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Evaluation of membrane bioreactor on removal of pharmaceutical micropollutants: a review

Chengcheng Li[a,b,c,*], Corinne Cabassud[a,b,c], Christelle Guigui[a,b,c]

[a]*Université de Toulouse, INSA, UPS, INP, LISBP, 135 Avenue de Rangueil, Toulouse 31077, France, Tel. +33 05 61 55 97 91; emails: chengcheng.li@insa-toulouse.fr (C. Li), corinne.cabassud@insa-toulouse.fr (C. Cabassud), christelle.guigui@insatoulouse.fr (C. Guigui)*
[b]*INRA, UMR792 Ingénierie des Systèmes biologiques et des Procédés, Toulouse 31400, France*
[c]*CNRS, UMR5504, Toulouse 31400, France*

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ABSTRACT

Municipal wastewater reclamation and reuse has become an important solution in many places around the world to deal with water scarcity problems. Among the available treatment approaches, membrane bioreactor (MBR) has a great potential to become a key element in municipal wastewater reclamation and reuse schemes due to its significantly higher treated effluent quality as compared to the conventional activated sludge process. As great concerns have been raised to some emerging trace pollutants found in aquatic environment in the last decade, notably the pharmaceuticals, removal of pharmaceutical micropollutants by MBR or MBR-related processes should be evaluated to further understand the status of MBR in different wastewater treatment and reuse schemes. This paper gives an overview on removal of pharmaceutical micropollutants by MBR or MBR-related processes, such as activated carbon-assisted MBR and combined membrane bioreactor and reverse osmosis process.

Keywords: Pharmaceutical micropollutants; Membrane bioreactor; Activated carbon-assisted MBR; MBR–RO; Wastewater treatment and reuse

1. Introduction

Water scarcity is still a big challenge facing humanity in many places around the world. Thus, municipal wastewater has been considered to be an alternative water source for various applications after proper treatment [1,2]. Membrane bioreactor (MBR) which couples the activated sludge process and membrane separation, i.e. microfiltration (MF) or ultrafiltration (UF), has a significant potential to become a key element in municipal wastewater reclamation and reuse schemes worldwide, since it greatly improves the treated effluent quality as compared to conventional activated sludge (CAS) process, especially for removal of pathogenic micro-organisms and micropollutants [3,4]. Besides, when higher effluent quality is required in some reuse applications, activated carbon could be added into MBR to further improve removal of organic contaminants [5]. Moreover, MBR could be employed as pre-treatment process for reverse osmosis (RO) which is served as a secondary barrier for the

*Corresponding author.

removal of pathogenic bacteria, viruses, and hazardous chemicals [6,7].

In the last decade, great attention has been paid to some emerging trace organic pollutants, also called micropollutants, such as endocrine-disrupting compounds, pharmaceuticals, and personal care products, found in aquatic environment [8,9]. Among these micropollutants, pharmaceuticals got special concerns since late 1990s [10–13], as pharmaceuticals are designed to have some biological effect and to be persistent to avoid being metabolized before having a curing effect [14]. Besides, concerns have been raised regarding the possibility that continuous discharge of antibiotics to aquatic environment may facilitate the development or proliferation of resistant strains in bacteria [15]. Moreover, chronic toxicity effects have been reported for aquatic organisms exposed to human pharmaceuticals at trace concentration [16–18]. Thus, the existence of pharmaceutical micropollutants in aquatic environment may pose a potential danger on human health as well as aquatic organisms.

Therefore, extensive studies have been carried out to remove pharmaceutical micropollutants in municipal wastewater by all kinds of treatment approaches. In the literature, several reviews have been performed on the removal of pharmaceutical micropollutants in municipal wastewater treatment [19–25]; however, no review has been conducted specially on the removal of pharmaceutical micropollutants by MBR or MBR-related processes, such as activated carbon-assisted MBR and combined MBR–RO process. This paper gives an overview on the removal of pharmaceutical micropollutants by MBR or MBR-related processes in order to evaluate the status of MBR in wastewater treatment and reuse schemes.

2. Sources and occurrence of pharmaceutical micropollutants

Nowadays, about 3,000 substances are registered in the EU for pharmaceutical purposes alone [23,26]. Also, there is evidence of occurrence of some 160 different drugs in effluent of wastewater treatment plants (WWTPs), surface water, and groundwater [27]. Pharmaceuticals found in aquatic environment can be divided into different therapeutic categories: analgesics and anti-inflammatory drugs, lipid regulators, anti-epileptic drugs, beta-blockers, antibiotics, cytostatic drugs, etc. [28,29]. After consumed by human body, pharmaceutical residues are discharged to sewers through urine and feces as unchanged compounds or metabolites. For unused or expired drugs, usually they are flushed down the drain or disposed of in the trash [27]. Thus, after domestic use, pharmaceuticals mainly enter WWTPs. Concerning the contribution of hospitals to concentration of pharmaceuticals detected in WWTP influents, normally it is low for most pharmaceuticals except for some specific pharmaceuticals, for example, some antibiotics [30–32].

Due to incomplete the removal of pharmaceuticals in conventional WWTPs, WWTP effluents become a major source of pharmaceutical micropollutants entering aquatic environment [29,33]. Many pharmaceutical micropollutants have been detected at concentration up to μg/L level in conventional WWTP effluents around the world. Table 1 summarizes the occurrence of typical pharmaceutical micropollutants in conventional WWTP effluents at concentration higher than 1.0 $\mu g\,L^{-1}$. Miège et al. [34] also confirmed these pharmaceutical micropollutants as among the most investigated pharmaceuticals in WWTPs.

Since the pharmaceutical micropollutants listed in Table 1 have been frequently detected in WWTP effluents at relatively high concentration, they might be insufficiently removed in conventional WWTPs. Therefore, these pharmaceutical micropollutants are selected in this review to examine the capacity of MBR or MBR-related processes on the removal of pharmaceutical micropollutants.

3. MBR process for the removal of pharmaceutical micropollutants

3.1. Removal mechanisms of pharmaceutical micropollutants in MBR

Table 2 lists the physico-chemical properties of selected pharmaceutical micropollutants that relate to their removal in MBR. The mechanisms involved in MBR for pharmaceutical micropollutant removal may include physical retention of membrane, biotransformation, air stripping, sorption, and photo-transformation [19,22,67–70]. Since the molecular size of most pharmaceuticals (molecular weight between 100 and 1,000 $g\,mol^{-1}$) is at least 100 times smaller than the pore size of membrane used for MBR process, no direct physical retention of the compounds by MBR membrane can be expected [67]. However, Sahar et al. [71] and Urase et al. [72] suggested the deposits formed on the membrane surface might act as an additional barrier and thus contributed to an enhanced removal of pharmaceutical micropollutants in MBR. Further investigations should be carried out to confirm this assumption. As for removal by volatilization or stripping, the Henry coefficient (dimensionless, $\mu g\,L^{-1}{}_{air}/\mu g\,L^{-1}{}_{wastewater}$) of a compound should be higher than 0.005 to have a significant removal

Table 1
Occurrence of typical pharmaceutical micropollutants in conventional WWTP effluents at concentration higher than 1.0 μg L^{-1}

Compound	Concentration (μg L^{-1})	Reference
Analgesics		
Ibuprofen	1.7–55.0	[28,35–49]
Diclofenac	1.2–5.4	[28,36,38,41,43,47,50–53]
Naproxen	1.0–8.0	[35–40,42,48,49,51,54]
Ketoprofen	1.1–3.9	[36,37,39,40,49]
Lipid regulator		
Bezafibrate	1.0–4.8	[28,36,38,47,52]
Gemfibrozil	1.3–5.5	[28,36,38,43,48,51,55,56]
Antiepileptic		
Carbamazepine	1.1–6.3	[28,36,37,43,47–50,52,53,57–60]
Antibiotics		
Erythromycin-H_2O	2.0–6.0	[57,61,62]
Trimethoprim	1.2–3.0	[56,57,63–65]
Sulfamethoxazole	1.5–2.0	[61,65,66]

Table 2
Physico-chemical properties of selected pharmaceutical micropollutants

Compound	MW	H	pK_a	Log K_{ow}	K_d	k_{biol}
Analgesics						
Ibuprofen	206.3	6.1×10^{-6}	4.91	3.79–3.97	7	9–22
Diclofenac	296.15	1.9×10^{-10}	4.15	4.02–4.51	16	<0.1
Naproxen	230.3	1.4×10^{-8}	4.15	3.10–3.18	13	0.4–0.8
Ketoprofen	254.3	8.7×10^{-10}	4.45	3.0–3.12	16	0.68–1.59*
Lipid regulator						
Bezafibrate	361.8	8.7×10^{-14}	3.61	4.25	20	3.4–4.5
Gemfibrozil	250.3	4.9×10^{-7}	4.75	4.77	75	0.5–1.8
Antiepileptic						
Carbamazepine	236.27	4.4×10^{-9}	13.9	2.25–2.45	1.2	<0.1
Antibiotics						
Erythromycin	734.0	2.2×10^{-27}	8.88	2.48–3.06	165	<1.1
Trimethoprim	290.3	9.8×10^{-13}	7.2	0.73–0.91	200	0.22
Sulfamethoxazole	253.3	3.9×10^{-11}	5.6	0.89–0.91	260	0.2

Notes: MW, molecular weight (g/mol); H, Henry coefficient (μg L^{-1}_{air}/μg $L^{-1}_{wastewater}$); pK_a, dissociation constant; Log K_{ow}, octanol-water partition coefficient; K_d, sorption coefficient for activated sludge (L kg_{SS}^{-1}); k_{biol}, degradation rate constant in MBR (L $g_{SS}^{-1}d^{-1}$); and all data from [20,22,26,68,74–79].
*data obtained from batch experiments using enriched nitrifier culture [79].

(5%) as found in a EU project POSEIDON [26,67]. Because most of pharmaceutical micropollutants have a Henry coefficient smaller than 10^{-5} [73] (also see Table 2), removal of pharmaceutical micropollutants via stripping is negligible. Since the turbidity of wastewater blocks most of the sunlight and no secondary clarifier is employed in MBR, the photodegradation of pharmaceutical micropollutants in MBR is not significant. Thus, the main possible mechanisms for removal of pharmaceutical micropollutants in MBR are sorption and biodegradation.

Sorption of organic micropollutants to activated sludge of MBR depends on two main mechanisms, absorption and adsorption: Absorption is the hydrophobic interactions of the aliphatic and aromatic groups of a compound with the lipophilic cell membrane of the micro-organisms or with the lipid fraction of the sludge; Adsorption is the electrostatic interactions of positively charged groups of a compound with the negatively charged surface of the micro-organisms [23,67]. Since sorption coefficient K_d (L kg_{SS}^{-1}) is defined as the partition of a compound

between the sludge and the water phase [23], K_d does not only depend on hydrophobicity of a compound, but also depends on the presence of positively charged groups (e.g. amino groups) in its structure. In addition, the relation between K_d and Log K_{ow} is not obvious for acidic pharmaceutical micropollutants ibuprofen, diclofenac, naproxen, ketoprofen, and gemfibrozil as indicated in a study [80]. Because of the carboxyl functional group in their structures, these compounds are negatively charged (see their pK_a values in Table 2) at neutral pH. Thus, they are hydrophilic in the ionic state at neutral pH with their low K_d values (less than 100 L kg_{SS}^{-1}) even though their Log K_{ow} values are high (see their K_d and Log K_{ow} values in Table 2). For compounds with K_d value less than 500 L kg_{SS}^{-1}, their removal by sorption in activated sludge process was found to be negligible [77,81]. Since the K_d values of most pharmaceutical micropollutants, including all compounds listed in Table 2, are less than 500 L kg^{-1} and sludge production in MBR is generally smaller than CAS process, the removal of pharmaceutical micropollutants via sorption in MBR is of minor importance. In particular, carbamazepine has a K_d value of 1.2 L kg^{-1}, far away from the critical value of 500 L kg^{-1}, indicating that it is not sorbed to activated sludge to a significant degree. For antibiotics trimethoprim and sulfamethoxazole, although their K_d values are relatively high (higher than 200 L kg^{-1}), their sorption to activated sludge was not significant [63,82]. However, attention should be paid for the antibiotics ciprofloxacin and norfloxacin, the major mechanism relevant for their removal is sorption to activated sludge, due to their high K_d values (higher than 15,000 L kg^{-1}) [83,84]. Ciprofloxacin and norfloxacin are not listed in Table 1 due to their relatively low detected concentration in WWTP effluents.

Therefore, the main mechanism for removal of most pharmaceutical micropollutants in MBR is via biodegradation. Due to their trace level concentration in municipal wastewater, co-metabolism probably occurs for biological transformation or degradation of pharmaceutical micropollutants, in which case the bacteria accidentally break down or partially convert the micropollutant and do not use it as a carbon source for their growth [23]. In addition, the biodegradability of pharmaceutical micropollutants in MBR varies greatly in the range from zero to complete biotransformation [85]. Joss et al. [26] divided the pharmaceutical micropollutants into three different classes according to their degradation constant k_{biol} values in municipal wastewater treatment process: compounds with $k_{biol} < 0.1$ L $g_{SS}^{-1}d^{-1}$ are not removed to a significant extent (<20%), compounds with $k_{biol} > 10$ L $g_{SS}^{-1}d^{-1}$ are transformed by more than 90% and for compounds with k_{biol} in between, moderate removal efficiency is expected. Therefore, the remarkably poor removal of carbamazepine and diclofenac in biological wastewater treatment process is due to their low biodegradability with k_{biol} values less than 0.1 L $g_{SS}^{-1}d^{-1}$ as well as their low sorption potential to activated sludge with K_d values less than 20 L kg^{-1} [69]. Based on the degradation of a heterogeneous group of 35 compounds, Joss et al. [26] concluded that state of the art biological treatment schemes, including MBR, for municipal wastewater treatment is not efficient in degrading pharmaceuticals: only 4 out of 35 compounds are degraded by more than 90% while 17 compounds are removed by less than 50%.

3.2. Removal of typical pharmaceutical micropollutants in MBR

Table 3 summarizes the removal efficiency of typical pharmaceutical micropollutants in aerobic MBR. The removal efficiency range as well as average removal efficiency together with standard deviations is presented. According to the data from Table 3, these typical pharmaceutical micropollutants could be classified into four groups: (1) compounds that are very easily biodegraded in MBR with average removal efficiency higher than 95% (ibuprofen); (2) compounds easily biodegraded in MBR with average removal efficiency higher than 90% (bezafibrate); (3) compounds moderately biodegraded in MBR with average removal efficiency of 50–80% (naproxen, ketoprofen, gemfibrozil, erythromycin, trimethoprim, and sulfamethoxazole); and (4) compounds poorly biodegraded in MBR with average removal efficiency less than 40% (diclofenac and carbamazepine). Notably, carbamazepine is removed with average removal efficiency of only 7% in MBR. Due to the persistency of carbamazepine in the biological treatment process and aquatic environment, Clara et al. [86] proposed carbamazepine as a possible anthropogenic marker in the aquatic environment. Moreover, it is interesting to note that negative removal efficiency of diclofenac and carbamazepine in MBR was observed. This could be attributed to enzymatic cleavage of the glucuronic conjugates of those pharmaceuticals and consequently to the release of the parent compounds in the treated effluent [59,69], or analytical uncertainty and sampling uncertainty occurred during the analysis process [87]. Similarly, Göbel et al. [88] attributed the observed high variability of sulfamethoxazole elimination to the possible transformation of N^4-acetylsulfamethoxazole, main human metabolite of sulfamethoxazole, back to

Table 3
Removal of selected pharmaceutical micropollutants in MBR

Compound	Removal efficiency (%)	Average removal ± SD (%)	Reference
Analgesics			
Ibuprofen	90–100	96 ± 3	[47,52,77,85,89–103]
Diclofenac	−19–87	32 ± 27	[47,52,77,85,89–103]
Naproxen	16–99	69 ± 27	[77,85,89,91–98,100–104]
Ketoprofen	44–100	75 ± 20	[85,91,93–98,100,101,103,104]
Lipid regulator			
Bezafibrate	77–98	91 ± 6	[47,52,85,91,93–96,98,103]
Gemfibrozil	28–99	70 ± 29	[85,93–95,98,100–103]
Antiepileptic			
Carbamazepine	−24–58	7 ± 18	[47,52,77,85,89,90,92–95,98–103,105,106]
Antibiotics			
Erythromycin	25–91	60 ± 29	[71,85,88,89,94,105]
Trimethoprim	17–95	62 ± 30	[71,85,88,89,101,102,104,107]
Sulfamethoxazole	24–92	63 ± 16	[47,71,85,88,89,92,94,101,102,104–106,108]

sulfamethoxazole and a simultaneous elimination of sulfamethoxazole itself during biological treatment.

Thus, majority of pharmaceutical micropollutants are moderately biodegraded in MBR. In addition, degradation constant k_{biol} could be used as an effective parameter to predict the removal of pharmaceutical micropollutants in MBR. The k_{biol} values of the poorly removed compounds diclofenac and carbamazepine are less than 0.1 L $g_{SS}^{-1}d^{-1}$; the k_{biol} values of moderately removed compounds (naproxen, ketoprofen, gemfibrozil, erythromycin, trimethoprim, and sulfamethoxazole) are between 0.1 and 2 L $g_{SS}^{-1}d^{-1}$; the k_{biol} value of easily removed compound (bezafibrate) is in range from 2 to 5 L $g_{SS}^{-1}d^{-1}$. The k_{biol} value of very easily removed compound (ibuprofen) is higher than 5 L $g_{SS}^{-1}d^{-1}$.

3.3. Factors affecting the removal of pharmaceutical micropollutants in MBR

3.3.1. Solid retention time

Solid retention time (SRT) seems to be the most important parameter affecting the removal of pharmaceutical micropollutants in MBR. Table 4 summarizes the effect of SRT on removal of selected pharmaceutical micropollutants in MBR.

Removal of diclofenac, ketoprofen, gemfibrozil, trimethoprim, and erythromycin in MBR was found to be significantly affected by SRT [47,88,90,97,103,104]. Clara et al. [47] reported that no removal of diclofenac was observed with a SRT of approximately 10 d, while with increasing SRT a partial removal was observed. Kimura et al. [97] reported that the MBR operated with a longer SRT of 65 d significantly improved the elimination of ketoprofen and diclofenac as compared to the MBR with a shorter SRT of 15 d, from 82 to 98% and from 50 to 82%, respectively. Bernhard et al. [90] observed that the removal efficiency of diclofenac in a lab-scale MBR was between 8 and 38% with an SRT increased from 20 to 48 d, and 59% with an SRT of 62 d. Maeng et al. [103] found that the removal efficiencies of gemfibrozil and ketoprofen were increased from 41 to 88% and from 64 to 90%, respectively, when SRT was increased from 20 to 80 d. Göbel et al. [88] reported that for trimethoprim and erythromycin, a two-to-three times higher removal rate was seen for these compounds at a SRT of 60–80 d, up to 87–90% removal, as compared with the removal rate observed at SRT of 16 ± 2 and 33 ± 3 d.

No significant effect of SRT on removal of ibuprofen, bezafibrate, naproxen, carbamazepine, and sulfamethoxazole was observed in MBR [23,52,88,90,97,103,104]. Ibuprofen and bezafibrate were effectively removed when SRT is higher than a critical value, about 10 d [23,52,103]. While, carbamazepine was found to be recalcitrant to degradation in MBR regardless of the change in SRTs and microbial activity [90,103]. Concerning naproxen, Tambosi et al. [104] found that removal of naproxen in MBR was in the range of 85–90% at SRT of 15 and 30 d. Kimura et al. [97] observed removal efficiency of naproxen higher than 95% in MBR operated at SRT of 15 and 65 d. Maeng et al. [103] found that the removal efficiency was about 25% for naproxen in MBR at SRT of 20 and 80 d. As for sulfamethoxazole, Göbel et al. [88] reported removal efficiency of about 40% for sulfamethoxazole and about 80% for sulfamethoxazole together with its main human metabolite N^4-acetylsulfamethoxazole in MBR, with no dependence on SRT from 16 to 80 d.

Table 4
Effect of SRT on removal of selected pharmaceutical micropollutants in MBR

Compound	Significantly affected by SRT	Not significantly affected by SRT	Reference
Analgesics			
Ibuprofen		×	[22,23,52,103]
Diclofenac	×		[47,90,97]
Naproxen		×	[97,103,104]
Ketoprofen	×		[97,103,104]
Lipid regulator			
Bezafibrate		×	[23,52,103]
Gemfibrozil	×		[103]
Antiepileptic			
Carbamazepine		×	[23,90,103]
Antibiotics			
Erythromycin	×		[88]
Trimethoprim	×		[88,104]
Sulfamethoxazole		×	[23,88,104]

High SRT allows the enrichment of slow-growing micro-organisms (e.g. nitrifying bacteria) and consequently the establishment of a more diverse bacteria population, which favors the removal of pharmaceutical micropollutants in MBR [52]. Thus, the effect of SRT on removal of some moderately removed pharmaceutical micropollutants is quite significant, for example, ketoprofen, gemfibrozil, trimethoprim, and erythromycin. Terne et al. [23] concluded that the biological transformation of a pharmaceutical compound depended on the age of the activated sludge; Bezafibrate, sulfamethoxazole, and ibuprofen required a sludge age of 2–5 d for significant degradation; diclofenac needed 5–15 d; Carbamazepine was not degraded even at a sludge age >20 d. Similarly, Clara et al. [52] defined a critical SRT for effective removal of pharmaceutical micropollutants, e.g. amounting to about 5 d for ibuprofen and to about 10 d for bezafibrate. Thus, SRT of higher than about 15 d is recommended to significantly improve the removal of pharmaceutical micropollutants in municipal wastewater treatment system [23,52,76].

3.3.2. pH

Although sorption of most pharmaceutical micropollutants to activated sludge in MBR is negligible at neutral pH, enhanced sorption was observed for some acidic pharmaceuticals at lower pH. Urase et al. [72] reported that the removal rate of acidic pharmaceuticals—gemfibrozil, ibuprofen, ketoprofen, and diclofenac in MBR was much higher at pH of 4.3–5.0 than that at pH of 6.8–7.6 and 7.5–8.0. On the other hand, the removal of neutral pharmaceutical carbamazepine was not significantly affected by pH. The authors explained that in the neutral pH condition, these acidic pharmaceuticals were ionized; however, in the acidic pH condition, these pharmaceuticals were not ions and their hydrophobicity was increased, resulting in their sorption onto activated sludge. Moreover, it was found that the target substances attached to the sludge were not accumulated in the sludge phase, and they were biologically degraded. Tadkaew et al. [109] studied the removal of sulfamethoxazole, carbamazepine, diclofenac, ibuprofen, and ketoprofen in a batch-scale MBR at different pH (pH 5–9). The results showed that the influence of mixed liquor pH on the removal of pharmaceuticals was quite dramatic for all four ionizable compounds (sulfamethoxazole, diclofenac, ibuprofen, and ketoprofen), with highest removal at pH 5; in contrast, no apparent variation in removal efficiency of the neutral compound carbamazepine was observed.

3.3.3. Redox conditions

Monsalvo et al. [110] observed a poor removal, lower than 15%, for diclofenac, carbamazepine, ibuprofen, gemfibrozil, and ketoprofen, partial removal for trimethoprim and naproxen, i.e. 35.4 and 70.3%, respectively, and high removal of 95.2% for sulfamethoxazole in anaerobic MBR, suggesting the poor capacity of anaerobic MBR on removal of most pharmaceutical micropollutants. In contrast, Hai et al. [106] observed that during near-anoxic operation with dissolved oxygen concentration in the bioreactor about 0.5 mg L^{-1}, an exceptionally high removal (68 ± 10%) of carbamazepine was achieved in MBR as compared to its low removal efficiency (12 ± 11%) under aerobic conditions; on the other hand, an average removal efficiency of 65% for sulfamethoxazole was achieved irrespective of the DO concentrations.

3.3.4. Nitrifying biomass

The enrichment of nitrifying bacteria was reported to enhance the removal of pharmaceutical micropollutants in biological wastewater treatment system [79,103,111–113]. "Maeng et al. [103] found" that the removal of gemfibrozil, diclofenac, bezafibrate, and ketoprofen was enhanced by ammonium-oxidizing bacteria in MBR. Suarez et al. [113] reported the removal efficiency of diclofenac, from 0 to 74%, in the aerobic reactor was positively correlated with nitrifying biomass concentration rather than SRT. Tran et al. [79] reported that the enriched nitrifier culture enhanced degradation of gemfibrozil, ketoprofen, naproxen, diclofenac, and carbamazepine with their increased biodegradation constant k_{biol}, especially for carbamazepine and diclofenac. Besides, the authors found that removal efficiency of these compounds by enriched nitrifier culture increased with the increase of initial ammonium concentration in batch reactors. Similarly, Fernandez-Fontaina et al. [112] reported high biodegradation efficiencies of ibuprofen, naproxen, trimethoprim, and erythromycin were obtained with nitrifying activated sludge working at high nitrogen loading rates.

3.3.5. Molecular structures

Some authors related the removal of pharmaceutical micropollutants in MBR to their compound structures. Tadkaew et al. [101] reported that the removal of pharmaceuticals possessing only electron donating groups (like hydroxyl groups and primary amine groups), such as ibuprofen, ketoprofen, and sulfamethoxazole, was usually higher than 70%, while the removal of pharmaceuticals possessing only electron withdrawing groups (like a chlorine atom or amide group), such as carbamazepine and diclofenac, was usually lower than 20%. Kimura et al. [96] attributed the poor removal of diclofenac in MBRs to the presence of chlorine in their structures. Bouju et al. [114] attributed high removal of ibuprofen to its simple molecular structure.

3.4. Effects of pharmaceutical micropollutants on MBR process

The presence of pharmaceutical micropollutants in MBR may affect microbial activity and microbial community structure of micro-organisms in activated sludge [115–117]. Besides, the presence of pharmaceutical micropollutants in MBR may also induce protection mechanism of micro-organisms to produce some extracellular polymeric substances (EPS) [118,119], which could affect membrane fouling of MBR [118].

3.4.1. Effects on microbial activity and microbial community structure

Aubenneau et al. [115] examined the effect of trace concentration of carbamazepine on mixed microbial communities of activated sludge taken from MBR. The authors reported that in presence of 1 μg L^{-1} carbamazepine, higher endogenous respiration rates, lower exogenous respiration rates, and smaller flocs size were observed. The authors explained that the increase in endogenous respiration rates suggested an increase in maintenance requirements of bacteria in order to manage the chemical stress induced by carbamazepine; and the decrease of exogenous respiration rates indicated a change in the metabolic pathways of the substrate or a change in the active bacterial species. Delgado et al. [118] also reported an increase in the endogenous respiration of heterotrophic micro-organisms after continuous addition of about 5 μg L^{-1} cytostatic drug cyclophosphamide and its principal metabolites (CPs) in MBR. The authors attributed the high microbial activity in endogenous conditions to their adapting to the presence of CPs. Wang et al. [116] reported a 39, 39, and 19% decrease, respectively, in specific oxygen uptake rate when there was the presence of 10 μM naproxen, ketoprofen, and carbamazepine in activated sludge in batch experiments. The results indicated that the presence of some pharmaceuticals may inhibit microbial activity of some activated sludge micro-organisms. The authors also found shifts in microbial community structure in the presence of ketoprofen and naproxen via DGGE analysis. Through T-RFLP analyses of the bacterial 16S rRNA genes, Kraigher et al. [120] observed a minor but consistent shift in the bacterial community structure in activated sludge of the bioreactor supplied with pharmaceuticals (ibuprofen, naproxen, ketoprofen, and diclofenac) at concentration of 50 μgL^{-1}, compared to the control reactor operated without the addition of pharmaceuticals; Moreover, a greater structural divergence was observed in the reactors operated with higher concentration of pharmaceuticals.

3.4.2. Effects on MBR performance and MBR fouling

Delgado et al. [118] studied the effects of continuous addition of 5 μg L^{-1} CPs in MBR on characteristics of activated sludge and membrane fouling. In presence of CPs, formation of small particles and higher-soluble EPS concentration in activated sludge were observed. Meanwhile, higher transmembrane pressure and higher specific cake resistance of activated sludge were observed, which indicated faster membrane fouling. However, no effect on removal of COD and total

nitrogen by MBR was observed in the presence of CPs. Lay et al. [121] observed increase in the protein and polysaccharide ratio for both soluble and bound EPS in the activated sludge after the addition of 20–25 μg L^{-1} carbamazepine, diclofenac, ibuprofen, and naproxen in the feed tank of a Novel Osmotic Membrane Bioreactor (OMBR). The authors attributed the increase in protein content to a natural microbial response or occurrence of cell lysis and release of intracellular polymers under the pharmaceutical stress. Avella et al. [119] reported that the continuous addition of trace concentration CPs in MBR induced an increase in soluble EPS (mainly proteins of about 18 KDa and polysaccharides of about 6 KDa) in bulk solution and to a much lower degree in bound EPS in the sludge. The authors attributed the increase of these macromolecular species to a protection mechanism of micro-organisms and attributed the more important membrane fouling to retention of these macromolecular species by the membrane. However, Jacob [122] observed stable operation of MBR using real municipal wastewater that contained pharmaceutical micropollutants (diclofenac 0.7 μg L^{-1}, naproxen 0.7 μg L^{-1}, ketoprofen 1.6 μg L^{-1}, bezafibrate 0.6 μg L^{-1}, and carbamazepine 0.5 μg L^{-1}) during 164 d, which indicated that acclimation of micro-organisms to pharmaceutical stress may happen in this situation and no significant additional fouling was induced by the presence of these pharmaceutical micropollutants in raw wastewater.

4. MBR-related processes for the removal of pharmaceutical micropollutants

Since MBR alone is not sufficient to completely eliminate all pharmaceutical micropollutants in municipal wastewater, hybrid or combined processes based on MBR get much attentions. Among MBR-related processes, the capacity of activated carbon-assisted MBR and combined MBR–RO process on the removal of pharmaceutical micropollutants has been well investigated. Table 5 summarizes the removal efficiencies of selected pharmaceutical micropollutants in activated carbon-assisted MBR and combined MBR–RO process. Other MBR-related processes, such as MBR–Ozone [123], MBR–UV [124], MBR–TiO_2 [125], and OMBR [121,126], were also reported to be significantly enhance the removal of pharmaceutical micropollutants; however, more studies are required to fully understand their capacity.

Activated carbon-assisted MBR system can be further divided into two categories: MBR–powdered activated carbon (PAC) hybrid process and combined MBR–GAC process. In MBR–PAC hybrid process, PAC is added into MBR, while in combined MBR–GAC process, granular activated carbon (GAC) column is used as post polishing unit after MBR. The coupling of activated carbon with MBR enables the activated carbon-assisted MBR system to increase the removal of some pharmaceutical micropollutants that are originally difficult to be removed in MBR, such as carbamazepine and diclofenac [95,98,127–129]. Serrano et al. [129] reported that after a single addition of 1 g L^{-1} of PAC directly into the aeration tank of MBR, an immediate and sharp removal increase was observed for the recalcitrant pharmaceutical micropollutants such as carbamazepine, diclofenac, and trimethoprim, with removal efficiencies in the range of 93–99%. Besides, the moderately degraded substance, erythromycin, was completely removed after PAC addition (97–99%). Moreover, microbial ecology present in the biomass showed a higher abundance of ammonium-oxidizing bacteria after PAC addition, which may enhance the degradation of pharmaceutical micropollutants in MBR. Nguyen et al. [128] reported that the removal of hydrophilic and biologically persistent pharmaceutical micropollutants (ketoprofen, naproxen, diclofenac, and carbamazepine) was immediately improved to above 95%, after the addition of only 0.1 g/L PAC into MBR. While, the gradual decrease in removal underscored the requirement for the addition of fresh PAC during the continuous operation. Li et al. [127] reported that the removal efficiencies of sulfamethoxazole and carbamazepine increased to 82 ± 11% and 92 ± 15% from the levels of 64 ± 7%, and negligible removal, respectively, when the PAC dosage was raised from 0.1 to 1.0 g L^{-1}. Moreover, it is interesting to note that after the PAC addition, the MBR membrane achieved significant additional removal of both micropollutants, especially for carbamazepine, as compared to the situation in MBR without addition of PAC. The authors attributed the enhanced removal to their sorption onto membrane cake layer. Nguyen et al. [98] reported that the GAC post treatment could significantly improve removal of the pharmaceutical micropollutants which were poorly removed by MBR. For example, the compounds, which were removed by MBR with efficiencies below 40% (ketoprofen, naproxen, diclofenac, and carbamazepine), achieved overall removal efficiencies of 98% or above following GAC treatment. Since some pharmaceutical micropollutants could not be biodegraded in MBR, replacement or regeneration of activated carbon should be required to maintain high removal of pharmaceutical micropollutants during the long-term operation for activated carbon-assisted MBR systems.

The combined MBR–RO process is one of the dual membrane systems often used for production of reclaimed water besides the CAS-MF/UF-RO process

Table 5
Removal of selected pharmaceutical micropollutants in MBR-related processes

Compound	Removal efficiency (%) in MBR–PAC[a]	Removal efficiency (%) in MBR–GAC[b]	Removal efficiency (%) in MBR–RO[c]
Analgesics			
Ibuprofen	>95	>98	>95
Diclofenac	>93	>98	>88
Naproxen	>95	>98	>95
Ketoprofen	>95	>98	>95
Lipid regulator			
Bezafibrate	n.a.	n.a.	
Gemfibrozil	>95	>98	>95
Antiepileptic			
Carbamazepine	>92*	>98	>82
Antibiotics			
Erythromycin	>97	n.a.	>95
Trimethoprim	>97	n.a.	>95
Sulfamethoxazole	82*	n.a.	>95

[a][127–129].
[b][98].
[c][74,92,99,102,105,124,130,131].
*The influent concentration in the experiment is 750 $\mu g\,L^{-1}$; n.a. = not available.

[132]. Alturki et al. [74] reported that the combination of MBR and a low-pressure RO membrane resulted in more than 95% removal or removal below the analytical detection limit of all 40 trace organic compounds including most typical pharmaceutical micropollutants. Dolar et al. [105] reported that the combination of MBR and RO treatment showed excellent overall removal of 20 detected pharmaceutical micropollutants in WWTPs with removal efficiencies above 99%. Cartagena et al. [99] also found that the post-RO process can significantly improve the removal of pharmaceutical micropollutants like carbamazepine and diclofenac after MBR treatment in real municipal wastewater. However, the total removal of carbamazepine and diclofenac by MBR–RO process was not complete, 82.1–93.1% and 88.3–95.9%, respectively. Similarly, Joss et al. [130] also reported the incomplete removal of carbamazepine and diclofenac by MBR–RO process. Snyder et al. [102] reported almost complete removal of all detected pharmaceuticals in the tested MBR–RO pilots. While, Sahar et al. [131] reported that RO cannot serve as an absolute barrier for pharmaceutical removal in MBR–RO process since ibuprofen and diclofenac were detected in the effluent in the range of 28–223 $ng\,L^{-1}$, although most pharmaceutical micropollutants investigated were removed in high efficiencies, higher than 93%, by MBR–RO process. Kimura et al. [133] reported that in the filtration tests with MBR effluent, no significant variance of rejection of the pharmaceutical micropollutants was observed for RO membrane as compared with deionized pure water spiked with the pharmaceutical micropollutants, suggesting that the main mechanism for rejection of pharmaceutical micropollutants by RO membrane is size exclusion.

5. Conclusions

The presence of pharmaceutical micropollutants in the aquatic environment has become a serious problem for municipal wastewater reclamation and reuse around the world. MBR process with high SRT is a good choice to replace the CAS process in water reuse projects due to its better removal of micropollutants. Although the MBR process alone could not assure the complete removal for the majority of pharmaceuticals, the possibility of MBR to be coupled with other processes, such as activated carbon adsorption and RO membrane filtration, enables it to significantly improve removal of pharmaceutical micropollutants. Thus, MBR would play a more important role in wastewater treatment and reuse applications in the future.

It can be concluded that the main mechanism for removal of most pharmaceutical micropollutants in MBR is biodegradation; In terms of operation conditions, higher SRT, lower pH, higher nitrogen loading rate, and anoxic condition favor removal of some pharmaceutical micropollutants in MBR; while, no evidence was found concerning the effect of MBR configuration

(flat sheet or hollow fiber) on removal of pharmaceutical micropollutants in MBR; In addition, the presence of pharmaceutical micropollutants in MBR could affect the microbial activity and microbial community structures of micro-organisms in activated sludge and cause more serious membrane fouling. However, the difficulty to compare data from different scales of MBR or MBR-related processes (lab scale, pilot scale, and full scale), the difficulty in quantifying sorbed mass content of pharmaceutical micropollutants in sludge phase, the uncertainty in analysis of pharmaceutical micropollutants and their metabolites in liquid phase, and even sampling procedures make it hard to draw reliable conclusions from the literature.

Still, many questions are remained unanswered. Regarding the mechanisms for removal of pharmaceutical micropollutants, distinguish between sorption and biodegradation should be further investigated, taking into account the fact that the sorbed pharmaceutical micropollutants in sludge phase may be further biodegraded by activated sludge and sorption may play an important role in biodegradation of pharmaceutical micropollutants in terms of mass transfer. Also, the function of deposits on membrane surface as an additional barrier for removal of pharmaceutical micropollutants should be further examined. In addition, more studies should be performed to identify the bacterial species that favor removal of pharmaceutical micropollutants in MBR and determine the optimal operation conditions that help to enrich these bacterial species. Last but not least, it is recommended that more studies concerning the risk assessment of pharmaceutical micropollutants on human health and aquatic organisms must be conducted to evaluate the necessity of advanced wastewater treatment processes, like MBR and MBR-related processes, to be employed in the wastewater treatment and reuse schemes.

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