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Review

Anaerobic membrane bioreactors for pharmaceutical-laden wastewater treatment: A critical review

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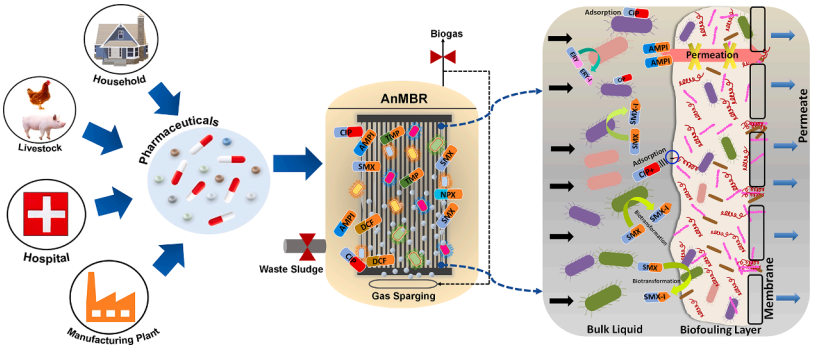
HIGHLIGHTS

- Fate and removal of diverse pharmaceuticals in AnMBR system are critically reviewed.
- Potential role of different AD stages in pharmaceuticals biotransformation is elucidated.
- Key microbial communities in conjunction with pharmaceuticals removal are unraveled.
- Membrane biofouling layer play a positive role in pharmaceuticals removal.
- Advances in AnMBR configurations for mitigating biofouling are critically discussed.

GRAPHICAL ABSTRACT



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ABSTRACT

Pharmaceuticals are a diverse group of chemical compounds widely used for prevention and treatment of infectious diseases in both humans and animals. Pharmaceuticals, either in their original or metabolite form, find way into the wastewater treatment plants (WWTPs) from different sources. Recently, anaerobic membrane bioreactors (AnMBR) has received significant research attention for the treatment of pharmaceuticals in various wastewater streams. This review critically examines the behaviour and removal of a wide array of pharmaceuticals in AnMBR with primary focus on their removal efficiencies and mechanisms, critical influencing factors, and the microbial community structures. Subsequently, the inhibitory effects of pharmaceuticals on the performance of AnMBR and membrane fouling are critically discussed. Furthermore, the imperative role of

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membrane biofouling layer and its components in pharmaceuticals removal is highlighted. Finally, recent advancements in AnMBR configurations for membrane fouling control and enhanced pharmaceuticals removal are systemically discussed.

1. Introduction

Pharmaceuticals play an indispensable role in revolutionizing modern life with their colossal usage as drugs for human therapy and veterinary applications. They are a large group of chemical compounds possessing both pharmacologic and physiologic properties and available as prescribed, non-prescribed, and over-the-counter therapeutic drugs (Mandaric et al., 2019). Pharmaceuticals are categorized based on their characteristics and applications, including antibiotics, β-blockers, analgesics, hormones, antidepressants, antiepileptics, anti-inflammatory drugs, X-ray contrast media, and blood lipid regulators. Exponential increase in pharmaceuticals consumption has been evidenced globally in terms of total quantity usage and their types. For instance, between 2000 and 2015, human antibiotic consumption increased by 65.0%, attributing to rapid urbanization and higher occurrence rate of infectious diseases (Klein et al., 2018). The global pandemic associated with the SARS-CoV-2 virus also contributed to the increased use of antibiotics with several early reports suggesting high antibiotic consumption in COVID-19 patients for treating bacterial co-infections (Pulia et al., 2020).

High consumption of pharmaceuticals leads to greater environmental concern as they cannot be completely metabolized by living biota, resulting in the excretion via feces and urine as a mixture of parent compounds or conjugate derivatives (Tiwari et al., 2017). Moreover, other principal sources that contribute to the release of pharmaceuticals are effluents from pharmaceutical manufacturing industries (Wang et al., 2021), hospitals (Kovalova et al., 2012), animal farms and aquaculture (Zhi et al., 2018), and disposal of unused and/or expired medicines in toiletries and drains (Vatovec et al., 2017). The discharged pharmaceuticals eventually reach the wastewater treatment plants (WWTPs) at concentrations ranging between ng/L to μg/L. Although occurrence of pharmaceuticals has been reported in trace concentrations, they can potentially cause toxic and endocrine disruptive effects along with proliferation of resistant strains of bacteria (Schultz et al., 2011). Thus, pharmaceuticals, recognized as contaminants of "emerging concern" or pseudo-persistent pollutants, demand effective and advanced treatment technologies for their removal from wastewater streams.

The presence of pharmaceuticals in effluents and their detection in surface, ground, and drinking water provides evidences of inadequacy of the existing conventional activated sludge process (ASP). In this regard, membrane bioreactors (MBRs), recognized as a promising alternative to ASP, have been ubiquitously deployed for higher and wide range of pharmaceuticals removal (Radjenović et al., 2009; Tran et al., 2016). Nevertheless, efforts had been laid to transform existing WWTPs to energy-neutral, resulting in the evolution of anaerobic membrane bioreactor (AnMBR). AnMBR combines the membrane separation processes, such as microfiltration (MF) and ultrafiltration (UF), with conventional anaerobic digestion (AD) process. The low sludge yield, efficient resource recovery, high removal rate, efficient solid–liquid separation, better effluent quality, and a smaller environmental footprint, make the AnMBR highly attractive alternative to aerobic process for wastewater treatment (Lin et al., 2011; Wang et al., 2014). AnMBR has been successfully applied for the treatment of industrial and municipal wastewaters, both at pilot and full-scale as an alternative to the conventional wastewater treatment processes (Lin et al., 2013). MBR studies on removal of pharmaceuticals until date focused mostly under aerobic conditions (Hamon et al., 2018). There are very limited studies on pharmaceuticals removal using AnMBR, where different microbial communities and redox conditions exist, facilitating their removal (Monsalvo et al., 2014; Wei et al., 2019; Zarei-Baygi et al., 2019). For instance, effective removal of pharmaceuticals, including sulfamethoxazole (SMX) (99.6%), trimethoprim (TMP) (97.5%), and acetaminophen (ACT) (85.9%), was observed in AnMBR at an initial concentration of 5.0 μg/L, predominantly via biotransformation (Wijekoon et al., 2015). More importantly, current studies limit to determining their effluent concentrations, with very little insights on mechanisms and biotransformation pathways. Nevertheless, several critical reviews examining the fate and removal of different emerging contaminants in AnMBR with insights on removal efficiencies, pathways, and critical influencing factors have been published (Cheng et al., 2018; Ji et al., 2020; Lim et al., 2020; Zhang et al., 2021). However, an in-depth analysis of the biodegradation mechanisms (including functional microorganisms and catabolic enzymes and genes involved) of different classes of pharmaceuticals in AnMBR system is still lacking. Additionally, the effects of pharmaceuticals on the methanogenesis and membrane fouling also need to be critically examined for stable and efficient AnMBR operation.

Thus, the overarching goal of this review is to provide a comprehensive yet synthesized information on the fate of pharmaceuticals during AnMBR treatment process, with emphasis on removal efficiencies, mechanisms, pathways, and the key design and operational factors. Moreover, the effects of pharmaceuticals on the overall treatment process and the potential role of the membrane biofouling layer in pharmaceuticals removal are critically discussed. Furthermore, recent advancements in AnMBR configuration as a potential strategy to control membrane fouling are highlighted. Finally, the challenges and perspectives related to the operation of AnMBR are elucidated to promote its widespread application for removal of emerging contaminants.

2. Potential sources and occurrence of pharmaceuticals in wastewater

High concentration of pharmaceuticals is common in wastewater from hospitals and pharmaceutical manufacturing industries (Yao et al., 2021). Fluoroquinolones (FQs), sulfonamides (SAs), and TMP are amongst the most ubiquitous classes of antibiotics in hospital effluents with concentrations ranging from 0.36 to 179.0 μg/L (ciprofloxacin (CIP)), 0.02 to 710.0 μg/L (SMX), 0.02 to 192.0 μg/L (TMP), respectively (Cai et al., 2022; Hamon et al., 2018; Kalaboka et al., 2020; Mir-Tutusaus et al., 2017; Wiest et al., 2018; Yao et al., 2021). High levels of CIP (5.3 mg/L), doxycycline (DOX) (6.8 mg/L), levofloxacin (LEV) (6.2 mg/L), ofloxacin (OFL) (4.1 mg/L), and oxytetracycline (OTC) (9.4 mg/L) were detected in a pharmaceutical manufacturing industrial effluent in Lahore, Pakistan (Hussain et al., 2016). The concentration of pharmaceuticals in WWTPs may differ amongst the countries, depending on the consumption pattern and population. For instance, high levels of antibiotics release from Asian countries, including India, China, Vietnam, Taiwan, and Korea, have been reported, whilst much less information is available for other geographic regions of the world, including the United States and the European Union (Thai et al., 2018). Analgesics and non-steroidal anti-inflammatory drugs (NSAIDs), including ibuprofen (IBU), ACT, naproxen (NPX), diclofenac (DCF), and ketoprofen (KET), are some of the most prescribed groups. These drugs are frequently detected at very high concentrations relative to other pharmaceuticals in municipal wastewater with concentrations ranging from 0.03 to 410.0 μg/L (DCF), 0.13 to 221.0 μg/L (IBU), and 0.04 to 240.0 μg/L (ACT) (Madikizela and Chimuka, 2017; Praveenkumarreddy et al., 2021; Sörengård et al., 2019; Yan et al., 2021). The high concentrations of these compounds are not surprising, given the fact that

they are critically relevant for public health and often consumed at a high daily dose. Moreover, many of these drugs can be purchased over-the-counter.

Carbamazepine (CBZ), a widely used anticonvulsant drug, has been reported as high as 183.9 μg/L in municipal wastewater (Ravichandran et al., 2021). β-blockers such as atenolol (ATN) are widely prescribed medications for the treatment of hypertension, cardiac dysfunction, and angina pectoris. The occurrence of this drug is frequently reported in sewage and hospital effluents with concentration varying between 0.05 and 26.5 μg/L and 0.004 and 12.9 μg/L, respectively (Afsa et al., 2020; Thiebault et al., 2017; Xu et al., 2019). Compared to other pharmaceuticals, the detection frequency of stimulant caffeine (CAFF) is higher in domestic wastewater (6.2–250.0 μg/L) and hospital effluents (0.28–902.0 μg/L), attributing to its daily high consumption (Afsa et al., 2020; Ravichandran et al., 2021; Wang et al., 2018). Though there are several classes of pharmaceuticals, this review focuses on eight major classes, including antibiotics, anti-inflammatory, analgesic, anticonvulsant, β-blocker, lipid regulator, antidepressant, and stimulant mostly used for human and veterinary applications. The global occurrence and physical–chemical properties of the target pharmaceuticals in wastewaters from varied sources are summarized in Fig. 1 (see also supplementary material).

3. Overview of AnMBR technology: Process and configuration

AnMBR is an integrated system coupling anaerobic bioreactor with membrane filtration. The incorporation of a membrane module decouples hydraulic retention time (HRT) from solids retention time (SRT), extending its applicability for treating various strengths of wastewater (Liu et al., 2020a). The recent attention in AnMBR technology is largely attributed to the key benefit of "resource recovery" combined with "high-quality" permeate with good operational resilience (Liu et al., 2018). The membrane pore size, material, and configuration are important design considerations having significant effect on treatment performance. The two main AnMBR configurations are: external/side-stream and submerged/immersed (see supplementary material). MF and UF are the most predominantly used membrane modules in hollow fiber (HF), flat sheet (plate or frame), or tubular configuration with organic (polymeric), inorganic (ceramic), and metallic material of construction (Abdelrahman et al., 2021; Lu et al., 2021). Most commercial membranes are composed of polysulfone, polyether sulfone, polypropylene, polyethylene, and polyvinylidene fluoride (PVDF) hydrophobic polymers, attributing to the low cost and superior chemical, thermal and mechanical properties (Stuckey, 2012). However, these membranes are susceptible to fouling which is often irreversible. Regardless of membrane configuration, continuous stirred-tank reactor (CSTR) is the most commonly used bioreactor system due to its ease of operation and maintenance. Alternatively, up-flow anaerobic sludge blanket (UASB) reactor and anaerobic fluidized bed reactor (AFBR) have also been explored for better biomass retention.

4. AnMBR application in pharmaceuticals removal

Pharmaceuticals removal by MBR has been extensively studied and significant progress has been made in understanding their fate during wastewater treatment. However, previous investigations focused exclusively on aerobic MBR (AMBR). Considering the increasing interest in anaerobic wastewater treatment technologies, the fate of pharmaceuticals in such systems is becoming critically important. Some specific studies reported the application of AnMBR for pharmaceuticals removal with satisfactory chemical oxygen demand (COD) removal and methane yield (Table 1). However, large variations in the removal of pharmaceuticals, including SMX ranging from (78.0% [250.0 μg/L] to 99.6% [5.0 μg/L]) (Wijekoon et al., 2015; Zarei-Baygi et al., 2020), TMP (35.4% [1.6 μg/L] to 97.5% [5.0 μg/L]) (Monsalvo et al., 2014; Wijekoon et al., 2015), IBU (1.0% [1.7 μg/L] to 28.0% [5.0 μg/L]) (Liu et al., 2020a; Monsalvo et al., 2014), ACT (18.0% [20.0 μg/L] to 85.9% [5.0 μg/L]) (Wei et al., 2016; Wijekoon et al., 2015), CBZ (0.3% [2.0 μg/L] to 39.2% [5.0 μg/L]) (Wijekoon et al., 2015; Xiao et al., 2017), ATN (12.0% [20.0 μg/L] to 76.5% [5.0 μg/L]) (Wei et al., 2016; Wijekoon et al., 2015), and amitriptyline (AMI) (47.0% [1.1 μg/L] to 99.6% [5.0 μg/L]) (Monsalvo et al., 2014; Wijekoon et al., 2015), were reported, depending on the pharmaceuticals type, concentration, membrane types, and operating conditions (Table 1).

Biotransformation was the dominant removal mechanism for CIP, amoxicillin (AMOX), SMX, and TMP in the AnMBR process (Cheng et al., 2021; Do and Stuckey, 2019; Huang et al., 2018; Wei et al., 2019). Further in-depth analysis indicated the role of physical–chemical properties including hydrophobicity and molecular structural features (i.e., electron-withdrawing groups (EWGs) and electron-donating groups (EDGs), presence of nitrogen, sulfur, and halogen substitute) in pharmaceuticals biotransformation (Monsalvo et al., 2014; Wijekoon et al., 2015). Biodegradable pharmaceuticals (e.g., TMP, AMI, ATN, CAFF, ACT, NPX, gemfibrozil (GMF)) containing strong EDGs (-NH_2, -NHR,

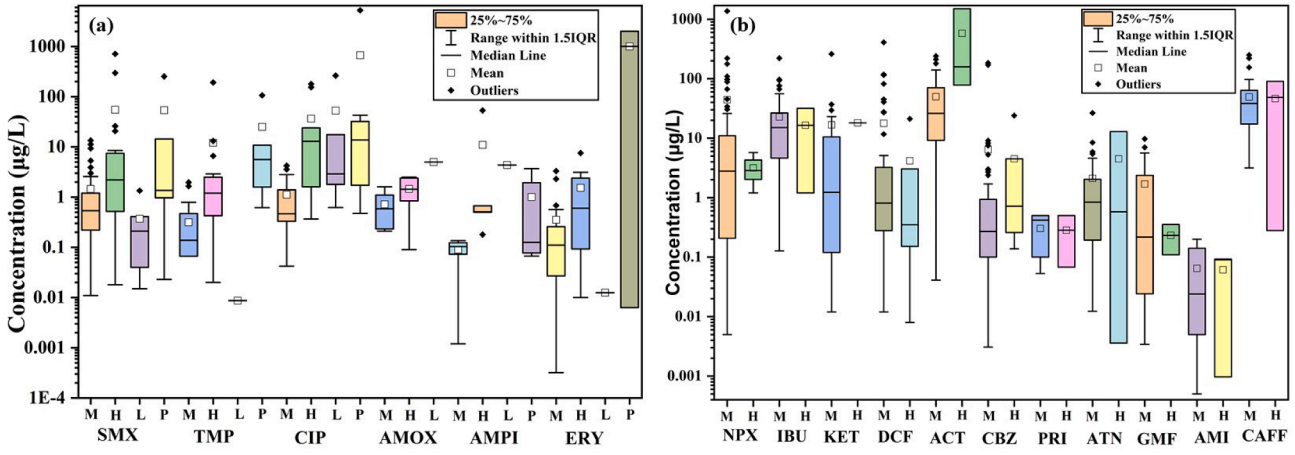

Fig. 1. Occurrence of commonly detected pharmaceuticals in wastewater from different sources, including municipal (M), hospitals (H), livestock farms (L), and pharmaceutical (P) industries effluent. Pharmaceuticals included antibiotics (SMX = Sulfamethoxazole, TMP = Trimethoprim, CIP = Ciprofloxacin, AMOX = Amoxicillin, AMPI = Ampicillin, ERY = Erythromycin); anti-inflammatory (NPX = Naproxen, IBU = Ibuprofen, KET = Ketoprofen, DCF = Diclofenac); analgesic (ACT = Acetaminophen); anticonvulsant (CBZ = Carbamazepine, PRI = Primidone); β-blocker (ATN = Atenolol); lipid regulator (GMF = gemfibrozil); antidepressant (AMI = Amitriptyline); stimulant (CAFF = caffeine). Data was taken from studies published between 2016 and 2022 in different geographical regions. Concentration ranges of pharmaceuticals are summarized in supplementary material.

Table 1
Summary of system performance and pharmaceuticals removal in different AnMBR configuration.

AnMBR configuration	Critical operating conditions	COD/TOC concentration (mg/L)	Pharmaceuticals initial concentration	Biogas and CH_4 yield	COD removal efficiency (%)	Pharmaceuticals removal efficiency (%)	References
Submerged AnMBR with MF flat-sheet membrane Pore size: 0.2 μm	HRT: 6 h SRT: 300 d Temp: 35 °C	COD: 489.0	0.5–4.7 mg/L	CH_4: 0.15–0.25 L/g_{COD} removed	78.0–98.0	CIP: 20.0–76.4	(Do et al., 2022)
Submerged Upflow with PVDF HF membrane Pore size: 0.07–0.1 μm	HRT: 22 h Temp: 22 °C OLR: 3.3 kg $COD/m^3/d$	COD: 3000.0	100.0 μg/L	CH_4: 0.2 L/g_{COD} removed	95.6–96.5	SMX: 87.3–91.7; SMZ: 20.6–43.7; SDZ: 22.4–46.8	(Cheng et al., 2021)
Glass reactor with external ceramic MF membrane Pore size: 0.4 μm	HRT: 48 h SRT: 250 d Temp: 35 °C	TOC: 2153.0	5.0 μg/L	Biogas: 0.4 L/g_{COD} added	>98.0	CBZ: 34.0; KET: 24.0; NPX: 52.0; IBU: 28.0; GMF: 30.0; DCF: 14.0; PRI: 34.0; AMI: 98.0	(Liu et al., 2020a)
CSTR with submerged flat sheet ceramic MF membrane Pore size: 0.1 μm	HRT: 16 h SRT: 300 d Temp: 25 °C	COD: 453.0	250.0 μg/L	CH_4: 0.5 L/d	90.0	SMX: 69.0–78.0; ERY: 40.0–58.0; AMPI: 89.0–98.0	(Zarei-Baygi et al., 2020)
CSTR with side-stream crossflow PVDF HF UF membrane Pore size: 0.03 μm	HRT: 24 h SRT: 700 d Temp: 35 °C pH: 7.0	COD: 800.0	SMX: 0.01–100.0 mg/L	CH_4: 0.1–0.2 L/g_{COD} removed	86.2–96.0	88.0–97.5	(Wei et al., 2019)
CSTR with submerged flat sheet ceramic MF membrane Pore size: 0.1 μm	HRT: 16 h SRT: 300 d Temp: 25 °C	COD: 500.0	10.0–250.0 μg/L	Biogas: 0.04 L/d	>93.0	SMX: 71.0–85.0; ERY: 67.0–88.0; AMPI: 94.0–98.0	(Zarei-Baygi et al., 2019)
UASB + external crossflow UF membrane (PVDF HF) Pore size: 0.02 μm	HRT: 48 h SRT: 250 d OLR: 2.4 kg $COD/m^3/d$	COD: 4746.0	AMOX: 19.5 mg/L CEFT: 7.2 mg/L CEFO: 2.1 mg/L AMPI: 9.4 mg/L	Biogas: 0.2 L/g_{COD} removed CH_4: 0.1 L/g_{COD} removed	90.3	AMOX: 73.2; CEFT: 46.7; CEFO: 79.4; AMPI: 34.6	(Huang et al., 2018)
CSTR with flat sheet membrane Pore size: 0.2 μm	HRT: 5 d Temp: 55 °C	COD: 42.4 g/L	470.0 mg/L	–	–	CAFF: 92.8	(Chen et al., 2018)
CSTR with submerged flat sheet MF membrane Pore size: 0.05 μm	pH: 7.0 Temp: 35 °C Infinite SRT	COD: 2500.0–10000.0	50.0–215.0 mg/L	–	85.0–90.0	Etodolac: 15.0–49.0	(Kaya et al., 2017)
AnMBR with submerged flat sheet MF membrane	HRT: 6 h SRT: 213 d Temp: 35 °C	COD: 500.0	2.0 μg/L	CH_4: 1.7 L/d	93.9	TMP: 94.2; SMX: 67.8; CBZ: 0.3; DCF: 15.0	(Xiao et al., 2017)
Stainless steel reactor with external ceramic MF membrane Pore size: 0.1 μm	HRT: 5 d SRT: 140 d Temp: 35 °C	COD: 6000.0	2.0 μg/L	Biogas: 0.4–0.6 L/g_{COD} added	TOC: 98.0	ACT: 32.0; CAFF: 51.0; TMP: 90.0; CBZ: 22.0; NPX: 60.0; IBU: 22.0; PRI: 20.0; AMI: 98.0	(Song et al., 2016)
CSTR with side stream crossflow PVDF HF UF membrane Pore size: 0.3 μm	HRT: 12 h SRT: 700 d Temp: 35 °C pH: 7.0	400.0	10.0–20.0 μg/L	CH_4: 0.2–0.3 L/g_{COD} removed	97.0	ATN: 12.0; ACT: 18.0; SMX: 92.0; CAFF: 23.0; TMP: >80.0; DIL: 10.0; CBZ: 10.0; PRI: 12.0; AMI: 99.0; FLU: 98.0; DIPH: 93.0	(Wei et al., 2016)
Stainless steel reactor with external ceramic membrane Pore size: 1.0 μm	HRT: 4 d SRT: 180 d Temp: 35 °C	OLR: 1.3 gCOD/L/d	5.0 μg/L	CH_4: 0.2 L/g_{COD} removed	84.0	ATN: 76.5; ACT: 85.9; SMX: 99.6; CAFF: 90.4; TMP: 97.5; CBZ: 39.2; KET: 27.2; NPX: 74.7; IBU: 25.3; GMF: 12.2; DCF: 2.8; PRI: 16.6; AMI: 99.6; OME: 99.0; DIAZ: 61.6	(Wijekoon et al., 2015)
UASB with submerged HF membrane Pore size: 0.04 μm	HRT: 6 h SRT: 30 d Temp: 30 °C pH: 7.5	COD: 240.0 TOC: 125.0	Conc (μg/L): ATN: 1.8; ACT: 1.7; SMX: 1.6; CAFF: 1.6; TMP: 1.6; DIL: 1.9; CBZ: 1.6; KETO: 1.6; NPX: 1.9; IBU: 1.7; GMF: 0.9; DCF: 0.6; PRI: 1.7; ENA: 1.9; VER: 1.7; METF: 1.5; AMI: 1.1	–	TOC: 89.0	ATN: 15.8; ACT: 58.1; SMX: 95.2; CAFF: 76.9; TMP: 35.4; DIL: 21.4; CBZ: 4.8; KET: 14.9; NPX: 70.3; IBU: <1.0 GMF: 13.1; DCF: <1.0; PRI: 1.8; ENA: 36.6; VER: >99.0; METF: >99.0; AMI: 47.0	(Monsalvo et al., 2014)

MF = Microfiltration; UF = Ultrafiltration; HF = Hollow fiber; UASB = Up-flow anaerobic sludge blanket; PVDF = Polyvinylidene fluoride; ENA = Enalapril; METF = Metformin; VER = Verapamil; OME = Omeprazole; DIAZ = Diazepam; FLU = Fluoxetine; DIPH = Diphenhydramine.

-NR_2, -OR) in their molecular structure are prone to electrophilic attack and microbial catabolism. Several hydrophilic pharmaceuticals (e.g., DCF, KET, primidone (PRI), CBZ, IBU) are poorly removed by AnMBR due to their poor biodegradability associated with strong EWGs (-$CONH_2$, -CONHR, -$CONR_2$) (Wijekoon et al., 2015). Increase in redox potential and electrophilicity of a compound occurs by withdrawing electron density away from the aromatic ring in the presence of EWG. The resulting electron deficiency of the aromatic moiety decreases the compounds' susceptibility to biotransformation (Barber et al., 2020). However, for some pharmaceuticals (e.g., SMX) containing both strong EDG (-NH_2) and EWG (-SO_3H), biodegradability depends on the relative strength of their electron-donating and withdrawing capabilities (Wei et al., 2016). Since most of the pharmaceuticals have a complex molecular structure with several functional groups, that might undergo different enzymatic reactions, it is difficult to predict their biotransformation pathways.

Furthermore, compared to AMBR, AnMBR demonstrated more effective removal of nitrogen containing compounds, including DCF (14.0% vs. 8.0%), CBZ (32.0% vs. 4.0%), and AMI (98.0% vs. 80.0%) at initial concentration of 5.0 μg/L (Liu et al., 2020a). This is in stark contrast to the removal of other pharmaceuticals without sulfur or nitrogen in their molecular structure, e.g., IBU (26.0% in AnMBR vs. 99.0% in AMBR), KET (26.0% in AnMBR vs. 98.0% in AMBR), NPX (54.0% in AnMBR vs. 99.0% in AMBR), and GMF (30.0% in AnMBR vs. 97.0% in AMBR). The reported removal efficiencies of the commonly detected pharmaceuticals in AnMBR and AMBR treatment systems are shown in Fig. 2. The observed difference in removal efficiencies between anaerobic and aerobic treatment could be attributed to the role of nitrogen and sulfur-reducing bacteria (Liu et al., 2020a; Wijekoon et al., 2015). Indeed, it is well established that these bacteria could augment the removal of trace organic contaminants during anaerobic treatment (Mashtare et al., 2013). Nevertheless, biotransformation was the main mechanism of pharmaceuticals removal in both AMBR and AnMBR systems. Adsorption on biological sludge can be a more relevant removal pathway in aerobic systems, however; it is less relevant in anaerobic sludge systems ascribing to the long SRT (>30 d) (do Nascimento et al., 2021a).

Recently, a few studies have examined the biodegradation mechanisms, elucidating the fate of pharmaceuticals during the treatment processes (Do and Stuckey, 2019; Harb et al., 2021; Wei et al., 2019). Transformation products from SMX and ampicillin (AMPI) suggested the cleavage of isoxazole and β-lactam rings, respectively, while, in case of aerobic process, SMX derivatives were detected in the effluent (Harb et al., 2021). This finding indicated the difference in SMX intermediates and pathways between aerobic and anaerobic treatment systems.

Influence of different factors, such as HRT (Huang et al., 2018; Xiao et al., 2017), organic loading rate (OLR) (Huang et al., 2018), antibiotics loading rate (ALR) (Huang et al., 2018), high sulfate (Song et al., 2018a), and high salinity (Song et al., 2016), on pharmaceuticals removal has been extensively investigated. OLR and ALR negatively correlated with treatment efficiency of the AnMBR fed with the wastewater containing AMOX, ceftriaxone (CEFT), cefoperazone (CEFO), and AMPI (Huang et al., 2018). The removal of pharmaceuticals under high sulfate and salinity concentrations was directly dependent on hydrophobicity and molecular structure. For instance, unlike hydrophilic compounds (i.e., CAFF, ACT, NPX, PRI, IBU), no effect of high salinity was evident on the removal of hydrophobic compounds (Song et al., 2016). Inhibition of sludge metabolic activity at the elevated salinity concentrations significantly reduced the removal of most hydrophilic compounds. SRT is the most critical factor, and a SRT of 30 days or higher facilitated enhanced removal of pharmaceuticals in the AnMBR system (Monsalvo et al., 2014; Wijekoon et al., 2015). Long SRT enriched slow-growing microbes, providing greater diversity in the microbial population thereby contributing to biotransformation (Do and Stuckey, 2019).

4.1. *Microbial community structure in the AnMBR treating pharmaceuticals*

Pharmaceuticals in wastewater potentially impact the ecology of the microbial community, influencing the reactor performance and membrane permeability. Given the complexity of anaerobes involved in degrading pharmaceuticals, it is important to understand the structure and dynamics of microbial populations for an effective AnMBR operation. Nevertheless, only a few studies have characterized the dominant microbial communities in conjunction with pharmaceuticals removal.

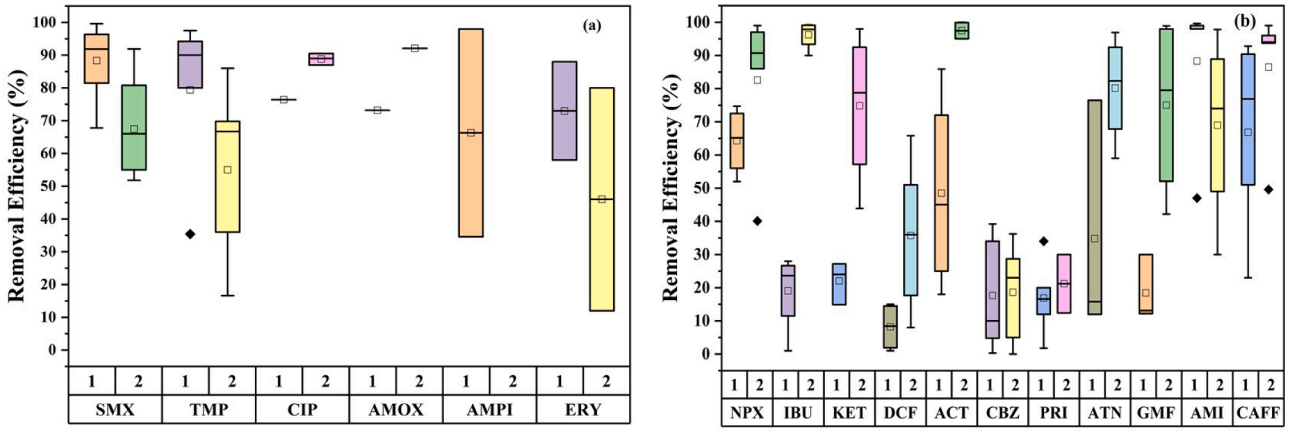

Fig. 2. Comparative overview of the reported removal efficiencies of the commonly detected pharmaceuticals in anaerobic and aerobic membrane bioreactor (AnMBR vs AMBR). 1 and 2 refers to AnMBR and AMBR, respectively. Pharmaceuticals included antibiotics (SMX = Sulfamethoxazole, TMP = Trimethoprim, CIP = Ciprofloxacin, AMOX = Amoxicillin, AMPI = Ampicillin, ERY = Erythromycin); anti-inflammatory (NPX = Naproxen, IBU = Ibuprofen, KET = Ketoprofen, DCF = Diclofenac); analgesic (ACT = Acetaminophen); anticonvulsant (CBZ = Carbamazepine, PRI = Primidone); β-blocker (ATN = Atenolol); lipid regulator (GMF = gemfibrozil); antidepressant (AMI = Amitriptyline); stimulant (CAFF = caffeine). AnMBR data was taken from: Chen et al., 2018; Cheng et al., 2021; Do et al., 2022; Huang et al., 2018; Liu et al., 2020a; Monsalvo et al., 2014; Song et al., 2016; Wei et al., 2016, 2019; Wijekoon et al., 2015; Xiao et al., 2017; Zarei-Baygi et al., 2020. AMBR data was retrieved from: Alobaidi et al., 2021; Chtourou et al., 2018; García Galán et al., 2012; Liu et al., 2020a; Park et al., 2017; Phan et al., 2015; Radjenović et al., 2009; Schröder et al., 2012; Tadkaew et al., 2011; Tambosi et al., 2010; Tiwari et al., 2019; Tran et al., 2016; Trinh et al., 2012.

The suspended biomass is mainly composed of fermentative, syntrophic, and methanogenic microbes (Cheng et al., 2019a). Firmicutes, Bacteroidetes, Chloroflexi, and Proteobacteria are the most abundant phyla (Ng et al., 2016; Zarei-Baygi et al., 2020). *Anaerolineaceae*, *Desulfomonile*, *Parabacteroides*, *Bellilinea*, *Syntrophaceae*, *Syntrophorhabdus*, *Parabacteroides*, unclassified *Fusobacteriales*, unclassified *Chromatiaceae*, and unclassified *Clostridia* are the other prominent bacterial groups (Harb et al., 2021; Zarei-Baygi et al., 2020). The family *Syntrophaceae* and *Syntrophorhabdus* include *Smithella propionica* and *Syntrophorhabdus aromaticivorans*, respectively (Harb et al., 2016). Both of these bacterial species are known to facilitate the degradation of aromatic compounds and are possibly involved in erythromycin (ERY) and AMPI biotransformation (Harb et al., 2021). Moreover, the selective enrichment of *Alkalitalea saponilacus*, *Prolixibacter bellariivorans*, and *Microbacter margulisiae* elucidated the potential role of fermentative bacteria in the biotransformation (Harb et al., 2016).

The archaeal communities of the AnMBR are mainly dominated by *Methanothrix, Methanomicrobiales*, *Methanomethylovorans, Methanosarcina, Methanimicrococcus*, *Methanomassiliicoccus,* and *Methanobrevibacter* (Do et al., 2022; Harb et al., 2021; Ng et al., 2016). *Methanomethylovorans* and *Methanosarcina* are the other dominant unique genera utilizing methylated compounds as carbon and energy source (Harb et al., 2021; Hu et al., 2018). Thus, stable reactor operation and effective pharmaceuticals degradation are likely attributed to the diverse metabolic capabilities of the methanogens present in the suspended biomass. In fact, methanogenesis is a key driver for the biotransformation of antibiotics including SMX (Cetecioglu et al., 2016; Gonzalez-Gil et al., 2018).

Recently, studies have revealed the key roles of the biofilm-specific microbial communities on membrane surfaces in biotransformation of ERY, SMX, and AMPI. Compared to anaerobic suspended sludge, the anaerobic biofilm communities have higher relative abundances of methanogens (*Methanothrix, Methanosarcina,* and *Methanomethylovorans*), syntrophs (*Syntrophaceae* and *Syntrophorhabdus*), and sulfate-reducers (*Desulfomonile*) (Harb et al., 2021). Furthermore, the presence of exoelectrogens such as *Geobacter* spp. and *Desulfovibrio* spp. in AnMBR biofilms also aid in the degradation of antibiotics (BouNehme Sawaya and Harb, 2021). *Methanomethylovorans* and *Methanosarcina* are likely to utilize methyl groups of ERY and SMX, aiding their biotransformation. In addition, the role of sulfate-reducing bacteria during the SMX biotransformation via isoxazole ring cleavage was evidenced (Jia et al., 2017, 2019), and thus their contribution cannot be overlooked. Nevertheless, the positive influence of the microbial communities on membrane biofilms has only been lately realized, and more in-depth studies are required to elucidate their specific role during biotransformation of pharmaceuticals.

4.2. Potential impact of pharmaceuticals on AnMBR performance

The occurrence of pharmaceuticals in WWTPs though inhibits the microbial communities, their presence may also exert a selective force on a few microbial populations. Therefore, it is important to have a comprehensive understanding of the microbial community structure and its response to pharmaceutical selection pressure for stable and efficient WWTP operation. The following section critically discusses the inhibitory and toxic effects of different pharmaceuticals on the AnMBR treatment system which is important for design and operation of AnMBR.

Anaerobic process involves a series of interdependent redox biochemical reactions carried out by diverse groups of microorganisms, of which methanogens are the most sensitive microbial communities. In fact, continuous exposure to the selected pharmaceuticals changes the composition and diversity of key microbial populations in AnMBR thereby resulting in adverse effects, including: (i) decreased COD removal and methane yield (Cheng et al., 2021; Do et al., 2022; Wei et al., 2019); (ii) inhibition of specific metabolic reaction, resulting in accumulation of volatile fatty acids and low molecular weight soluble microbial products (SMP) (i.e., aromatic and N-containing compounds) (Do et al., 2022; Wang et al., 2018); (iii) increased production of extracellular polymeric substances (EPS), contributing to enhanced membrane biofouling; and (iv) change in biological sludge properties (i.e., floc size, cell lysis) (Cheng et al., 2021; Wang et al., 2018). Microbial groups that were most affected include acetogenic bacteria (e.g., *Lutispora*), fermentative bacteria (e.g., Anaerolineales, Bacteroidales, Coriobacteriales, Lactobacillales, *Petrimonas,* and Selenomonadales), syntrophic bacteria (e.g., *Syntrophobacter*, *Smithella*, and *Propionicimonas*), and methanogens (e.g., *Methanothrix*) (Cheng et al., 2021; Do et al., 2022; Harb et al., 2016).

Typically, pharmaceuticals occur as mixture and may have both synergistic and/or antagonistic effects. Despite this, only a few studies have investigated the effect of pharmaceuticals mixture on AnMBR performance. The simultaneous addition of SMX, sulfadiazine (SDZ), and sulfamethazine (SMZ) (100.0 μg/L) not only decreased COD removal and methane yield but also negatively affected membrane fouling. This could be attributed to the stimulated production of SMP and EPS, especially increase in protein/polysaccharide ratio as a stress response mechanism (Cheng et al., 2021).

5. Anaerobic biotransformation of pharmaceuticals

Comprehensive understanding of biotransformation pathways is essential for effective elimination of the transformation products and to predict their environmental risks. More specifically, the contribution of different biological stages of AD (i.e., hydrolysis, acidogenesis, acetogenesis, and methanogenesis) involving different microbial population and enzymes to biotransformation is still incipient. This section synthesizes the current knowledge of the biotransformation mechanisms of the selected pharmaceuticals bearing different functional groups/structural moieties, with emphasis on intermediates formed, pathways, and catabolic enzymes involved.

The fermentative bacteria and methanogens play vital roles in anaerobic biotransformation of pharmaceuticals. However, the relative contribution of each stage differs with pharmaceuticals, depending on their chemical structure and enzymatic activities involved. For instance, ERY and roxithromycin (ROX) showed higher removal during the acidogenic stage, possibly by the higher activity of glycosylases catalysing cleavage of hexose sugar (i.e., cladinose) (also detected as intermediate in AnMBR effluent) (ERY-I) (see supplementary material) (Carneiro et al., 2020; Gonzalez-Gil et al., 2019). On the contrary, NPX biotransformation was enhanced during methanogenic phase, which could be attributed to the increased acetate kinase activity, a key acetoclastic methanogenic enzyme responsible for phosphorylation of the hydroxyl groups (NPX-IA) (see supplementary material) (Gonzalez-Gil et al., 2017; Gonzalez-Gil et al., 2019).

Biotransformation of SMX by several anaerobic microbial populations, including fermentative bacteria (Carneiro et al., 2020), homoacetogens coupled with hydrogenotrophic methanogens (Cetecioglu et al., 2016), methanogens (Gonzalez-Gil et al., 2018), sulfate-reducing bacteria (Jia et al., 2017), through two biotransformation pathways (i.e., reductive transformation and isoxazole ring cleavage) has been reported. In addition, another SMX intermediate, characterized by the removal of sulfonyl group after the initial opening of the isoxazole ring, was detected in the AnMBR effluent. The cleavage of N–O bond through hydrogenation was catalyzed by cytochrome-c or membrane-bound hydrogenases involved in acetoclastic methanogenesis and glucose catabolism (SMX-I) (see supplementary material) (Gonzalez-Gil et al., 2019). While in anaerobic sulfate reducing environment, the reaction was probably catalyzed by NADH-dependent reductases, such as sulfite reductase (Jia et al., 2019). In the case of NPX and TMP, the biotransformation efficiency was higher in the overall AD than in acidogenic or methanogenic phases, indicating possible involvement of other microbial populations or anaerobic steps. This was further

supported by the study of Wolfson et al., (2018), who revealed that NPX is possibly O-demethylated to 6-O-desmethylnaproxen (catalyzed by O-methyltransferases) via syntrophic relationship between homoacetogens, acetate oxidizers, and hydrogenotrophic methanogens (NPX-IB) (see supplementary material). Incidentally, recent research targeting TMP degradation in anaerobic sulfate-reducing sludge system has identified TMP transformation product with O-demethylation at C-5 position, mainly catalyzed by CYP450 enzymes (TMP-I) (see supplementary material) (Jia et al., 2019).

Moreover, acetate kinase was also identified as the crucial enzyme in the anaerobic biotransformation of highly persistent pharmaceuticals with carboxyl groups and relatively low steric hindrance (e.g., DCF and IBU) likely by phosphorylation (DCF-I) (see supplementary material) (Gonzalez-Gil et al., 2017). Additionally, DCF could be degraded by reductive dechlorination followed by decarboxylation of phenylacetate carboxylic acid group (catalysed by decarboxylase) under anaerobic conditions (DCF-II) (see supplementary material) (Ghattas et al., 2017; Gonzalez-Gil et al., 2019; Granatto et al., 2020).

Despite being a novel and nascent research area, the role of different enzymes and microbial populations involved in anaerobic biotransformation of pharmaceuticals is gaining prominence. In this regard, identification of pure microbial cultures would enable deeper understanding of the functional enzymes involved in biotransformation. Furthermore, whole-genome sequencing, proteomics, and transcriptomics analyses can aid in identifying key genes or proteins.

6. Membrane fouling and its potential role in pharmaceuticals removal

Membrane fouling shortens membrane life and increases overall maintenance cost, limiting the practical application of AnMBR (Yang et al., 2019). Therefore, membrane fouling mitigation has received considerable attention. The occurrence of membrane fouling is generally characterized by initial pore blocking and subsequent cake layer formation, attributing to the deposition of microorganisms, colloids, solutes, and cell debris (Charfi et al., 2012). Microbial metabolites such as EPS and SMP are the major constituents of membrane fouling. Membrane fouling is a complex process influenced by operational conditions (e.g., SRT, HRT, and temperature), membrane properties (e.g., module type, material, surface charge, hydrophobicity, and pore size), sludge concentration and properties (e.g., particle size and EPS), and reactor configurations (Lin et al., 2009; Lin et al., 2014; Teng et al., 2020; Wu et al., 2020). Fouling is usually more severe in anaerobic environments, partly due to lower sludge filterability (Cheng et al., 2018). Most commonly adopted membrane fouling control strategies include pretreatment of wastewater, chemical backwashing using NaOH and NaClO (Yue et al., 2018), gas sparging (Zhang et al., 2017), addition of adsorbents (e.g., powdered activated carbon (PAC), granular activated carbon (GAC), and biochar) (Chen et al., 2020; Lei et al., 2019; Yang et al., 2019), modification of membrane surfaces (CuO and ZnO nanoparticles) (Cheng et al., 2019b), and changes in membrane properties (modified PVDF HF membranes with multiwalled carbon nanotubes (CNTs)) (Cao et al., 2020). Additionally, the development of electrically assisted AnMBR using conductive membrane cathodes has shown great potential in reducing membrane fouling through an in-situ gas scouring effect (discussed in section 7.4) (Werner et al., 2016; Zhao et al., 2021). Current research interests have shifted towards quorum quenching as an emerging anti-fouling strategy where bacterial communication is disrupted to reduce the cake layer formation on the membrane surface (Liu et al., 2019). Extensive efforts have been made to understand the fundamental mechanisms of membrane fouling and its control strategies in AnMBR (Charfi et al., 2012; Chen et al., 2012; Yao et al., 2021), and thus not elaborated in this review. This section, however, focuses on elucidating the positive aspects of membrane fouling layer towards removal of pharmaceuticals in AnMBR.

The potentially positive roles of the dense membrane fouling layer in emerging contaminants removal from wastewater have been demonstrated (Cheng and Hong, 2017; Harb et al., 2021; Zarei-Baygi et al., 2020). Pharmaceutical's physical–chemical properties and the components of the fouling layers are the critical factors in their removal (Monsalvo et al., 2014). Various removal mechanisms (biotransformation, adsorption, and reduced permeation) for different emerging contaminants and their interaction with biofilm layer are illustrated in Fig. 3. Considering the cross-linked structural properties and principal components of the membrane fouling layer, EPS and SMP (both proteins and polysaccharide fractions) exhibited positive correlation with the removal of different plasmid-borne antibiotic resistance genes (ARGs) (i.e., $bla_{\text{NDM-1}}$, $bla_{\text{CTX-M-15}}$, and $bla_{\text{OXA-48}}$) in AnMBR (Cheng and Hong, 2017). The modification of membrane surface characteristics and hydrodynamic factors, and effective pore size reduction via pore blocking are the factors responsible for the rejection/retention of antibiotics and ARGs in the presence of fouling layer. Additionally, EPS and SMP carry charged functional groups (i.e., carboxyl, hydroxyl, phosphoric, sulphydryls, phenols, and amines) possessing both hydrophilic and hydrophobic sites for ARGs and pharmaceuticals adsorption (Cheng et al., 2018; More et al., 2014). Protein like substances such as tyrosine and tryptophan are identified as the dominant components of EPS involved in adsorption through hydrophobic interactions (Zhang et al., 2018). Although a few studies have elucidated the role of EPS on antibiotics removal via sorption through both hydrophobic partitioning and hydrophobicity-independent mechanisms (Zhang et al., 2018), to the best of our knowledge, no studies have elucidated the role of SMP on antibiotics adsorption. Furthermore, Monsalvo et al., (2014) identified that reversible fouling layer on hollow-fiber membrane surface is the critical barrier in the rejection/retention of the pharmaceuticals and other trace organics during AnMBR operation.

Besides the physical retention, the prospective roles of biofilm specific anaerobic microbial communities in biotransformation of pharmaceuticals have been highlighted (Harb et al., 2021). The presence of distinctively different microbial communities and high relative activities of syntrophic bacteria (*Syntrophaceae*), specific methanogens (*Methanomethylovorans* and *Methanothrix*), and sulphate-reducing bacteria (*Desulfomonile*) in the membrane biofouling layer likely confer advantage that aided in the enhanced biotransformation of the SMX, AMPI, and ERY. Such enhanced microbial activity is mainly due to the reduced mass-transfer limitation and direct interspecies electron transfer between methanogens and their syntrophic partners (Smith et al., 2015). Despite the recent findings on the role of membrane fouling in pharmaceuticals and ARGs removal, there is still inadequate information, considering the dynamic nature of biofilm matrices. Future studies should assess the performance of AnMBR while strategically maintaining the biofilm layer on the membrane, considering the trade-off between the increased transmembrane pressure and enhanced removal. If achievable, this would provide a sustainable basis for reducing the risk of pharmaceuticals release to the environment (BouNehme Sawaya and Harb, 2021).

7. Novel AnMBR configurations for enhanced pharmaceuticals removal and fouling mitigation

In recent years, several state-of-art AnMBR configurations have been proposed and developed, specifically focusing on the removal of pharmaceuticals and mitigating membrane fouling. This section discusses the recent advances in AnMBR systems, including their removal efficiency and mechanisms, critical bioreactor operating conditions, and membrane fouling control mechanisms (see supplementary material).

7.1. Integration of AnMBR with physical–chemical treatment technologies

Despite major advancements, AnMBR systems are only moderately effective in removing CBZ, DCF, and IBU due to their resistance to biodegradation (Monsalvo et al., 2014; Wijekoon et al., 2015). Thus,

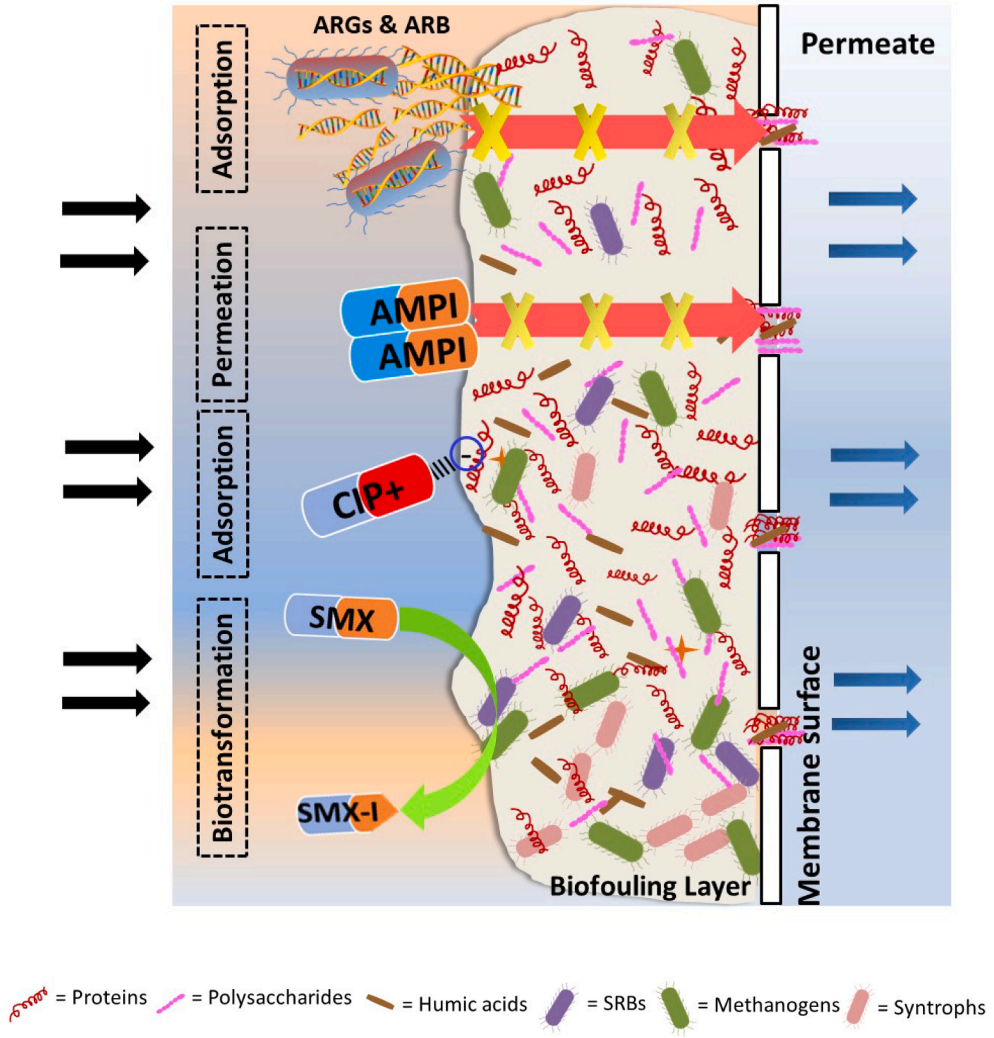

Fig. 3. Schematic showing the positive effect of the membrane biofouling layer and its components (EPS, SMP, and microbial communities) towards enhanced removal of different pharmaceuticals (SMX = Sulfamethoxazole, CIP = Ciprofloxacin, AMPI = Ampicillin), antibiotic resistance genes (ARGs), and antibiotic resistant bacteria (ARB) via various mechanisms (biotransformation, adsorption, and reduced permeation).

AnMBR can be integrated with physical–chemical treatment processes, such as activated carbon adsorption, membrane filtration (e.g., nanofiltration (NF) and membrane distillation (MD)), and advanced oxidation process (AOP) (e.g., UV/H_2O_2 and ozonation), among others. For instance, addition of 1.0 g/L PAC in the AnMBR increased SMX removal efficiency from 68.0% to 96.0% (initial SMX concentration of 2.0 μg/L), attributing to enhanced sorption and biotransformation (Xiao et al., 2017). PAC, characterized by high specific surface area (of order 10^2 to 10^3 m^2/g) and number of active sites/functional groups, facilitates adsorption of pharmaceuticals on their surface. Thus, PAC aids in longer retention of the sorbed pharmaceuticals within the bioreactor with a higher likelihood of biotransformation (Alvarino et al., 2018). Also, biochar has emerged as a low-cost adsorbent with abundant functional groups, besides large specific surface area and porosity. Biochar addition (0.5 g/L) into AnMBR improved SMX, SDZ, and SMZ removal from swine wastewater by acting as a biocarrier for microorganisms, improving the biodegradation of antibiotics (Cheng et al., 2021). Besides, biochar also improves the electron transfer efficiency between exoelectrogenic microorganisms. Furthermore, the integration of AnMBR with NF and MD has revealed promising results (Song et al., 2018b; Wei et al., 2016). For example, Song et al., (2018b) demonstrated that the application of MD-AnMBR resulted in complete rejection of pharmaceuticals. The synergistic role of MD in the hybrid system (MD-AnMBR) was most significant for removal (overall efficiency from 76.0% to complete removal) of PRI, KET, IBU, DCF, CBZ, and GMF that were poorly removed (15.0–25.0%, initial concentration of 2.0 μg/L each) by AnMBR. Similarly, Wei et al. (2016) reported 80.0–92.0% rejection of CBZ, dilantin (DIL), PRI, ACT, and ATN via NF-AnMBR. MD and NF rejection resulted in a longer retention of compounds in the bioreactor, enhancing their biodegradation.

Integration of AOP (e.g., UV/H_2O_2 and direct ozonation) with AnMBR has also been proposed for pharmaceuticals removal (Augsburger et al., 2021; Kaya et al., 2017). The hybrid ozonation-AnMBR system effectively removed etodolac (NSAID) (removal efficiency >90.0%) at an initial concentration of 50.0–215.0 mg/L (Kaya et al., 2017). The pre-ozonation process reduced the inhibitory effect that occurred in the AnMBR due to the high etodolac concentration in chemical synthesis-based pharmaceutical wastewater. In UV/H_2O_2 system, the removal of ATN, CBZ, and estrone (>90.0%, at an initial concentration of 50.0 μg/L) was driven by the hydroxyl radicals generated from H_2O_2 (10.0 mg/L), while UV exposure (fluence of 311 mJ/cm^2) governed the inactivation of antibiotic resistant bacteria (ARB) and ARGs in ammonia-rich AnMBR effluent (Augsburger et al., 2021). It is worth mentioning that most studies focussed on the parent compounds removal, while little is known about the fate of the degradation intermediates and their potential environmental toxicity.

7.2. Anaerobic osmotic membrane bioreactor (AnOMBR)

Anaerobic osmotic membrane bioreactor (AnOMBR) is a high retention membrane system integrating forward osmosis (FO) membrane separation process with anaerobic treatment (Gao et al., 2020). With FO membrane replacing the pressure-driven MF or UF membranes, AnOMBR offers unique advantages, such as lower fouling propensity and energy demand, and high fouling reversibility, effluent quality, and methane yield (Chen et al., 2014; Gao et al., 2020). More importantly, FO membrane resulted in higher pharmaceuticals rejection via synergistic mechanisms, such as electrostatic repulsion, steric hindrance, and retarded forward diffusion (Liu et al., 2020b; Viet et al., 2019). For example, in an AnOMBR, the FO rejections of CAFF, ATN, and atrazine were 96.0%, 99.6%, and 96.5%, respectively, while in an AnMBR with an UF, CAFF and ATN were not removed, and atrazine removal was only 20.0% (Kim et al., 2017; Wei et al., 2016). Similarly, Wang et al. (2018) demonstrated excellent removal (>95.6%) of eight cytostatic drugs from wastewater at an initial concentration of 100.0 μg/L. In fact, the removal of cyclophosphamide in the AnOMBR (99.3%) was much higher compared to conventional MBR (20.0–80.0%) (Kovalova et al., 2012; Wang et al., 2018). The higher FO membrane rejection combined with the extended retention time in the reactor ensures effective removal of all cytostatic drugs.

Despite the demonstrated promises of AnOMBR for pharmaceuticals removal, the technology still suffers challenges, such as membrane fouling, salt accumulation, and low stable water flux, which ultimately impact the microbial community structure and overall performance (Liu et al., 2020b; Xu et al., 2020). An integration of a side-stream MF/UF unit with AnOMBR removed the excess salinity buildup, maintaining a stable water flux (Hu et al., 2017). Furthermore, coupling AnOMBR with desalination techniques such as MD elucidated to regenerate dilute draw solutions towards the production of freshwater (Cong Nguyen et al., 2020; Liu et al., 2020b). Studies in this direction have demonstrated >96.0% removal efficiency of several pharmaceuticals present in municipal wastewater (initial concentration of 2.0 μg/L each) (Arcanjo et al., 2021; Caroline Ricci et al., 2021).

Recently, innovative reactor configurations including upflow anaerobic sludge-forward osmotic membrane bioreactor (Chang et al., 2019) and electro-assisted anaerobic forward osmosis membrane bioreactor (AnOMEBR) (Xu et al., 2020) have also gained momentum to treat pharmaceutical-laden wastewater, simultaneously mitigating membrane fouling. The use of conductive FO membrane both as a separation unit and as a cathode resulted in low SMP and PN/PS in AnOMEBR, mitigating the membrane fouling layer (Xu et al., 2020). Given the early stages of technological development and limited full-scale applications of the innovative AnOMBRs, more comprehensive investigations are necessary pertinent to a wide range of pharmaceuticals.

7.3. Anaerobic fluidized bed membrane bioreactor (AnFMBR)

Staged anaerobic fluidized bed membrane bioreactor (AnFMBR) has been investigated as an alternative to AnMBR, combining AFBR with AnFMBR using GAC as carrier medium in both stages (Kim et al., 2011). The addition of GAC ensures dual benefits: (i) provides mechanical scouring thereby controlling membrane fouling, and (ii) promotes the interspecies electron transfer owing to their conductive properties (Dutta et al., 2014; ElKik et al., 2021; Zhang et al., 2017). The fluidization of GAC particles achieved by recirculating the bulk solution has a standalone advantage of low-energy consumption (Kim et al., 2011). The synergistic role of GAC fluidization in AnFMBR was evident with the reduced membrane fouling at a low energy consumption (0.06 kWh/m^3) compared to the most commonly used biogas recirculation method (0.69–3.41 kWh/m^3) for fouling control (Kim et al., 2011; Martin et al., 2011). AnFMBR has elucidated its effectiveness in removing CIP (100.0%, initial concentration of 0.16 μg/L), cephalexin (95.8%, 2.91 μg/L), ERY (86.3%, 0.32 μg/L), SMX (100.0%, 0.27 μg/L and 100.0 μg/L), TMP (100.0%, 0.016 μg/L); anticonvulsant including CBZ (96.4%, 0.025 μg/L); NSAIDs including IBU (90.9%, 2.5 μg/L), DCF (78.2%, 0.06 μg/L), NPX (96.4%, 0.43 μg/L), and β-Blockers including ATN (100.0%, 0.47 μg/L) (Dutta et al., 2014; Lim et al., 2019; McCurry et al., 2014). The removal of SMX in the AnFMBR (100.0%) with GAC was much higher compared to conventional AnMBR with biogas sparging (47.6%) at an initial concentration of 1.0 mg/L (Lee et al., 2021). GAC is characterized by high specific surface area (of order 10^2 to 10^3 m^2/g) and number of active sites/functional groups (e.g., carboxyl, carbonyl, ether, and lactone) (Gutiérrez et al., 2021). The high specific surface area is a resultant of vast internal network of pores (macro, meso, or micro) created during the activation process (Lim et al., 2019; Piai et al., 2019). The presence of mesoporous surface structures can facilitate diffusion, resulting in higher adsorption rates. Thus, GAC promotes biotransformation of pharmaceuticals by providing longer retention time for the sorbed pharmaceuticals within the bioreactor. Apart from adsorbing the pharmaceuticals, the porous structure of the GAC allows colonization of the microorganisms and inevitably leads to the surface biofilm formation. The pharmaceuticals present in the aqueous phase can thus be adsorbed on the GAC biofilm layer via both electrostatic and hydrophobic interactions (Gutiérrez et al., 2021). As a result, the pharmaceuticals are concentrated on the GAC surface thereby increasing the contact time between the biomass and compound with a high likelihood of biotransformation. Overall, adsorption on GAC surface and sorption and biotransformation by biofilm formed on surface are the two potential pathways responsible for pharmaceuticals removal in AnFMBR (Dutta et al., 2014; Lee et al., 2021; Lim et al., 2019; McCurry et al., 2014).

With the measured success of AnFMBR thus far, further improvements in the system are being explored. For instance, use of ceramic membranes consisting of metal oxide particles such as Al_2O_3 in lieu of polymeric membranes due to their excellent thermal and chemical stability has been proposed for better fouling control at low energy cost (Aslam et al., 2018). Recently, coupling AnFMBR with single-chamber microbial electrolysis cell (MEC) as a novel configuration was demonstrated for synthetic wastewater treatment with enhanced methane yield and reduced membrane fouling (ElKik et al., 2021). However, considering the early stages of development, more detailed studies are required to optimize the process design, operation, and material components (e.g., electrodes and membrane).

7.4. Anaerobic electrochemical membrane reactor (AnEMBR)

The application of electric field via polarized electrodes has been investigated as a cost-effective strategy in controlling membrane fouling, coined as anaerobic electrochemical membrane reactor (AnEMBR). The technology relies on the operating principle of a MEC with anaerobic filtration (Katuri et al., 2014). In such truly integrated systems, the cathode serves dual functions, effluent filtration and cathodic reduction (usually resulting in the H_2 evolution). Generally, metal- and carbon-based conductive membranes are used as cathode materials for treating organic wastewaters. The first proponent of the concept used nickel-based hollow fiber membrane (Ni-HFM) (Katuri et al., 2014). The study remarkably concluded the significance of applied potential in reducing the sludge cake layer on the membrane surface. However, subsequent investigations suggested that the conductive metal membranes may not only limit the water flux but also leach metal ions in the permeate water, increasing the downstream purification cost (Cao et al., 2021; Yang et al., 2019). Fortunately, with the use of carbon-based conductive membranes, such as CNTs-HFM (Yang et al., 2019), multiwalled CNTs-PVDF-HFM (Cao et al., 2021), and graphene HFM (Gr-HFMs) (Werner et al., 2016) as cathode materials provide new opportunities for AnEMBR to circumvent the above-stated drawbacks. The excellent electrochemical performance of the CNTs-HFM, attributing to high mechanical strength, good hydrophilic

characteristics, large specific surface area, and high electrical conductivity, can thus be an apt candidature for environmentally benign fouling mitigation strategy (Cao et al., 2020). Recent studies with CNTs-HFM at an applied voltage of −1.2 V revealed slower transmembrane pressure increasing rates and better recovery in AnMBR in comparison to PVDF-HFM and CNTs-HFM, in the absence of electrical stimulation. Two major hypotheses have been laid to suppress the membrane fouling activity in the AnEMBR. Firstly, the negatively charged foulants in the bulk electrolyte would suffer an electrostatic repulsion from the cathode and be driven away from the membrane surface (Yang et al., 2019; Zhang et al., 2021). Secondly, change in the bulk electrolyte properties including particle size distribution, the surface charge of sludge flocs, the composition of EPS and SMP are responsible for improved filterability (Zhang et al., 2021). Furthermore, electrode material, reactor configuration, inter-electrode distance, applied current densities, and the duration of external potential application are the critically important operating factors (Borea et al., 2019; Ding et al., 2018).

Recently, a novel AnEMBR using stainless-steel MF membrane as a cathode coupled with sacrificial iron anode resulted in excellent water permeation and reduced fouling (Zhao et al., 2021). Numerous studies have highlighted the potential of integrating electrochemical processes in AMBR for effective removal of antibiotics, anti-inflammatory, antiepileptic substances, and β-blockers (Borea et al., 2019). However, there are no reported findings on the degradation mechanisms and pharmaceuticals removal pathways in AnEMBR. Moreover, the current studies on AnEMBR are mainly limited to the laboratory-scale systems (working volume ≤1.0 L) with shorter operation periods. Thus, it is necessary to explore the performance and membrane fouling control mechanisms in the large-scale AnEMBR systems for a long-term operation, especially, to understand the relationship between the applied electric field and the increased pharmaceuticals removal.

7.5. Microaeration-based anaerobic membrane bioreactor systems

The beneficial effects of microaeration i.e., dosing a small amount of air or oxygen (typically ranging between 5.0 and 5000.0 mL O_2/L reactor/day) on anaerobic systems have been investigated (Nguyen and Khanal, 2018). Despite being initially proposed to improve the overall stability of the AD process, this strategy has been recently reported to enhance the biotransformation of recalcitrant compounds, such as benzene, toluene, ethylbenzene, xylene (Firmino et al., 2018), and emerging pollutants including pharmaceuticals (e.g., SMX, TMP, and DCF), hormones, bisphenol A (Buarque et al., 2019; do Nascimento et al., 2021b), surfactants (Cheng et al., 2018), and parabens (do Nascimento et al., 2021c) in anaerobic reactor systems (e.g., UASB and AnMBR). For instance, do Nascimento et al. (2021b) observed a considerable increase in the removal efficiency of DCF (200.0 μg/L) from 22.0% (under anaerobic conditions) to 88.0% in microaerated (air, 4.0 mL/min) UASB reactor treating synthetic wastewater. The underlying rationale behind enhanced removal is the augmentation in both microbial richness and diversity (i.e., hydrolytic and fermentative bacteria and hydrogenotrophic methanogens), favouring the growth of oxygenase-producing microorganisms (do Nascimento et al., 2021b; Firmino et al., 2018).

The microaeration rate and the method (i.e., use of air or oxygen, injection in aqueous or gaseous phase) are the critical influencing factors (Nguyen and Khanal, 2018). A precise control of oxygen dosing is needed to prevent the inhibition of obligate anaerobic methanogens. Besides conventional time-based on–off control, supervisory control, data acquisition (SCADA) for proportional-integral-derivative controllers, and oxidation–reduction potential based systems can be employed to precisely control air/oxygen dosing.

Thus, supplementing anaerobic membrane bioreactor systems with low amounts of oxygen could enhance the removal of the recalcitrant CBZ, IBU, PRI, and DCF that are otherwise poorly biotransformed under anaerobic conditions. More in-depth investigations should be conducted with pharmaceuticals belonging to different therapeutic classes to fully understand the underlying biotransformation mechanisms, pathways, enzymatic activity, and microbial community structure under a microaerobic condition. Furthermore, the automatic process control of microaeration is a challenging task for effective implementation, especially for full-scale applications.

7.6. Anaerobic dynamic membrane bioreactor (AnDMBR)

The fouling of MF/UF membranes has always been considered a major drawback in the widespread application of AnMBR. However, the cake layer formed during the biofouling process can function as an additional filter enhancing the retention of various pollutants (Hu et al., 2020). As the cake layer is formed on the membrane surface, the pollutant retention is more dependent on the cake layer as such, rather than on the underlying membrane properties (Ersahin et al., 2016). Based on this concept, anaerobic dynamic membrane bioreactor (AnDMBR) has been developed wherein the large pore sized less expensive filtration materials (such as stainless steel or nylon meshes, woven or non-woven filter cloth) are used as support medium enabling the formation of dynamic membrane (DM) layer achieving effective solid–liquid separation (Siddiqui et al., 2021). The selection of appropriate supporting material and pore size (typically ranging between 10.0 and 200.0 μm) which is highly dependent on the wastewater characteristics, forms the crucial basis in DM formation, optimization, and filterability (Ersahin et al., 2016; Siddiqui et al., 2021).

AnDMBR can be a potential alternative to address the major limitations of conventional AnMBR possessing low flux, high capital and operating costs, high energy and chemical consumption, and rapid membrane fouling (Shrestha et al., 2022). Moreover, the DM layer can be removed by physical methods, including backwashing and biogas sparging (Ersahin et al., 2017). The versatility of AnDMBR systems has been demonstrated for the treatment of domestic and industrial wastewater, food waste, sewage sludge, and landfill leachate (Cayetano et al., 2019; Chen et al., 2021; Xie et al., 2014). However, to the best of our knowledge, no studies have applied AnDMBR for treating wastewater containing pharmaceuticals. Although AnDMBR has attracted significant research attention, the technology is still emerging and its application is in nascent stages. Studies so far mainly focused on the operational parameters of AnDMBR in treating various wastewater streams at laboratory-scale, however, in-depth studies are essential to elucidate the DM formation process and mechanism.

8. Perspectives

AnMBR is increasingly being employed in municipal and industrial wastewater treatment, contaminants removal, and resource recovery. In recent years, considerable progress has been made to understand the fate, and removal of pharmaceuticals in AnMBR. Prior studies focused primarily on the pharmaceuticals removal efficiency and rate, whilst information about removal mechanisms for a diverse pharmaceuticals and key microbial communities involved is still lacking. Therefore, future research should elucidate major biotransformation pathways and metabolic intermediates formed. The potential toxicity and fate of intermediates during biotransformation need to be carefully assessed for broader environmental implications. An in-depth elucidation of the key microbial groups will be critical in designing and operating the AnMBR system for the effective treatment of pharmaceutical-laden wastewater.

Although the membrane biofouling is one of the critical barriers to widespread application of AnMBR, the sludge cake layer on the membrane surface can potentially improve the effluent quality. The fouling layer can reduce the permeation of ARGs and antibiotics. With the limited number of studies investigating its role, it can be concluded that the bacteria and archaeal communities are distinctively diverse in biofilms compared to the suspended biomass. The preferential selection of

specific microbial communities is probably dependent on membrane surface properties and the microorganisms themselves. Thus, biofouling layer morphology and structure, including EPS and microbial community composition, need to be characterized more comprehensively to fully understand microbial interactions and their roles in biofilm-driven pharmaceuticals biotransformation. Optimized reactor configurations and effective operational strategies are required to achieve a dynamic equilibrium between fouling growth and decomposition for stable AnMBR operation and effective pharmaceuticals removal. Lately, studies have also focused on predicting and modelling for effective control of membrane fouling in AnMBR. This new approach would be a beneficial strategy to optimize the operating conditions.

While standalone AnMBR is promising in treating organics and provide opportunities for energy recovery, however, addressing the need for complete removal of emerging contaminants still requires additional strategies. Hybrid AnMBR systems have attracted significant research and development interest for achieving the dual goals of pharmaceuticals removal and fouling mitigation. Integration of high rejection membrane separation processes, including NF, MD, and FO, into an AnMBR can be an effective strategy for retaining the pharmaceuticals, providing higher retention time for enhanced biotransformation. Nevertheless, most of the novel AnMBR configurations are still in their infancy, and further investigations are warranted to evaluate their robustness in terms of treatment performance with real wastewater under continuous operation.

9. Conclusions

AnMBR can be a prudent technology for pharmaceuticals removal and sustainable wastewater treatment. However, more in-depth investigations on the biotransformation mechanisms outlining the involvement of key microbial communities is required in understanding the fate of pharmaceuticals, especially in the presence of membrane biofouling layer. The common negative perception regarding fouling layer needs to be revisited with more targeted research that elucidates its positive role in removal of pharmaceuticals. Development of different hybrid-AnMBR systems can be promising strategies for effective removal of pharmaceuticals and fouling mitigation. The technical feasibility and economical viability of such systems should be examined under real conditions to fully realize their practical applications.

CRediT authorship contribution statement

Akashdeep Singh Oberoi: Conceptualization, Methodology, Formal analysis, Data curation, Writing – original draft, Writing – review & editing. **K.C. Surendra:** Writing – review & editing. **Di Wu:** Writing – review & editing. **Hui Lu:** Writing – review & editing. **Jonathan W.C. Wong:** Funding acquisition, Resources, Supervision, Writing – review & editing. **Samir Kumar Khanal:** Conceptualization, Supervision, Project administration, Writing – review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.biortech.2022.127667.

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