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Review

Review on fate and mechanism of removal of pharmaceutical pollutants from wastewater using biological approach

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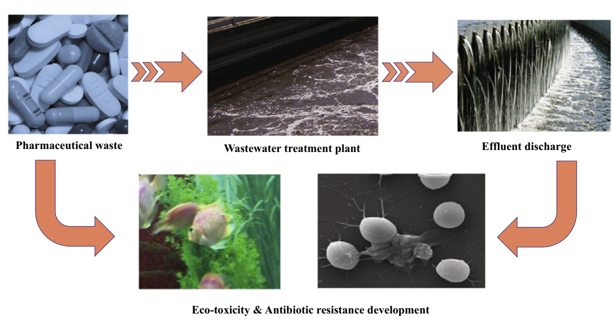
HIGHLIGHTS

- Pharmaceutical residues in aquatic environment causes ecotoxicity.
- CAS process is not efficient in removal of pharmaceuticals residues.
- MBR process would be a promising techniques in removal of these micro-pollutant.
- Metagenomics study of HWWTP will help in development of optimized MBR process.

GRAPHICAL ABSTRACT



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ABSTRACT

Due to research advancement and discoveries in the field of medical science, maintains and provides better human health and safer life, which lead to high demand for production of pharmaceutical compounds with a concomitant increase in population. These pharmaceutical (biologically active) compounds were not fully metabolized by the body and excreted out in wastewater. This micro-pollutant remains unchanged during wastewater treatment plant operation and enters into the receiving environment via the discharge of treated water. Persistence of pharmaceutical compounds in both surface and ground waters becomes a major concern due to their potential eco-toxicity. Pharmaceuticals (emerging micro-pollutants) deteriorate the water quality and impart a toxic effect on living organisms. Therefore, from last two decades, plenty of studies were conducted on the occurrence, impact, and removal of pharmaceutical residues from the environment. This review provides an overview on the fate and removal of pharmaceutical compounds via biological treatment process.

Contents

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1. Introduction

Pharmaceuticals are biologically active compounds that are known to have a particular mode of action in human and animals. Before the beginning of 19th century, natural compounds were the principal source of therapeutic. Plants crude extracts, shrubs are the herbal medicines, which are used for pain relief, healing wounds, and for treating various types of illness. For easy and fast production of therapeutic products to meet the needs of urgent requirements of pharmaceuticals during the world war and due to restriction in patenting of therapeutic plant products, pharmaceutical companies focused their research on the development of synthetic analogs of therapeutic products. Liquid chloroform was the first synthetic compound used as an anesthetic drug in the late 1800s. Advancement in the field of medical science contributed to the development of various synthetic therapeutic compounds towards the end of the 19th century and the 20th century such as naphthalene, acetanilide, aspirin, ephedrine, arsphenamine (Sneader, 2005). Until now, thousands of pharmaceuticals have been developed, and the numbers continue to increase because of their growing demand. A recent study reported the two-fold increase in defined daily dosage of antihypertensive, cholesterol lowering, antidiabetic and antidepressant drugs in OECD (Organization for Economic Co-operation and Development) member countries in last 13 years (2000–2013) (Indicators, 2015).

High consumption of pharmaceuticals led to concomitant concern observing its presence in the environment because a large proportion of these therapeutic compounds cannot be assimilated and metabolized by the human body, thus excreted via feces and urine and enters into municipal wastewater treatment plant (WWTP). The main constituents of pharmaceutical waste are antibiotics, chemotherapy products, hormones, analgesic, antipyretic and antidepressants. Many studies revealed that the presence of various pharmaceutical in the aquatic environment. Ferrando-Climent et al. (2014) confirmed the presence of anticancer drug tamoxifen and ciprofloxacin in the river at a concentration range of 25–38 and 7–103 ng L^{-1} respectively. Kim et al. (2014) reported the presence of clarithromycin, metformin, atenolol, carbamazepine, and trimethoprim at high concentrations (>500 ng L^{-1}) in the effluent of membrane bioreactor WWTP. The environmental concentrations of antibiotics, antidepressants, chemotherapy products, analgesic compounds, hormones and lipid regulators range from 0.04 to 6.3 $\mu g\ L^{-1}$ (Jones et al., 2001).

The primary sources of pharmaceutical pollutants in the environment are pharmaceutical industries, hospitals, animal waste, research activities utilizing therapeutic compounds and discharge of expired medicine in the environment (Fig. 1). Among various sources, hospitals are the major contributors of pharmaceuticals release in the environment. Water consumption in hospitals would be between 400 and 1200 L/bed/day (Gautam et al., 2007; Deloffre-Bonnamour, 1995; Paris-Nord, 1999). Effluent coming from hospital contains the pathogen, pharmaceutical residues and their metabolites, drug conjugates, radioactive elements and other chemicals. The discharge of hospital effluent into the municipal WWTP (even at diluted pharmaceutical concentrations) decreases the biodegradation process of the organic contaminant in WWTP (Pauwels and Verstraete, 2006). Continuous introduction of diclofenac in anoxic sludge treatment process causes a reduction in gas production and reduce the denitrifying potential of microbial community present in WWTP (Ozdemir et al., 2015).

Direct discharge of treated effluent (containing pharmaceuticals) from WWTP to natural water bodies raised concern regarding the effect of these persistent (escaped) compounds on the aquatic ecosystem. The presence of these pharmaceutical contaminants in the receiving environment causes disturbance of aquatic flora and fauna and risk to human health. Many short-term toxicity studies reported that the drug molecules do not have an acute toxic effect on aquatic organisms because of their presence in low concentration, but their constant release and exposure to aquatic biota have long-term (chronic) effects. In laboratory studies, it was observed that estrogen induce vitellogenesis in male *Oryzias latipes* (Japanese medaka) and high estrogenicity increases the mortality rate of fish (Jukosky et al., 2008). Prolonged exposure to pharmaceuticals in low concentration leads to the change in species trait and behavior of aquatic organisms. The well-known example of the shift in species trait is the feminization of male fish due to the presence of estrogen in the aquatic environment (Gross-Sorokin et al., 2005). Exposure to dutasteride causes reduction in fish fecundity and also affects reproductive functions of male and female fishes (Margiotta-Casaluci et al., 2013). Oaks et al. (2004), found that large decline in vulture population in Asia is due to the presence of veterinary drug diclofenac in their food that causes visceral gout and renal failure and death. The occurrence of tetracycline concentration around 10–100 $\mu g\ L^{-1}$ caused low periphyton (nematode, bacteria and algae) populations in mesocosm stream (Quinlan et al., 2011).

Many research studies concerning removal of pharmaceutical residues were conducted. The major removal mechanisms of these compounds in WWTP using biological approaches are conventional activated sludge treatment (CAS), Membrane Bio-Reactor (MBR), attached growth MBR, constructed wetland, algae photobioreactor and stabilization ponds (Fernandes et al., 2015; Kruglova et al., 2016; Krustok et al., 2016; Zhao et al., 2015). Present review complied and discusses the studies conducted on fate and removal of pharmaceutical pollutants in conventional activated sludge process and membrane bioreactor technique. The role of microbial community structure and composition in WWTP has also been discussed.

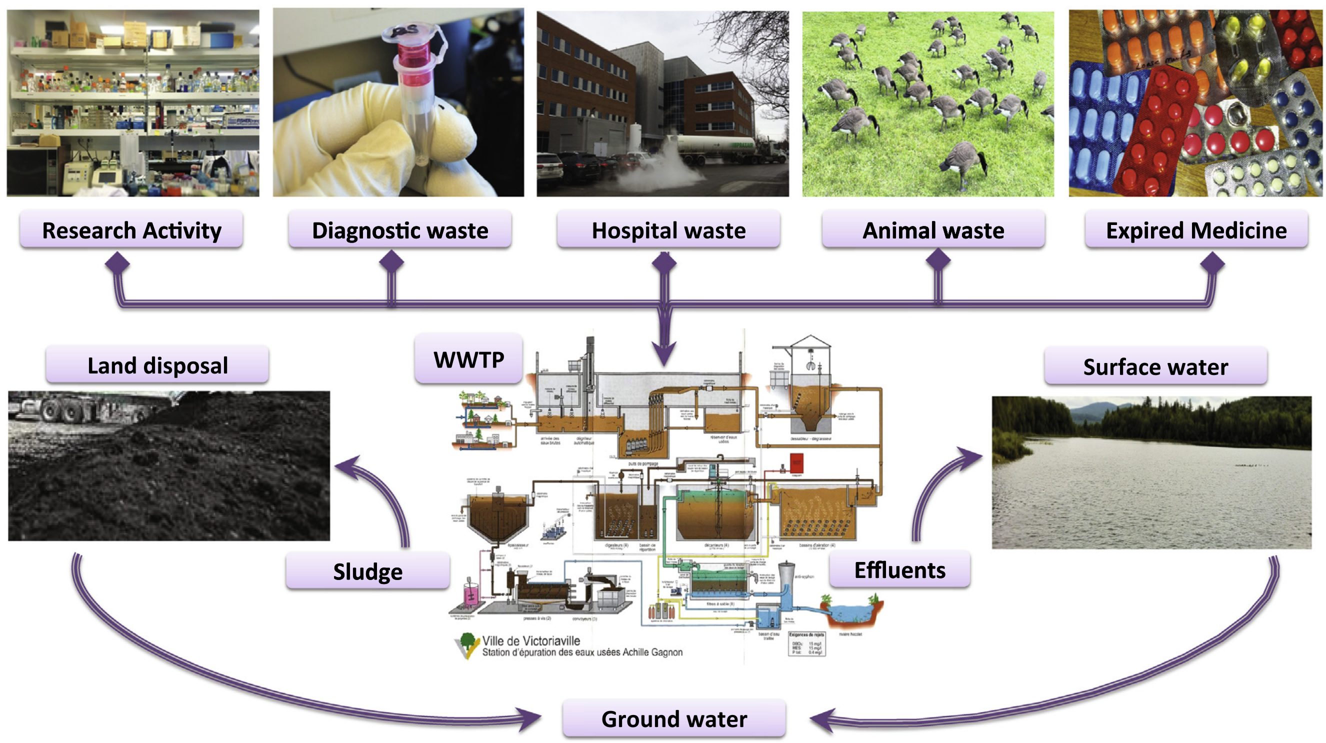

Fig. 1. Source and entry pathway of Pharmaceutical residues in the environment.

2. Pharmaceutical contaminants

Pharmaceuticals are widely used to prevent and treat the diseases in human and as veterinary drugs. These biologically active chemicals are regarded as emerging contaminant due to their persistence and potential deleterious effect on the aquatic ecosystem. These refractory emerging contaminants (RECs) (analgesics, anti-inflammatories, anti-epileptics, and antibiotics) fall mostly into the category of endocrine disrupting compounds, which continuously enters into the aquatic environment in small concentration. They remain active even in low concentrations and deteriorate water quality and have an adverse impact on the ecosystem and human health. The most prevalent and persistent pharmaceutical products in the aquatic environment are summarized below.

2.1. Antibiotics

Since last decade, global consumption and use of antibiotics raised up to >30%, i.e., approximately from 50 to 70 billion standard units (SU) (Gelbrand et al., 2015). Antibiotics are often regarded as pseudo-persistent compound because of its continuous introduction in environment and presence. The occurrence and release of antibiotics are prone to be of specific concern since they are designed to kill and inhibit the growth of microorganism thus, they will hinder the activity of beneficial microbes in WWTP operation and involved in their removal. Moreover, due to constant exposure to antibiotics, microbial community dwelling in wastewater develops resistant mechanism more readily than rest of another microbial world. A presence of numerous antibiotic compounds was detected in untreated wastewater in both aqueous and solid phase. Sulfonamides, macrolide and fluoroquinolone antibiotics are commonly found and persisted in both surface water and wastewater. Yan et al. (2013) observed five groups of antibiotics (Chloramphenicol, sulfonamides, fluoroquinolones, tetracycline and macrolide) in surface water at a concentration range of 0.05–23.5 ng L^{-1}. The class of tetracycline, generally utilized as a broad spectrum antibiotic (4-epitertracyline) were, observed in both untreated and treated wastewater at a concentration ranging between 80 and110 ng L^{-1} (Kim et al., 2014). Members of tetracycline and fluoroquinolone antibiotics conjugate with a metal cations, present in wastewater and form more complex compounds and become more abundant in sewage sludge. Overall, occurrence and persistent of antibiotics in water bodies raise concern, because approximately 90% of antibiotics consumed by human body were excreted via urine and feces.

2.2. Therapeutic hormones

Therapeutic hormones are the synthetic analog of animal or plant natural hormones, which affect the endocrine system and have impacts on humans and animals health. The most commonly found hormones in the environment are estrogens. A synthetic estrogenic steroid used as a birth control agent and in estrogen substitution therapies. Thus estrogen and its metabolite become the abundant class of emerging pharmaceutical contaminants. The metabolite of 17β ethinyl estradiol, estrone (E1) is one of the most powerful EDCs creating impacts in aquatic organisms. Their presence in the river environment causes adverse reproductive and developmental effect in non-targeted organisms (Gross-Sorokin et al., 2005). Baronti et al. (2000) reported that women daily excrete 10–100 µg of estrogen, and excretion increases up to 30 mg in pregnancy. The average human excretion of estrone and 17β-estradiol was 10.5 µg day^{-1} and 6.6 µg day^{-1}, respectively (Johnson and Williams, 2004). Several studies confirmed that the presence of estrogen in both influent and effluent of municipal wastewater treatment plants, at a concentration ranging from 5 to 188 ng/L and between 0.3 and 12.6 ng/L, respectively (Joss et al., 2004). Fick et al. (2015) reported that the high concentration of estrone (0.23–25 ng L^{-1}) in WWTP effluent compared to parental compound 17β-estradiol.

2.3. Analgesic pharmaceuticals

Analgesic is the widely used drug for pain relief and to treat inflammation. Drugs belonging to the class of analgesics such as naproxen acetaminophen, ibuprofen, diclofenac, meprobamate were regarded as important environment pollutants due to their persistence in the aquatic (ground and surface water) environment (Radjenović et al., 2009).

Approximately, 15% of ibuprofen was excreted after administration and 26% as its metabolite. The metabolite of ibuprofen is more toxic to aquatic organisms than parental compound (Evgenidou et al., 2015). Valcarcel et al. (2011) reported that the presence of ibuprofen, diclofenac, naproxen, frusemide (furosemide), gemfibrozil and hydrochlorothiazide in the river at a concentration ranging from 2 ng L^{-1} to 18 μg L^{-1}. The presence of meprobamate, were detected in tap water in ng L^{-1} range (Benotti et al., 2009). The occurrence of these xenobiotics compounds in natural water bodies represents a significant concern for human health as little information is available on the effect of long-term ingestion of these compounds through drinking water. Thus, complete and efficient removal of pharmaceuticals in WWTP before the discharge of final effluent in water bodies is recommended.

2.4. By-product and metabolites

Pharmaceuticals compounds undergo a set of biochemical transformation in human and animal body and form polar, hydrophilic and biologically active metabolites, which are excreted through urine and feces and enter WWTP. These active metabolites such as 10,11-dihydro-10,11-epoxy-carbamazepine, N4-acetylsulfamethoxazole, 4-hydoxydiclofenac are accumulated in tissues of aquatic organisms, and they have the potential to bind covalently to their cellular protein and may evoke an immune response or exert toxic effects (Zhou et al., 2005). For example norfluoxetine and desmethyl sertraline metabolite of fluoxetine and sertraline were detected in a concentration greater than 0.1 ng/g in *L. macrochirus*, *I. punctatus*, and *P. nigromaculatus* from stream discharged with municipal effluent (Brooks et al., 2005). These metabolites are reported to be 50% more toxic than their parental compounds. Study and analysis of metabolites of pharmaceutical compounds are more relevant because of their higher concentration and toxicity and also to determine the fate of their parent compounds. The poorly metabolized parental pharmaceutical substances undergo a transformation and affect the action of microbial community present in the WWTP. These metabolites are persistence due to their weaker sorption potential and high mobility, thus, detected in environmental samples. For instance, the biologically transformed metabolite of phenazone and propyphenazone were detected in polluted ground water (Zuehlke et al., 2007). The metabolite of acetylsalicylic acid (salicylic acid and gentistic acid) are detected in μg L^{-1} concentration in rivers and effluent of WWTP in Germany (Ternes, 1998). Both salicylic acid and gentistic acid are reported to have acute and chronic effects on the fish embryo, *Daphnia magna* and *Daphnia longispina* (Marques et al., 2004). Literature reported that the concentration of the metabolite in influent and effluent of WWTP are often higher than their parental compounds, and their fate depends on the environmental conditions such as salinity, temperature, pH and microbial diversity. The concentration of hydroxyl ibuprofen, carboxyl ibuprofen and their parent compound ibuprofen were observed in WWTP are 23, 46 and 15%, respectively (Weigel et al., 2004). Desmethylcitalopram metabolite of citalopram was detected in higher concentration than citalopram in WWTP (Vasskog et al., 2008). A comparative study revealed that the concentration of ibuprofen, hydroxyl-ibuprofen and carboxyl-ibuprofen are similar in WWTP, but their concentration varies in fresh and marine water. In fresh water, hydroxyl-ibuprofen is the dominant compound while in sea water carboxyl-ibuprofen concentration is higher which implies that their fate varies with environmental conditions. Hydroxyl-ibuprofen is formed due to biodegradation in aerobic condition while carboxyl ibuprofen is formed in anaerobic condition (Weigel et al., 2004). However, this biotransformation accounts only for 10% of their total concentration indicating that the large fraction is contributed as excreted product. Thirty-two metabolites were formed in the human body from highly metabolized drug carbamazepine. Among these, five metabolites were detected in WWTP, and their removal is negligible as their parent compound (Miao et al., 2002). High removal of N4-acetylsulfomethoxyzole, metabolite of antibiotic sulfamethoxazole was reported in WWTP. However, the degradation of its parent molecules is insignificant (Behera et al., 2011). Pharmaceutical compounds undergo a various degree of biological transformation and form different metabolite. In WWTP, these metabolite combines and form conjugate (novel) compounds whose toxicity might be higher than their parent molecule and known metabolite. Overall, an occurrence of pharmaceutical metabolites, either as a human metabolite or transformed metabolite (due to microbial activity) raise concern regarding their potential eco-toxic impacts on aquatic organisms. Therefore, evaluation of complete metabolic pathway during the design of the new drug, its excretion pattern, fate in WWTP and assessment of risk associated with the accidental introduction of the drug to non-targeted species is required. Many studies on removal of pharmaceutical compounds from wastewater have been conducted, and many treatment technologies of hospital wastewater treatment have been developed. Treatment of pharmaceutical residues using conventional activated sludge and membrane bioreactor processes was discussed in the following sections.

3. Conventional activated sludge process

Municipal wastewater treatment plants are intended to eliminate soluble organic pollutants, suspended solids and flocculated matter and to produce high-quality effluent before environmental discharge. It is ancient technique and used worldwide for the treatment of wastewater. However, the treatment system is not sufficient enough for the removal of persistent micro-pollutant in WWTP due to their nature and lower quantity.

The presence of 32 pharmaceutical compounds was detected in the effluent of conventional WWTP (Ternes, 1998). Heberer (2002) monitored the presence of diclofenac in both influent and effluent of WWTP and confirmed its presence in surface water due to the incomplete removal of diclofenac in conventional activated sludge process (Heberer, 2002; Ternes, 1998). The removal efficiency of phenazone, clofibric acid and carbamazepine are lower than the average removal rates. Lipid regulators (Gemfibrozil, Bezafibrate, the active polar metabolite of clofibrate, fenofibrate and etofibrate), Antiphlogistics drugs (diclofenac, indomethacin, ibuprofen), a beta blocker (metoprolol, propranolol, betaxolol) were detected (from ng to μg L^{-1}) in the rivers and stream water, which receives sewage treatment plant (STP) effluent (Ternes, 1998). Carballa et al. (2004) studied the fate of 8 pharmaceutical compounds and three hormones in municipal WWTPs. It was found that the removal efficiency of the targeted compounds, during the primary treatment was in the range of 20–50%; however, the removal efficiency of secondary treatment (activated sludge process) was increased and varied from 30 to 70%. The total removal efficiencies of wastewater treatment plant could achieve 80% for galaxolide and 83% for tonalide, 65% for ibuprofen, 50% for naproxen, approximately 65% for 17β-estradiol, and 60% for sulfamethoxazole while iopromide was not degraded and remained in the aqueous state.

The removal rates of ibuprofen and naproxen are common ranges between 75% and 85% and 50–60%, respectively. A possible explanation for the high removal rates of ibuprofen is elimination in the form of metabolites, i.e., hydroxyl and carboxyl ibuprofen. Research indicates that the removal efficiency of beta blockers in the conventional activated sludge process depends on sludge retention time (SRT) of the system. Compound diclofenac revealed low and varied removal rate ranging from 10 to 50%; Diclofenac has a chlorine atom in their structure, which contribute to its persistence in the effluent of the WWTP (Joss et al., 2004). Castiglioni et al. (2006) reported an elimination of 10% for atenolol during the winter months. Concerning hormones, the removal efficiencies of estrone (E1), 17β-estradiol (E2), and 17α-ethinylestradiol (EE2) vary dependently on the operating conditions. Nakada et al. (2008) observed a high removal rate (80%) of estrone. High removal efficiencies were viewed for E1, E2 and EE2 in activated sludge treatment and its range is 49–99%, 88–98% and 71–94%, respectively. However, the biodegradation of estrogen (comprise of E1, E2, EE2) is higher in primary sludge compared to mixed sludge (Joss et al., 2004). Yu et al. (2013) monitored the seasonal variation in the concentration of 13 endocrine disrupting compound and pharmaceutical compounds in the wastewater. The cumulative concentration of pharmaceuticals in influent of WWTP was 10–15 μg/l higher in winter as compared to summer. Variation is due to the high consumption of pharmaceutical in winter and faster degradation in summer. Castiglioni et al. (2006) reported 39% and 84% removal of ranitidine in winter and summer, respectively in STP. However, it is not clear that the fluctuation in effluent concentration of STP is due to high consumption or due to temperature variation. Literature suggests that temperature variation might have an influence on degradation efficiency. In a study that investigates the removal mechanism of pharmaceutical compounds like ibuprofen, naproxen in WWTP, it was found that biodegradation was the major removal mechanism for pharmaceutical pollutants in WWTP (Samaras et al., 2013). Jelic et al. (2011) investigated that the removal of 21 pharmaceutical compounds is due to the adsorption of pharmaceuticals in sludge. Hence both the sorption and biodegradation play a major role in the elimination of these recalcitrant compounds. However, due to short SRT and low biomass concentration in conventional activated sludge process lead to the escape of pharmaceuticals from WWTP and its persistent in the aquatic environment. In this regard, membrane bioreactor technology is a promising technique for removal of the persistent drug molecule. MBR provides relatively high SRT and biomass concentration, which contribute greater biodegradation efficiency than CAS. Table 1 compares the removal efficiency and removal mechanism of pharmaceutical pollutants in conventional activated sludge process and MBR.

4. Membrane bioreactor

The MBR innovation joins conventional activated sludge treatment with a low-pressure membrane. The membrane separation process gave a physical hindrance to contain microorganisms. MBR system is often regarded as more efficient as compared to conventional activated sludge process in the removal of micropollutant due to reduction in sludge production, extremely low or negligible presence of suspended solids in permeate, high removal of pathogen and viruses and production of high-quality effluent (Sipma et al., 2010). The long SRT, efficient nitrogen removal by slow growing autotrophic bacteria in MBR provides its characteristics features of high organic pollutant removal. High SRT increases the growth of nitrifying bacteria which lead to the high removal rate of biodegradable micro-pollutant. It was viewed that in synthetic wastewater which mimics municipal wastewater, the removal of COD, suspended solids, phosphorous was increased in MBR. The ratio of volatile suspended solids to total suspended solids (TSS) in MBR were in the range of 0.46–0.55 (Seung, 2004), which is lower than the 0.75–0.90 reported in the CAS. The membrane provides the physical barrier for particulate, inert matter of mixed liquor and for soluble organic carbon which contributes to the generation of high-quality permeate. In 2004, Wen et al. (2004) reported that the removal of NH^{+4}-N, COD and turbidity by 93%, 80% and 83% respectively from the hospital wastewater in the submerged membrane reactor. High COD removal in MBR is attributed to stable biomass concentration and retention of particulate matter that provides a stable condition for the growth of specialized microbial community efficient in micro-pollutant biodegradation.

The utilization of Membrane Bioreactors (MBR) in hospital wastewater treatment has become a common practice in the previous decades. De Gusseme et al. (2009) reported 99% removal of

Table 1
Comparison of average removal efficiency of pharmaceutical in conventional activated sludge process and in MBR and their removal mechanisms.

Compound	%Removal MBR	%Removal CAS	Biodegradation%	Sorption	References
Ibuprofen	99	99	90–100	<5	Samaras et al. (2013) and Joss et al. (2006)
Naproxen	95	94	55–85	<5	Joss et al. (2004) and Jelic et al. (2011)
Diclofenac	32	50	5–45	<5	Behera et al. (2011)
Ketoprofen	99	50	70	0	Jelic et al. (2011)
Mefenamic acid	63	36	55–58	<30	Jelic et al. (2011) and Sipma et al. (2010)
Atenolol	96	64	<70	<5	Jelic et al. (2011), Behera et al. (2011) and Tadkaew et al. (2010)
Sulfamethoxazole	81	51.9	50–90	0	Behera et al. (2011)
Indomethacin	50	–	40	<5	Jelic et al. (2011) and Radjenović et al. (2009)
Carbamazepine	28	<25	<40	<5	Kim et al. (2014)
Gemfibrozil	30–40	–	90	<5	Jelic et al. (2011) and Radjenović et al. (2009)
Metoprolol	47	0	35	<5	Jelic et al. (2011) and Radjenović et al. (2009)
Fenofibric acid	99	99	0	100	Jelic et al. (2011)
Trimethoprin	90	90	90	<5	Verlicchi et al. (2012)
Sotalol	30	10	<50	<5	Jelic et al. (2011) and Radjenović et al. (2009)
Iopromide	59	51	20–95	<5	Joss et al. (2004) and Sipma et al. (2010)
Azithromycin	78	50	49	20*	Kim et al. (2014)
Tetracycline	97	71	0	98*	Kim et al. (2014)
Norfloxacin	90	80–90	0	98*	Kim et al. (2014)
Ciprofloxacin	89	–	0	98*	Kim et al. (2014)
Acetaminophen	99.8	99.1	100	0*	Kim et al. (2014) and Sipma et al. (2010)
Ofloxacin	93.5	75	0	86*	Kim et al. (2014) and Sipma et al. (2010)

* Values from MBR.

17β-ethinylestradiol in nitrifier-enriched biomass of MBR. Dawas-Massalha et al. (2014) demonstrated that high nitrifying activity enhance the degradation of pharmaceutical residues. Snyder et al. (2007) demonstrated that concentrations of caffeine, acetaminophen, sulfamethoxazole, carbamazepine, and gemfibrozil decreased as the compounds passed through the pilot MBR with removal efficiencies varying between 99.1% (sulfamethoxazole) and 99.9% (acetaminophen). Radjenović et al. (2009) found that the removal of acetaminophen from the aqueous phase by the MBR was greater than 99% (similar to the Conventional activated sludge process). No elimination of gemfibrozil took place by conventional activated sludge treatment, whereas the MBR eliminated 30–40% of this compound. In the same study, carbamazepine remained untreated by both techniques. Removal efficiencies of sulfamethoxazole were higher by the MBR technology (81%) than by the conventional activated sludge (75%). Kimura et al. (2005) reported high removal of ketoprofen and naproxen in MBR system whereas, the removal efficiency of clofibric acid, ibuprofen, diclofenac and mefenamic acid were same in CAS and MBR. The persistence and low removal of pharmaceutical residues in both systems are could be due to the presence of the aromatic ring or chlorine group in their structure.

MBR system is more efficient than CAS treatment for the removal of persistent micro-pollutant especially for those compounds that are not readily degradable. Bernhard et al. (2006) observed that with high SRT, MBR process had a better removal of polar compounds like diclofenac, sulfophenyl carboxylate and mecoprop. However for the compounds such as sotalol and hydrochlorothiazide removal efficiency was less compared to CAS process (Sipma et al., 2010). Studies revealed that increase in retention time in membrane bioreactor improved the degradation of estrogen (Joss et al., 2004). Radjenović et al. (2009) compare the degradation efficiency of pharmaceuticals compounds in MBR with conventional activated sludge process. The degradation efficiency of compounds like diclofenac, metoprolol and clofibric acid was 87.4%, 58.7% and 71.8% in MBR whereas in CAS process only 50% for diclofenac and 27% for clofibric acid. No removal of metoprolol was observed in conventional activated sludge process. The removal rate of sulfamethoxazole was varied considerably may be due to back conversion of N4-acetylsulfamethazole to sulfamethoxazole during the degradation process. The removal efficiency of ibuprofen remains same in both treatment processes. MBR treatment has a characteristic feature of retaining hydrophobic compounds and the slow growing nitrifying microorganism within the reactor with established biomass concentration makes MBR a better treatment technique than CAS (Huang and Lee, 2015). Low sludge production and high removal of pharmaceutical residues in MBR treatment suggest that MBR technology could be an economical solution for the generation of clean water. MBR technology is competent in the production of high-quality effluent than CAS; thus MBR treated water are directly released into the environment. MBR is one of the powerful technique to treat the emerging pollutants. However, the fouling of membrane and repeated washing are the factors that limit its application at large scale. Published investigation revealed that presence of supporting medium for microbial growth in MBR would be a useful technique for decreasing membrane fouling rate and for removal of highly persistent micro-pollutant (Wei et al., 2012). Attached growth bioreactor provides a diverse microbial group of the aerobic, anoxic and anaerobic zone, which offers high removal of persistent micro-pollutant. Arya et al. (2016) reported high removal of gemfibrozil and ciprofloxacin in submerged attached bio-filter as compared to MBR. Enhanced pollutant removal in MBR could be achieved by use of supporting medium to facilitate the biofilm growth and enhance the micro-pollutant retention.

4.1. Biological activated carbon coupled MBR

Application of activated carbon in MBR provides support for the attached bacterial growth and also absorbs low molecular weight contaminants. Activated carbon are porous carbonaceous substances, having characteristics features of the large surface area and pore volume, which makes its a suitable candidate for adsorption of micro-pollutant in WWTP. The extent of adsorption of compounds onto the activated carbon bed depended on the shape and size of activated carbon and also their influence on viscosity. The smaller activated carbon particle shows high adsorption as compared to big one. Activated carbon was utilized fundamentally for the removal of excess chlorine. Granular and Powdered Activated Carbon (GAC and PAC) were usually employed for adsorption of an organic compound such as for pesticides (Ternes and Joss, 2006). Degradation of pharmaceutical compounds such as diazepam, diclofenac and carbamazepine were increased by adding GAC of 0.5 g/L into the aeration tank of activated sludge. Activated carbon efficiently enhance the retention of slow-growing microbes such as nitrifiers in the system by providing support for bacterial attachment (Thuy and Visvanathan, 2006; Ma et al., 2012). Ng and Stenstrom (1987) demonstrated that the incorporation of 0.5–4 g/L of PAC may increase nitrification rates up to 97% in activated sludge treatment process, while some studies reported an increase in the removal rate of organic matter and also a critical decline of inhibitors of nitrification process (Serrano et al., 2011). Li et al. (2011) reported high removal of carbamazepine (up to 90%) in the presence of high concentration of PAC ($1\,g\,L^{-1}$) in MBR. Serrano et al. (2011) reported high removal of carbamazepine and diazepam and observed the large abundance of *Accumulibacter phosphatis* and *Nitrosomonas* in MBR after PAC addition. It was observed from the previous study that addition of a small fraction of activated carbon could reduce the permeate flux loss. The activated carbon addition can contribute to reducing the membrane fouling in MBR systems. The advantage of initiated carbon expansion enhances the MBR filtration performances, for example, the reduction in energy consumption, which is because of increase in transmembrane pressure (TMP). However, utilization of activated carbon in MBR requires consideration of sludge retention time and its dosage in MBR as overdose result in high membrane fouling, increase the viscosity of sludge and reduced sludge dewaterability.

5. Microbial community structure and composition

Microbial community is the essential component of WWTP due to their involvement in nutrient (carbon, N and P) and organic pollutant removal. The presence of filamentous and non-floc forming bacteria in WWTP affect the treatment and settling efficiency by causing sludge bulking and foaming. Nitrification and phosphate removal in WWTP are the key properties of the microbial community, which protects natural water bodies from subsequent eutrophication and toxicity. The microbial community responsible for nitrogen removal belongs to *Beta proteobacteria* and some genera of *Gamma proteobacteria* (*Nitrosospira, Nitrosococcus and Nitrosomonas*) (Wells et al., 2009). It was viewed that the *Rhodocyclales* genus from phylum *Proteobacteria* is responsible for phosphorus removal in WWTP by accumulating phosphorus inside their cells (Garcia Martin et al., 2006). In 2000, Lemmer et al. (2000) stated that three different groups of filamentous bacteria involved in sludge settling problems that are frequently found in municipal WWTPs. Sulfur bacteria such as type 021 N and *Thiothrix* sp., which can use organic substrates, reduced sulfur components as an energy source, and heterotrophic bacteria adapted to high sludge load [Food to microorganism (F/M) ratio >0.15 kg, BOD/kg, MLSS/

d], e.g. *Sphaerotilus* spp. and *Haliscomenobacter hydrossis*, are responsible for bulking sludge. The third group including heterotrophic bacteria adapted to low sludge load (F/M ratio <0.15 kg BOD kg^{-1} MLSS d^{-1}) is often found in nutrient removal plants with nitrogen elimination. Research studies indicated that settling and compaction properties of activated sludge depend on the structure of floc, which relies on chemical, physical and biological factors that affect the balance between filamentous and floc-forming microorganisms. Hence, population equilibrium of filamentous and floc-forming bacteria support the development of large, stable and strong flocs, which promotes adequate settling and compaction of the activated sludge. It has been shown that different groups of bacteria influence the floc strength to a different extent, i.e. *Beta*-, *Gamma*-, and *Delta Proteobacteria* form relatively stable microcolonies, while colonies of other bacteria like *Alpha Proteobacteria* and *Firmicutes* are rather weak (Klausen et al., 2004). It becomes clear that the bacterial community composition determines treatment efficiency. For efficient WWTP operation for the removal of pharmaceutical pollutant along with their metabolites and byproduct requires in-depth knowledge of composition and diversity of the microbial community that is responsible for their biological transformation to simpler and less toxic products.

Microbial community structure and diversity are the two critical factors, which governs the stability and performance of WWTP. It was observed that there is a variation in the microbial communities between municipal and industrial WWTPs. This distinction is due to the characteristics of wastewater and WWTP operational parameters (dissolved oxygen and pH) (Ibarbalz et al., 2013). Hu et al. (2012) reported the differences in microbial community structure in 16 activated sludge samples of 12 WWTP. Among them in 3 samples, *Proteobacteria* is the dominant phylum constitute up to 62.1% followed *Bacteroidetes* and *Acidobacteria* while in other samples members of *Bacteroidetes* phylum were in abundance. However, the distribution of microbial community structure and dynamics remains same for municipal WWTP at phylum level irrespective of the diverse operating conditions and geographical differences (Hu et al., 2012; Ibarbalz et al., 2013). A comparative study investigated the microbial community structure in attached and suspended form in integrated fixed-film activated sludge (IFAS) system. The study reported the preferential growth of *Actinobacteria*, *Firmicutes*, and *Bacteroidetes* in the reactor due to the presence of supporting medium, which prevents their washout from the system (Kwon et al., 2010). Ng et al. (2016) achieved higher COD removal in anaerobic bio-entrapped MBR (AnBEMR) than compared to MBR in anaerobic condition. This was due to the presence of *Elusimicrobia* and *Methanimicrococcus* genus in AnBEMR. For efficient performance and high productivity of treatment system the correlation between the treatment condition and microbial community in WWTP should be studied.

In the case of hospital WW, the microbial community analysis is critical as hospital wastewater contains antibiotics, analgesic, antimicrobial compounds, and pathogens. This wastewater hinders the growth of natural sludge-dwelling bacteria and also contributes to the development of multiple drug resistance bacteria. Chitnis et al. (2004) reported the presence of multiple drug resistance bacterial population ranging from 0.58 to 40% in hospital effluent. Research study found that antimicrobial-resistant *E. coli* was not eliminated in WWTP and were present in treated effluent samples (Galvin et al., 2010). The presence of multiple drug resistance bacteria and pharmacological products changes the structure and function of microbial community in sewage treatment plant treating hospital waste, however, only few study were reported on microbial community structure and its diversity in WWTP utilizing hospital wastewater.

Laboratory studies on removal of pharmaceutical compounds with the specified microorganisms revealed *gamma-proteobacteria* and *actinobacteria* (Table 2) are the dominant class having potential degradation capacity for pharmaceutical residues. Zhao et al. (2015) demonstrated that addition of pharmaceuticals in granular sludge sequencing bioreactor altered the microbial community structure at the genus level. After addition of pharmaceuticals, a significant fraction of the microbial community fell under the unclassified category. However, the presence of *Zoogloea* throughout the pharmaceuticals treatment process indicates that member of genus *Zoogloea* has significant role in the degradation process. Several pure and mixed culture batch studies demonstrated the ability of certain microbes in biodegradation of pharmaceutical compounds under optimum treatment condition (Table 2). A group of white rot fungus was reported for degradation of persistent pharmaceuticals like diclofenac, naproxen, carbamazepine and 17a-ethynylestradiol (Rodarte-Morales et al., 2012; Zhang and Geißen, 2012). The degradation is due to the enzymes

Table 2
List of micro-organisms reported to degrade pharmaceutical compounds.

Group	Degrading microbes	Pharmaceutical compound	References
Agaricomycetes	*Trametes versicolor* *Phanerochaete chrysosporium*	Naproxen	Rodarte-Morales et al. (2012)
Agaricomycetes	*Trametes versicolor*	Carbamazepine	Rodarte-Morales et al. (2012)
	Ganoderma lucidum	Carbamazepine	Marco-Urrea et al. (2009)
	Trametes versicolor	Clofibric acid	Marco-Urrea et al. (2009)
	Trametes versicolor	Ibuprofen	Marco-Urrea et al. (2009)
Gammaproteobacteria	*Pseudomonas* sp Strain CE22	Cefalexin	Lin et al. (2015)
Actinobacteria	*Microbacterium* sp	Sulfamethazine	Topp et al. (2013)
Gammaproteobacteria	*Pseudomonas psychrophila HA-4*	Sulfamethoxazole	Jiang et al. (2014)
Actinobacteridae	*Actinoplanes sp*	Diclofenac	Osorio-Lozada et al. (2008)
Gammaproteobacteria	*Raoultella ornithinolytica B6* *Pseudomonas aeruginosa* *Pseudomonas sp. P16* *Stenotrophomonas sp. 5LF 19TDLC*	Ketoprofen	Ismail et al. (2016)
Agaricomycetes	*Phanerochaete sordida*	Mefenamic acid	Hata et al. (2010)
Actinobacteria	*Streptomyces* sp	Flurbiprofen	Bright et al. (2011)
Zygomycetes	*Cunninghamella blakesleeana* *Cunninghamella echinulata*	Etonogestrel	Baydoun et al. (2016)
Eurotiomycetes & Sordariomycetes	*Aspergillus niger* *Gibberella fujikuroi*	6-Dehydroprogesterone	Ahmad et al. (2016)
Zygomycetes	*Cunninghamella blakesleeana*	Indomethacin	Zhang et al. (2006)
Actinobacteria	*Streptomyces MIUG 4.89*	Clofibric acid	Popa Ungureanu et al. (2016)
Actinobacteria	*Microbacterium* sp.	Norfloxacin	Kim et al. (2011)

lignin peroxidases, manganese-dependent peroxidases and laccase secreted by the fungal species. Lignin peroxidases were known to degrade polycyclic aromatic and phenolic compounds. Manganese-dependent peroxidases have a role in the oxidation of monoaromatic phenols and aromatic dyes. Laccase has been reported to catalyze the oxidation aromatic and aliphatic amines, diphenols (Yang et al., 2013). However, Haroune et al. (2014) suggested that biosorption of pharmaceuticals by fungal cells is a primary process responsible for removal of pharmaceutical compounds. A batch study reported high removal of sulfamethoxazole in a mineral salt medium at low temperature by *Pseudomonas psychrophila* (Jiang et al., 2014). However, factors like non-functioning of microbes at elevated temperature and pH, enzyme washout through ultrafiltration membrane in WWTP should be resolved before their implication to WWTP.

6. Factors influencing the fate of pharmaceutical pollutant

Physical and chemical properties (solubility, volatility, photo-degradation and biodegradability) of pharmaceutical pollutant and WWTP operational parameters [SRT, Hydraulic retention time (HRT), pH and temperature] control the fate and removal efficiency of pharmaceutical pollutants.

Solubility of pharmaceutical pollutants is determined by their octanol-water partition coefficient (Kow) which is a measure of hydrophobicity. Rule of thumb on the Kow values of pharmaceutical pollutant was applied for estimating sorption of pharmaceutical pollutant in sludge. Compounds with high log Kow have been shown to adsorb by soil and sediment particles in water (Rogers, 1996). Pharmaceutical pollutant with high sorption potential has higher removal rate than the compounds with low sorption potential.

Volatilization of the compound is defined by the Henry law constant (k_H). The k_H value >3×10^{-3} mol/(m^3 Pa) were required for significant volatilization. For pharmaceuticals, normally the value of k_H was <10^{-5} (Ternes et al., 2004). Therefore, volatilization of pharmaceutical pollutants in a wastewater treatment plant was negligible. In the case of WWTP, photo-degradation of pharmaceuticals present in wastewater was insignificant due to the high sludge concentration, which makes the wastewater turbid and blocks the penetration of sunlight in the top layer.

Biodegradation of pharmaceutical pollutants depends on their structure and bioavailability. Their degradability was also relied on redox potential, pH, stereo chemical structure and the chemical properties of both the sorbent and the sorbed molecules as these molecules favor intercalation. The biodegradability was governed by complexity and stability of compounds. The short side chains and unsaturated aliphatic compounds are easily biodegraded than aromatic or highly branched, long side chain compounds (Tadkaew et al., 2010). The fate and removal mechanism of pharmaceuticals pollutant in WWTP also governed by the presence of electron withdrawing/donating groups in their structure (Wijekoon et al., 2013). However, some researcher refutes the relationship between drug structure and biodegradability (Radjenović et al., 2009).

Diversity and size of the microbial community in WWTP are controlled by the sludge retention time. High SRT has been an advantage for proliferation and maintenance of microorganisms in WWTP. It was found that increased removal of pharmaceutical compounds with the longer SRT 26d, whereas decreased removal with shorter SRT of 8 d (Lesjean et al., 2005). The biological transformation of pharmaceutical compounds like ibuprofen, sulfamethoxazole, acetylsalicylic acid and bezafibrate require an SRT of 5–15 d (Ternes, 1998). Longer SRT facilitates the growth of slow growing microorganisms that are efficient in nitrogen removal and hence can enhance the removal of biodegradable pharmaceutical pollutant.

Hydraulic retention time (HRT) is the amount of time a compound remains in wastewater treatment plant. The removal of pharmaceutical pollutant having low sludge water distribution coefficient is more depend on HRT than the compounds having high sorption potential (Suarez et al., 2010). The acidity and alkalinity in wastewater treatment plant may have an effect on the nature of pharmaceutical pollutant and also influences the microbial community structure and increase or decrease microbial enzyme activity. It was viewed that removal of ionizable compounds such as ibuprofen and sulfamethoxazole greatly depends on pH for degradation. In acidic condition, these compounds exhibit hydrophobic form that results in higher elimination. However, the removal of non ionizable compounds like carbamazepine is independent of pH (Tadkaew et al., 2010). The pH of MBR system decreases as the rate of nitrification increases. It was viewed that 90% degradation of ibuprofen was achieved at a pH of 6. Ketoprofen was degraded up to 70% in MBR when the pH decreased below 5. The removal efficiency of wastewater treatment plant varies with seasonal variation. The high removal rate of ibuprofen, bezafibrate, atenolol, and sulfamethoxazole was reported in summer as compared to winter because of promoted microbial activity at a warmer temperature (Castiglioni et al., 2006). A possible strategy to combat with the seasonal variation in removal efficiencies is by increasing the SRT of the system. Temperature variation influences biological degradation of pharmaceutical pollutant. Due to promoted microbial activity at warmer temperature high micro-pollutant elimination can be achieved. However, some studies reported that removal of micro-pollutant was independent of temperature (Suarez et al., 2010).

7. Removal mechanisms

In WWTP, micro-pollutant removal mechanism is either a sorption or biodegradation process. Volatilization and photo-degradation in WWTP are negligible for the pharmaceutical pollutants (Kim et al., 2014). Sorption of drug compounds occurs due to the hydrophobic interaction of aliphatic and aromatic group, to lipid molecules of sludge or to cell membrane of microorganisms and due to electrostatic interaction of a positively charged compound to negatively charged microbes and sludge. It means sorption depends on the values of log Kow (octanol-water coefficient), K_d (sludge adsorption coefficient) and Pka (acid dissociation constant), Table 3 shows the physicochemical properties of several classes of pharmaceuticals. Compounds with high log Kow > 5 and high molecular weight tend to more sorbed than the compounds with low log Kow < 2.5. Sorption of most of the pharmaceutical compounds on sludge is insignificant due to their low K_d values. Ternes et al. (2004) reported that compounds with K_d values <500 L $kgSS^{-1}$ will be removed by <10% only via sorption. From Table 3, it is clear that sorption is the minor removal pathway of most of the pharmaceutical compounds. Despite the persistence of the drug pollutant, the major removal mechanism in WWTP is biodegradation. Many studies reported that the biodegradation of micro-pollutant such as ibuprofen, ketoprofen, naproxen, trimethoprim, in aerobic and anaerobic conditions (Jelic et al., 2011; Kim et al., 2014). Biodegradation of pharmaceutical residues in WWTP occurs by two principle mechanisms, i.e., either by co-metabolism, in which pharmaceutical pollutant was degraded by enzymes secreted by microbial community present in sewage sludge, or by sole substrate degradation, in which targeted compounds is sole carbon and energy source for microbes. Research study revealed that the fungus *Trametes versicolor* achieved efficient removal of carbamazepine, due to the secretion of laccase and peroxidase enzymes (Jelic et al., 2011). Several strains of *Pseudomonas* are reported to utilize antibiotic sulfamethoxazole as sole

Table 3
Physiochemical properties of pharmaceuticals.

Class	Compound	Pka	log Kow	Kd	References
Antibiotics	Sulfamethoxazole	5.6–5.7	0.89	0.77–1.79	Carballa et al. (2008)
	Trimethoprim	7.12	0.73	200	Sipma et al. (2010)
	Erythromycin	8.88	2.48	160	Sipma et al. (2010)
Chemotherapic products	Fluorouracil	8.02	0.89	–	Bank, 2012 .
	Methotrexate	4.7	1.85	–	Bank (2012)
Hormones	Estradiol	10.4	4.01	2.30–2.83	Carballa et al. (2008)
	Ethynylestradiol	10.4–10.7	3.6	2.08–2.85	Carballa et al. (2008)
	Norgestrel	17.91, −1.5	3.48	–	Bank (2012)
Analgesics	Ibuprofen	4.5–5.2	3.97	1.00–1.78	Carballa et al. (2008)
	Hydromorphone	10.11	0.11		Bank (2012)
	Carbamazepine	13.9	2.45	0.1	Sipma et al. (2010)
	Naproxen	4.2	3.18	1.03–1.71	Carballa et al. (2008)
Lipid regulator	Gemfibrozil	4.77	4.77	75	Lin et al. (2006) and Sipma et al. (2010)
	Bezafibrate	3.61	4.25	–	Vieno et al. (2007)
Beta blockers	Atenolo	9.6	0.16	64	Vieno et al. (2007) Sipma et al. (2010)
	Sotalol	8.3	0.85	–	Sipma et al. (2010)

carbon and energy source (Jiang et al., 2014). A comparative study between co-metabolic and single substrate degradation process demonstrated that the co-metabolic biodegradation was the major removal mechanisms for the ibuprofen, bezafibrate, and naproxen while ketoprofen was partially degraded as a sole substrate (Quintana et al., 2005). Pharmaceuticals of the same therapeutic group show considerable variation in their removal mechanisms. A study investigated the removal of pharmaceutical in MBR and reported that sorption was the primary removal mechanism for antibiotic like tetracycline, norfloxacin, ciprofloxacin (Table 1) while azithromycin and sulfamethoxazole were removed by degradation (Kim et al., 2014). Some studies (Radjenović et al., 2009) reported negligible removal of pharmaceutical pollutants like carbamazepine, sulfamethoxazole, erythromycin, in WWTP. Low removal of pharmaceuticals in WWTP was due to the transformation of human metabolites and conversion of formed metabolites into parental compounds.

7.1. Biological degradation of pharmaceutical compounds

Biological degradation or biodegradation is the breakdown of complex, toxic chemical compounds into simpler, less toxic products by the action of the enzymes secreted by the microorganisms. Biodegradation is the key mechanism, which is responsible for maximum removal of organic micro-pollutants in WWTP. Biodegradation efficiency of pharmaceutical pollutants mainly depends on their solubility in wastewater. If the solubility of micro-pollutant is low (hydrophobic compound) then it will be retained in sewage sludge and retention of these compounds in sludge provides more time for microbial degradation, i.e., micro-pollutant get degraded either by catabolic microbial enzymes or utilized by microorganisms as a carbon source. On the other hand, hydrophilic micro-pollutants escapes from WWTP without biodegradation along with permeate, and evades the biodegradation process. In the study of 25 pharmaceutical compounds degradation including antibiotic, hormones, antipyretic, analgesic, only ibuprofen, 17β-estradiol, paracetamol, (hydrophobic compounds) achieved 90% removal in the aerobic process (Joss et al., 2004). However, anaerobic degradation favors biodegradation of the persistent micro-pollutant through hydrolysis of amide and urea groups of carbamazepine and atenolol (Schwarzenbach et al., 2005). Degradation rate and efficiency vary from compound to compound in both aerobic and anaerobic digestion; it depends on the structure and functional group of the compounds. For instance, degradation of low chlorinated compounds during aerobic digestion is quite faster than anaerobic digestion; however, the degradation rate of polyhalogenated compounds is slower in aerobic digestion (Schwarzenbach et al., 2005). It was reported that long chain aliphatic compounds are more biodegradable than aromatic compounds having sulfate or halogen group in its complex ring structure (Schwarzenbach et al., 2005). Sludge retention time (SRT) is also one of the factors, which greatly influences the rate of biodegradation. Byrns (2001) reported that at low SRT, a vast majority of xenobiotics compounds are eliminated through sludge discharge due to the sorption not by degradation and at high SRT, the rate of elimination of sludge waste diminished due to increasing the contact time of microbial community with sludge. Operating parameters (retention time, temperature, pH), microbial community, complexity and bioavailability of micro-pollutant are factors, which determines the rate of biodegradation.

8. Future recommendations

Published investigation on the removal efficiency of pharmaceuticals compounds indicated that MBR system could be a promising technique for treatment of these emerging micro-pollutant. However, the biggest problem is a formation of toxic metabolite and conversion of metabolite into parental compounds under certain treatment conditions. Therefore, detailed studies should be conducted on the fate of pharmaceutical pollutants from production till release and degradation to evaluate their transformation pathway. This study extends our knowledge about metabolite formation, effect and fate of pharmaceutical in WWTP.

Many researchers studied the influence of operating conditions such as SRT, HRT, pH and temperature on the removal of pharmaceutical pollutant in MBR, however, individual or combined impact of these factors on the treatment system has neo been studied, therefore a systematic study is warranted to optimize MBR treatment process for efficient removal of pharmaceutical compounds.

Many studies involving biodegradation of pharmaceutical compounds by the pure and mixed culture of microbes has been conducted however the complete degradation pathway and microbial catabolic enzymes involve in degradation process is still unknown. Identification and development of bacterial enzymes and their corresponding degradation pathway are to be conducted.

More research for the compilation of data that correlates pharmaceutical concentration in the effluent, transport pathway, the behavior of metabolite and toxicity is to be known and documented. Research effort should be directed towards the understanding of dynamics of the microbial community of sewage sludge responsible for their degradation and characterization of degrading microbes, and their enzymes are necessary.

9. Conclusion

Literature indicates that pharmaceuticals use and release into the environment are unavoidable. However, their adequate treatment is important to protect the environment. The release of pharmaceutical compounds into environment causes disturbance of aquatic flora and fauna, a risk to human health and development of multi-drug resistant microbial strain. Published investigation revealed that MBR treatment could be an efficient treatment process for pharmaceuticals removal. Advancement in the field of research is required for the development of optimized MBR technology to protect the planet for future generations.

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