most effective and robust system to remove OMPs compared to a MBR and a CAS unit, although only slight differences in the effectiveness were observed between the MBR and the SABF.

5.2 Combination of different redox conditions

One of the trends in the development of innovative WWTP configurations is the application of different redox potentials to enhance the microbial diversity. The aim is to biotransform a wider range of complex pollutants while maintaining a high degree in the COD and nutrient removal processes (Luo et al., 2014). Aerobic processes are still the most applied in secondary wastewater treatment, despite of their energetic inefficiency. Aeration consumes around 40% of the total electric energy (McCarty et al., 2011), being 45 % of the total COD in the raw wastewater lost as carbon dioxide (Guo et al., 2010). A more sustainable alternative consists of applying methanogenic anaerobic digestion, which enables the recovery of energy in the form of biogas (Silvestre et al., 2015), with the consequent reduction in the net energy consumption (Dai et al., 2015). This justifies the progressive installation of new anaerobic methanogenic reactors in the water line followed by aerobic post-treatment steps, in order to promote the valorization of the organic matter contained in wastewaters (Bustillo-Lecompte et al., 2017; Lv et al., 2017; Buntner et al., 2011). The combination of the three redox potentials (anaerobic-anoxic-aerobic) allows achieving complete removal of nutrients, such as nitrogen and phosphorous (Zhang et al., 2016; Liu et al., 2013).

5.2.1 Methanogenic anaerobic steps

Most of the available information about the removal of OMPs under anaerobic conditions refers to the sludge line. The application of anaerobic conditions has shown to be positive for the removal of some OMPs, as TMP, SMX and KET, when wastewater is treated in an anaerobic MBR (Monsalvo et al., 2014). Several OMPs, such as diuron, DCF or TMP, require an anaerobic treatment to be biotransformed (Falås et al., 2016). In the case of the hormones E1, E2 and EE2, higher removals were reported under aerobic conditions compared to the results obtained under negative redox potentials in the water line (Zhang et al., 2015; Joss et al., 2004).

Alvarino et al. (2016) has studied the removal of OMPs in an methanogenic anaerobic reactor followed by an aerobic MBR post-treatment (anaerobic hybrid MBR process).

Biotransformation of OMPs prone to be removed under anaerobic conditions was reported (e.g. TMP or SMX), although most of the OMPs were mainly removed under aerobic conditions.

5.2.2 Non methanogenic anaerobic steps

Processes based on MBRs comprising different redox conditions (anaerobic, anoxic and aerobic) for carbon and nutrient removal have gained interest (Silva-Teira et al., 2017; Leyva-Díaz et al., 2016; Hu et al., 2014). In these systems, the internal recirculation (IR) ratio is one of the key operational factors for process optimisation. Phan et al. (2014) studied the removal of 30 OMPs, analyzing the IR rate between the aerobic and the anoxic stages in an anaerobic-anoxic-aerobic process. The supply of nitrate, as well as the dilution, mass transfer and the microaeration in the anoxic chamber are a function of the internal recirculation rate. For 9 OMPs evaluated, such as triclosan, o-nonylphenol (NP) or 17b-estradiol-17-acetate, removals above 50% were obtained under anaerobic and anoxic conditions without any influence of the IR rate. Negligible removal was observed under anaerobic conditions for 11 OMPs, such as KET, IBP, ASA or formononetin, which were biotransformed to a moderate extent under anoxic conditions. Suárez et al. (2012) studied the effect of the IR in a denitrification-nitrification single sludge unit and reported an improvement in the removal of IBP, NPX, CTL and FLX when the IR to the anoxic stage was increased. The enhancement was related to a more effective mixing and the transport of oxygen from the aerobic to the anoxic chamber. Xue et al. (2010) studied the removal of 19 OMPs in an anaerobic-anoxic-aerobic MBR process and observed a higher OMP elimination in the anaerobic compartment which was linked to several aspects: the rapid adsorption of OMP onto the sludge, the internal recirculation and the presence of readily biotransformable OMPs under anaerobic conditions.

5.2.3 Autotrophic nitrogen removal systems

One of the alternatives to conventional nitrification-denitrification is the autotrophic nitrogen removal process due to several advantages: i) lower energy consumption (less aeration is needed), ii) no need of external organic matter addition, iii) lower sludge production and, iv) lower greenhouse gases emissions (N_2O, NO and less CO_2 stripped) (Vázquez-Padín et al., 2014; Kartal et al., 2013, 2008; Okabe et al., 2011; Kuenen, 2008; Ruiz et al., 2006). De Graaf et al. (2011) studied the removal of several OMPs in a partial nitrification-anammox process, observing that IBP was mainly transformed in the anammox process (77%), whereas Falås et al. (2012), following IBP in kinetic batch experiments stated a clear effect of nitrification on its removal. Alvarino et al. (2015) correlated the removal of IBP with the nitritation rate in a nitration-anammox process, whereas no influence of the anammox activity was observed. In the case of the other anti-inflammatories, such as KTP, NPX or DCF, low removal in an anammox process was reported by Falas et al. (2012). The anammox activity exerts a positive influence on the removal of the antibiotic ERY, being a correlation with the nitrite removal rate reported by Alvarino et al. (2015). A low removal of DCF has been also reported by de Graaf et al. (2011), with efficiencies below 40% in a nitritation-anammox process. This behavior is similar to what has been obtained for DCF in a conventional nitrification-denitrification unit (Suárez et al., 2010). The recalcitrant behavior of CBZ and DZP has been consistently reported for the autotrophic and the heterotrophic biological nitrogen removal processes (Fernandez-Fontaina et al., 2012; de Graaf et al., 2011; Suárez et al., 2010).

5.3 The use of adsorbents in biological reactors

Sorption onto granular activated carbon (GAC) has been used conventionally as post-treatment in order to enhance the removal of OMPs after the biological processes (Nguyen et al., 2012). Although these systems are primarily based on the physico-chemical adsorption of the target pollutants, biotransformation can also occur as a result of the development of a biofilm layer on the GAC particles (Paredes et al., 2016; Matamoros et al., 2007). Another strategy consists on the simultaneous promotion of both, physicochemical and biological processes, inside one single reactor. In this sense, Sirotkin et al. (2001) proposed a direct dosing of powdered activated carbon (PAC) into a MBR. This has shown a number of positive effects: i) reduction of membrane fouling (Alvarino et al., 2017); ii) higher removal of conventional pollutants derived from the growth of a biofilm onto the activated carbon particles (Remy et al., 2009; Rice and Robson, 1982); iii) decrease of toxicity caused by certain inhibitors on the nitrification process (Widjaja et al., 2004), and iv) retention of the PAC by the membrane. This direct addition of PAC also showed promising results for OMPs, since high removal efficiencies for the recalcitrant compounds CBZ and DZP were achieved in a sequential batch reactor (SBR) coupled to a membrane filtration tank by Serrano et al. (2011). In such systems, the OMPs are removed either by biotransformation (promoted by the suspended biomass and the biofilm) or by sorption onto the sludge and the PAC. Alvarino et al. (2016c) determined an enhancement of the OMP biotransformations after the direct addition of PAC in an MBR, which was specially relevant for the compounds with moderate biodegradability.

6. Metabolism/cometabolism

The OMPs are present in municipal wastewaters at much lower concentrations than the macropollutants (i.e. organic matter and nutrients). Thus, it is expected that a primary substrate is necessary for inducing the enzymes for the OMP biotransformation by means of cometabolism. During this process, the persistent compounds are converted into more biotransformable intermediate products within the global metabolic pathways (Yi and Harper, 2007).

In the case of nitrification, several authors reported a simultaneous elimination of ammonia and OMPs, like EE2, IBP, NPX or trichloroethylene (TCE) (Fernandez-

Fontaina et al., 2012, Yi and Harper et al., 2007; Yi et al., 2006), through cometabolic biotransformations carried out by autotrophic aerobic bacteria. The ammonia monooxygenase produced by ammonium oxidizing bacteria can easily oxidize straight-chain hydrocarbons through hydroxylation (Hyman et al., 1988). Fernandez-Fontaina et al. (2016) reported a high removal of IBP and NPX under nitritation conditions due to the existence of secondary and tertiary carbons in the linear alkyl chains of these compounds, which are easy targets for nucleophilic attack by the AMO enzyme (Fig. 6). Yi and Harper (2007) reported a correlation between nitrification and the removal of the hormone EE2. They showed that the single aromatic ring of EE2 is the site of electrophilic initiating reactions because the frontier electron density of this carbon ring unit is higher than in the case of the other rings and that the pi electrons associated with this ring are sterically unhindered. Therefore, the ring cleavage was observed first in the aromatic ring of the hydroxylated EE2. In presence of the *Sphingobacterium sp.*, Haiyan et al. (2007) proposed another metabolic route, where EE2 is initially oxidized to E1. This pathway continues with the ring cleavage of the ring B, leaving the aromatic ring initially intact.

The presence of an external carbon source can lead to an enhancement in the removal of several OMPs, evidencing cometabolism for heterotrophic bacteria. Majewski et al. (2011) determined faster OMP removal efficiencies in the presence of a high number of active heterotrophs when a low SRT was applied. In the case of the antibiotic SMX, a clear positive effect on its removal under aerobic conditions was reported when an external biodegradable carbon source was added to the reactor with the aim of providing enough energy for biomass growth (Fernandez-Fontaina et al., 2016; Müller et al., 2013). The presence of heterocycles and amines, as well as the lack of alkyl side chains, hampers the biotransformation of SMX by the AMO enzyme (Boethling et al.,1994).

The positive effect of the presence of heterotrophs was also demonstrated by Larcher and Yargeau (2013) for EE2 biotransformation, for which medium-high removal efficiencies were determined when using several heterotrophic pure cultures (*B. subtilis, P. aeruginosa, P. putida, R. equi, R. erythropolis, R. rhodochrous, R. zopfii*). In the case of the pure culture *R. rhodochrous* even a total removal was achieved. Other studies on the synthetic hormone EE2 reported its biotransformation by both, heterotrophic and autotrophic bacteria (Larcher and Yargeau, 2013; Khunjar et al., 2011; Yi and Harper, 2007).

Fernandez-Fontaina et al. (2016) applied two cosubstrates alternatively (ammonium or organic matter) in order to determine their cometabolic effect on the removal of a selected group of OMPs, observing efficient removals (> 80%) of the antibiotics ERY and ROX independently of the cosubstrate used. Tran et al. (2009) studied the cometabolic removal of OMPs by the addition of several growth substrates (ammonium and organic substrates). It was observed that for most of the OMPs higher removal efficiencies were obtained by the use of growth substrates due to the induction of the activity of the specific enzymes involved in each process. These authors identified a cometabolic biotransformation of IBP (> 75%) and to a less extent of NPX, DCF, KET, fenoprofen (FEN) or gemfibrozil

(GEM), by the heterotrophic bacteria when a nitrification inhibitor (allylthiourea) was added.

Information about the OMP cometabolism under anaerobic conditions is scarce. Gonzalez-Gil et al. (2017) studied the cometabolic biotransformation of 20 OMPs during methanogenesis. The process key enzyme acetate kinase has shown to be able to biotransform OMPs that contain a carboxyl or hydroxyl group and have moderate steric hindrances, such as naproxen, nonylphenol, octylphenol or bisphenol A.

In the case of primary metabolism, the presence of the OMPs in sufficient concentrations is necessary for allowing the growth and maintenance of the sludge, as well as for the production of the enzymes and cofactors responsible for the OMP biotransformations (Tran et al., 2013). Müller et al. (2013) studied the biotransformation of SMX under aerobic conditions (50 mg L^{-1}) and determined that the sludge communities were able to use SMX both as energy supply and for growth support. More concretely, heterotrophic bacteria assimilated SMX as a carbon source, while autotrophic bacteria used SMX as N source. Other authors assessed the OMP biotransformations when being the sole available carbon source in pure cultures. For instance, *Sphingomonas Ibu-2* was capable of biotransforming IBP by metabolism (Murdoch and Hay, 2005), while *Pseudomonas aeruginosa TJ1* and *Novosphingobium JEM-1* were able to oxidize E2 (Iasur-Kruh et al., 2011; Zeng et al., 2009).

Conclusions

The interest of the scientific community on OMPs in wastewater in the last 17 years clearly focused on pharmaceuticals compared to other groups such as pesticides, PCPs or EDCs. The studies on the fate of these compounds has been increasing significantly according to the bibliometric study provided in this paper, moving from 38 scientific papers written by groups belonging to 14 countries in the period 2001-05 up to 264 articles by groups from 44 countries in 2011-15. Only in the last two years, 2016-2017, 138 articles were published by groups from 42 countries, with an increasing participation of developing countries all over the world. Not only the number of countries working on these issues has been increasing, but also the number of collaborations between research groups from different countries. As a result of this effort, the first regulations have recently started to appear (Switzerland) or are under discussion (USA, EU zone).

The trend in the study of OMPs during the secondary treatment of sewage has been moving from a general overview on the fate, to more specific works that analyse the contribution of different mechanisms on the OMP removal efficiencies. There is enough information available in bibliography in order to confirm the influence of different operational parameters on the removal of OMPs. This includes HRT, SRT and redox conditions as most frequently studied parameters, but other aspects as the biomass concentration and activity play also an important role on the results achieved.

In the last years, new advanced wastewater treatment technologies have been developed in order to achieve more sustainable processes using a holistic approach. Although OMPs removal has not been usually present in these considerations, the situation is changing as new processes are already featuring enhanced OMPs removals. In the last 17 years the 11% of publications on the fate of pharmaceuticals in wastewater tackled specifically technological aspects. Currently most of these works still focus on the differences between CAS and MBRs.

OMPs are normally removed by cometabolism due to their low concentrations in municipal wastewaters compared to macropollutants. This implies that the metabolic route for OMPs biotransformation is a function of the primary metabolic activity and the microbial diversity, besides the other operational conditions. Still very few studies have provided insights on these relations.

This review clearly demonstrates that pharmaceuticals in wastewater constitute a hot topic all around the world. An outstanding progress has been made since 2000 in determining the fate and main removal mechanisms of these compounds during wastewater treatment. However there are still important knowledge gaps that should be further studied in order to reach the desirable removal efficiencies during secondary wastewater treatments. The new technological options developed to achieve better results in terms of OMP removal should consider, besides working under different redox conditions, other factors such as the use of different biomass conformations and/or the addition of adsorbents into biological reactors. More information is needed about the cometabolic biotransformations of OMPs, since this would allow to adapt the primary metabolism to conditions favourable to the removal of these substances.

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