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Are Membrane Bioreactors Really More Efficient in Removing Pharmaceutical Substances?—Variance Component Analysis Of Micropollutant Removal

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Abstract This study evaluates the influence of micropollutant chemical characteristics on the removal of pharmaceutical substances through three different treatments: membrane bioreactor, full wastewater treatment with final filtration (WWTP), and secondary treatment through a conventional activated sludges system, operated in parallel at realistic sludge retention time (SRT) over three years and four sampling campaigns. Treated wastewater from the WWTP enters the local canal with a low dilution ratio. Therefore, the monitoring of water contamination is of particular interest for a reliable assessment of environmental risk. A total of 39 pharmaceutical substances were screened. While differences among the three types of treatments were found statistically not significant, data analysis performed through a generalized linear model showed that both the influent concentration and the physicochemical characteristics are strong predictors for the removal of micropollutant. SRT had no significance for the three types of treatment of this study. Finally, pharmaceuticals were divided into three major classes based on their influent concentration and removal. A canonical discriminant analysis was used to predict the removals and showed that the pharmaceuticals removal rates are strongly influenced by their hydrophobicity/hydrophilicity and enabled to predict their removal categories with high accuracy (*i.e.*, 65% of correct predictions).

Keywords Conventional activated sludge · MBR · Pharmaceutical substances · Physicochemical properties · Wastewater treatment

1 Introduction

Pharmaceutically active substances are referred to as "pseudo-persistent" in the environment (Ebele et al., 2017) since their removal in aquatic ecosystems is balanced by a continuous discharge into water bodies, where they pose risks on ecosystem and human health. In the last decade, the growing population and the related increasing consumption of medicines (Alvarino et al., 2018), together with a rising public concern, have elevated the interest in the occurrence and associated risks related to pharmaceutically active substances in the environment (Kosek et al., 2020).

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Wastewater treatment plants (WWTP) were indicated as hot spots for the release of such substances into the environment (Gutiérrez et al., 2022; Xu et al., 2016) either through discharge of treated effluent or by dispersion of digested sludge on agricultural fields. Knowledge about their fate in WWTP is still insufficient and pharmaceutical discharges are still not regulated in different European countries, but pharmaceuticals are already mentioned in the EU water reuse legislation (EU 2020/741) and included in the Watch list system since EU 2015/495 until the recent EU 2022/1307.

The removal of pharmaceutical substances, and in fact of any compounds, in biological wastewater treatment is imputable to different removal mechanisms. The removal is due either to biodegradation/transformation, adsorption on sludge, or volatilization (Gurung et al., 2019). In fact, biodegradation is generally the major removal process for hydrophilic substances. It was shown that co-metabolism is the most probable microbial degradation process occurring in bioreactors (Bouju et al., 2008). Indeed, as at such low concentrations (Kumar et al., 2019; Tran et al., 2018), the biomass activity is hardly sustained by the pharmaceutical substances themselves.

Adsorption on the biomass did not appear to be a major removal process for most of the targeted pharmaceuticals. Moreover, it was shown that at neutral pH conditions, which is the case in a majority of municipal WWTP, the water-sludge partition coefficient of acidic pharmaceuticals is low, and they likely remain in the water phase (Urase et al., 2005). Still, some of them, hydrophobic or presenting a positive charge, are likely to be adsorbed onto sludge particles (Grabic et al., 2022; Radjenović et al., 2009). Nevertheless, in general, the substances adsorbed to the sludge do not accumulate in the reactor and are successively biodegraded. As far as volatilization and stripping are concerned, it was shown that given their Henry's constant and their octanol–water partition coefficient, it should be negligible for a large majority of pharmaceutical substances (Besha et al., 2017; Gurung et al., 2019).

Several studies have reported the removal of pharmaceuticals in membrane bioreactors (MBR) (Femina Carolin et al., 2021; Ji et al., 2020; Nguyen et al., 2017; Park et al., 2017). Theoretically, MBR present few advantages, with respect to conventional processes, when facing pharmaceutical substances removal. Indeed, operating conditions observed in MBR may favor their adsorption and biodegradation. Moreover, MBR are usually operated at large SRT, which gives the possibility to the slowly growing biomass to develop, and therefore the biomass presents a larger biodiversity and broader physiological capabilities (Alvarino et al., 2018; Bhattacharyya et al., 2022; Bouju et al., 2008; Clara et al., 2005; Goswami et al., 2018). Elevated biomass concentrations may enhance the elimination of hardly biodegradable substances and lead to a better biodegradation rate (Bernhard et al., 2006; Hatoum et al., 2019). As for MBR, since the membrane retains big particles such as colloids inside the bioreactor, this increases the adsorption surface and therefore, micropollutants that present a tendency to sorb to the biomass will more likely adsorb onto suspended solids (Nghiem et al., 2020).

Some authors reported higher removal efficiencies in MBR, with respect to conventional processes (Besha et al., 2017; Monsalvo et al., 2014; Park et al., 2017). It was highlighted that MBR may show higher capabilities in removing pharmaceutical substances which are partially degraded in conventional activated sludge (CAS), but it does not impact the removal neither of recalcitrant substances, nor of readily biodegradable ones (Besha et al., 2017; Radjenović et al., 2009). Adversely, other authors have also shown that the use of MBR did not improve the removal of pharmaceutical substances (Sipma et al., 2010) and the different behaviors for each substance makes it difficult to establish a general trend (Melvin et al., 2016). As a matter of fact, in many studies MBR were operated at unrealistically high SRT or fed with synthetic feed. Hence, when comparing both processes operated in parallel and in comparable conditions, these results tend to show that the secondary treatment is critical for micropollutant removal.

The removal of micropollutants can also be viewed from another angle, linking the efficiency of removal to molecular physicochemical properties of substances. Three main properties were reported as important factors in micropollutant removal pKa, $\log K_{ow}$, and logKoc (Ofrydopoulou et al., 2022). Similarly, it is firmly established that pharmaceutically active compounds removal is partly ascribed to their physicochemical characteristics (Ebele et al., 2017), specifically hydrophobicity and hydrophilicity (Couto et al., 2019). However, few published studies consider

properties such as molar volume, water solubility, etc. Even more, most of these studies did not provide a robust statistical analysis of their data especially due to a short period of monitoring and the lack of validation data. In this perspective, the aim of this work is to assess the influence of various physicochemical parameters on the removal of different pharmaceuticals under three different treatment processes. Four 2-days sampling campaigns in three different years were performed.

In this study, two processes (a MBR pilot plant and a full-scale CAS /WWTP) were operated in parallel, receiving the same influent, and at comparable conditions, over three years. Moreover, different but realistic sludge retention times (SRTs) were applied to the MBR. The pharmaceutical substances removal efficiencies of the three systems are compared and discussed. The assessment of a large WWTP (Milano Nosedo) effluent quality, being poorly diluted and reused for irrigation, is of high importance particularly for what concerns emerging micropollutants, including pharmaceuticals.

2 Materials and Methods

2.1 Full Scale Treatment Plant (WWTP)

The full-scale wastewater treatment of Milano Nosedo (1,250,000 PE) is situated in the South-East of Milan, close to the Vettabbia channel and collects wastewater from the central-oriental area of Milan. It was operated at yearly average SRT of 35 days and an hydraulic retention time of 23 h calculated based on the average daily inflow of 432,000 m^3/d.

This municipal sewage treatment plant consists of a mechanical pretreatment; a conventional activated sludge process followed by sedimentation. Finally, the treated effluent goes through sand filtration (composed of two sections in parallel made of ten filtering cells, with homogeneous sand at a granulometry equals to 1.35 mm; their height is of 1.5 m) and chemical oxidation (peracetic acid). The biological treatment handles nitrogen removal through pre-denitrification (anoxic) and nitrification (aerobic) tanks. Average total suspended solids (TSS) and chemical oxygen demand (COD) concentration in the effluent were 5 ± 3 mgTSS/L and 12 ± 4 mgCOD/L, respectively. Regarding the sludge loading rate (SLR), it did not vary significantly during the four campaigns, remaining between 0.101 and 0.135 gCOD/gSST/d. The aerobic/anoxic biomass ratio was of 3.3 $gTSS_{AER}/gTSS_{ANOX}$.

2.2 MBR Pilot Plant

The MBR pilot plant was operated in parallel to the biological treatment of the full scale municipal WWTP of Nosedo located in the south-east area of Milan, Italy, and fed by the same influent as the WWTP biological treatment. To limit clogging of the membrane, the influent was pre-filtered in a filter bag (1 mm mesh, 20 cm diameter, 100 cm height) and collected in a 200 L cylindrical PVC tank.

The pilot consisted of an anoxic zone of 90 L and an aerobic one of 190 L (Fig. 1). The anoxic zone, for denitrification purposes, was connected to the aerobic zone via a gravity drain. A stainless-steel stirrer was placed in the middle of the tank to provide a continuous mixing of the mixed liquor. Operational parameters were monitored through temperature, pH, and dissolved oxygen sensor, as well as a manometer for the transmembrane pressure. Twice the inflow was recirculated continuously from the aerobic to the anoxic zone. After a stabilization phase of three times the SRT, the aerobic/anoxic biomass ratio was 3.1 $gTSS_{AER}/gTSS_{ANOX}$ for the four sampling periods. The calculated SLR variates from 0.064 gCOD/gSST/d during the third campaign to 0.173 gCOD/gSST/d during the first campaign.

The hollow fiber module (GE Healthcare ZeeWeed 10®) was submerged in the aerobic zone; it is characterized by a surface area of 0.93 m^2 and a nominal cut-off of 0.2 μm, microfiltration. Average TSS and COD concentration in the effluent were below 1 mgTSS/L and 8 ± 3 mgCOD/L, respectively.

2.3 Sampling and Analyses

In the whole three-years period, four sampling campaigns were performed (April year 1, April year 2, July year 3, December year 3). Sampling points were placed at the feeding points (MBR and CAS), the MBR permeate, the effluent of the biological treatment (CAS) and the final effluent of the WWTP (WWTP). The first and the third campaign had similar SRT for MBR and CAS of 35 and 25 days, respectively. The second campaign had an SRT of

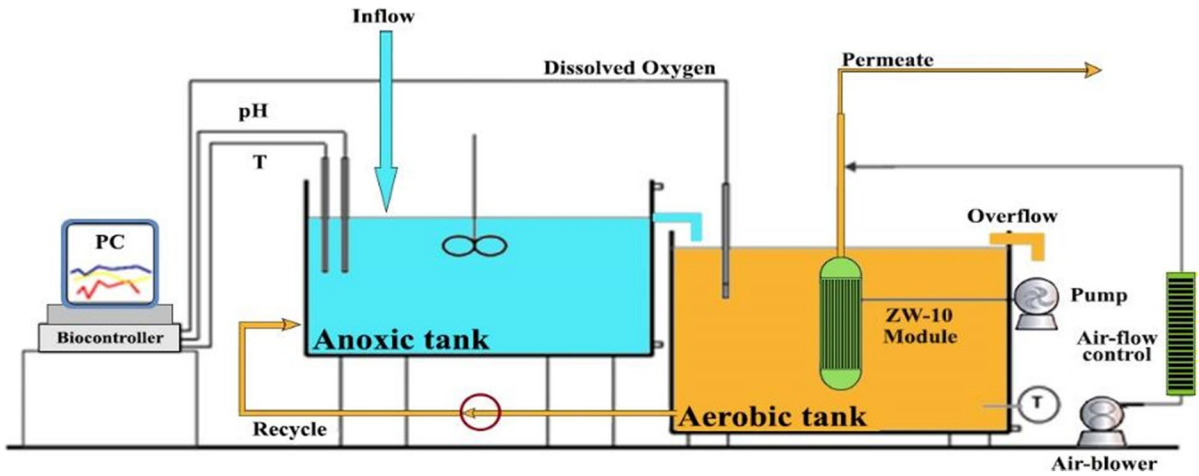

Fig. 1 Scheme of the MBR pilot plant

15 days for MBR and 43 days for CAS. Finally, the fourth campaign had an SRT of 50 days for MBR and 29 days for CAS. The data of this study can be found in Table S1. Samples were time-proportional 24 h composite samples. Immediately after collection, each sample was filtered on a 0.45 µm fiber glass filter and frozen at -20 °C until analyzed. Analyses were performed by means of HPLC/MS/MS by the Mario Negri Institute (Milan, Italy) as previously described (Castiglioni et al., 2006).

2.4 Statistical Analysis

All statistical analyses were performed using IBM SPSS Statistics. Firstly, Factor Analysis was applied through a preliminary principal component analysis (PCA) in order to reduce the number of variables while retaining most of variability in the original data (Afifi et al., 2003). For rotating the PCA axes, the Varimax rotation criterion was used which turns PCA into a Factor Analysis.

Then, Hierarchical Cluster Analysis (HCA) was run based on the extracted factors to group pharmaceuticals into similar subsets of removal values.

Moreover, in the attempt to develop a predictive model of pharmaceuticals removal as response of the physicochemical properties, influent concentration, and the type of treatment as predictors, a generalized linear model (GLM) regression analysis was run. GLMs are flexible linear models where residuals can follow a probability pattern other than normal distribution and qualitative predictors (*i.e.*, factors) can be also included. Finally, to predict micropollutant's removal categories determined through HCA, a canonical discriminant analysis was run. This latter is a dimension-reduction method like principal component analysis. Canonical discriminant analysis produces canonical variables (linear combinations of the interval variables) from a classification variable and several interval variables that summarize between-class variation and separate among categories in a manner similar to how principal components summarize total variance.

3 Results

3.1 Occurrence of Pharmaceuticals in South Milan Sewage Water

Out of the 39 substances analyzed, 10 were not detected at all (clofibric acid, estradiol, ethynilestradiol, omeprazole, oxytetracycline, sildenafil, spiramycin, tamoxifen, tilmicosine, and tylosin). Among the 29 substances detected at least once, 19 were detected in all the 4 sampling campaigns (*i.e.*, atenolol (ATE), bezafibrate (BZF), carbamazepine (CBZ), ciprofloxacin (COF), clarithromycin (CLA), cyclophosphamide (CYC), diazepam (DZP), diclofenac (DF), enalapril (ENA), estrone (EST), furosemide (FUR), gemfibrozil (GEM), ibuprofen (IBU), ketoprofen (KET), lincomycin (LCM), naproxen (NAP), ofloxacin (OFL),

ranitidine (RAN), and salbutamol (SAL)). More detailed information is provided in Table S1.

A great variability of influent concentrations between the various sampling campaigns were observed in general, and from one day to the other one, for all the sampling campaigns between low ng/L up to several µg/L (Fig. 2 and Table S1). Indeed, when considering each single sampling campaign, standard deviations up to 0.378 µg/L were observed, mostly for the substances present at concentrations in the higher range (*e.g.*, ibuprofen, atenolol, and ofloxacin). This could be explained by high variations in consumption rates between years and seasons, as previously reported (Collado et al., 2014). It is also important to note that the sewage network system going to the Nosedo WWTP covers a large area of Milan where the water table is close to the surface, likely causing infiltrations. Hence the influent arriving at the WWTP is quite diluted. Variations in the dilution ratio are also likely leading to influent concentration variability.

3.1.1 Pharmaceutical removal rate in MBR, CAS, and WWTP.

High variability in terms of removal was also observed (Fig. 3), generally in line with the literature. Many pharmaceutical compounds were highly removed. The highest removal rate was found for enalapril with 100% in the three types of treatment,

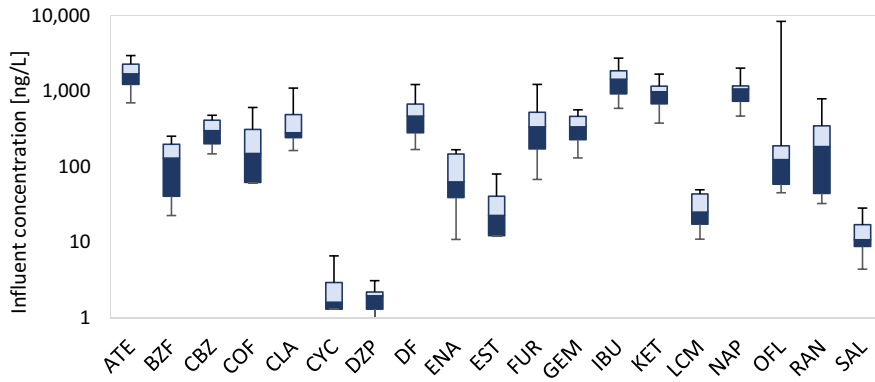

Fig. 2 Influent concentration of detected pharmaceutical compounds, average and standard deviation of the four sampling campaigns, logarithmic scale

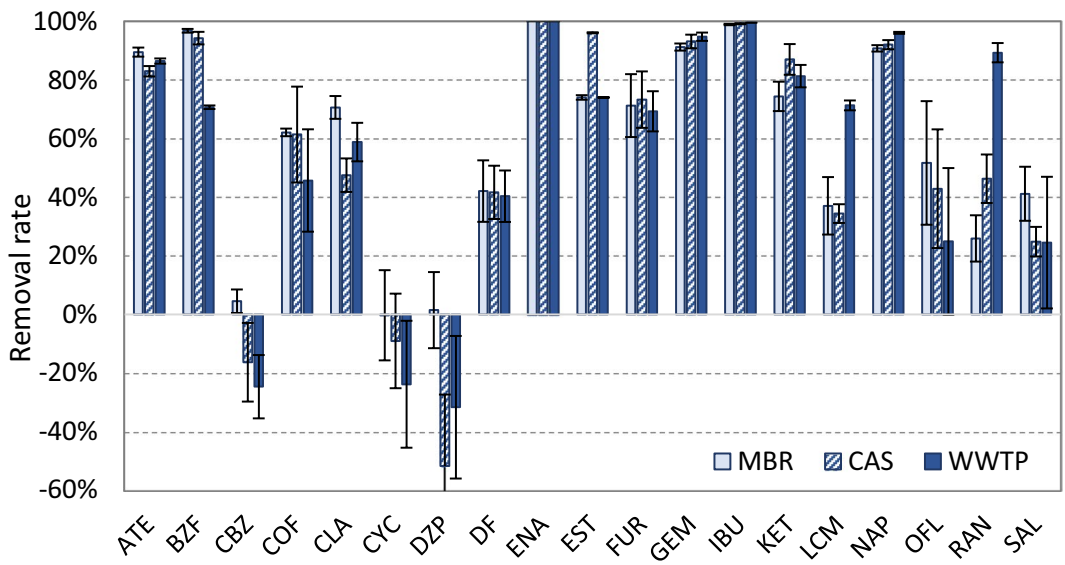

Fig. 3 Removal rate of the detected compounds for MBR, CAS, and full WWTP

in agreement with the literature (97%, Tadkaew et al., 2011). Also, atenolol (87%), naproxen (90%), ibuprofen (99%), were highly removed, in line with the literature (Wang et al., 2018). On the other hand, the lowest removal was for diazepam (-51% by CAS and -31% by WWTP), as also reported elsewhere (Sun et al., 2014; Wang et al., 2017). Carbamazepine had a low removal by MBR (5%), and diclofenac was partially removed (42%). Similar results can be found in the literature for carbamazepine, and higher for diclofenac (10% and 5%, respectively, Chon et al., 2011). Generally, carbamazepine is known for its relatively poor elimination in biologically-based treatments (Joss et al., 2005; Wang et al., 2018). It is worth pointing out that negative removal rates for some compounds can occur due to several reasons (Verlicchi et al., 2012). Microorganisms may transform conjugated forms back into parent compounds, increasing their concentration (Jelic et al., 2011). Adsorbed pharmaceuticals on suspended solids or biofilms can desorb into the water (Göbel et al., 2007). Additionally, some compounds are resistant to conventional treatment processes, resulting in their persistence in treated water (Vieno et al., 2007). Lastly, operational changes can cause the release of accumulated compounds from biofilms or sludge (Hou et al., 2019).

Similar removals were generally observed in the three treatments, with few exceptions like ofloxacin, ranitidine, or lincomycin. All the substances with a slightly higher removal either in the WWTP or in the MBR were partially removed (average removal rate below 80%) and exhibited large removal variability over the four sampling campaigns, as formerly confirmed (Urase et al., 2005; Tadkaew et al., 2011).

Other studies investigated the influence of some properties (Dolar et al., 2012; Wang et al., 2018) but it appears of great interest to evaluate, by means of multivariate statistical techniques, the influence of several physicochemical characteristics on the removal rate of active substances. In this work, 20 physicochemical characteristics, believed to have a certain level of impact on different removal mechanisms, have been considered. Table S2 summarizes the data subject to analysis.

Scientific studies indicate that ultrafiltration membranes, such as GE Healthcare Zee-Weed, remove pharmaceutical compounds from water without high impacts on their hydrophobicity and hydrophilicity. For example, Ren et al. (2021) describe the contribution of adsorption and catalytic oxidation in the decontamination of wastewater using high-performance ultrafiltration membranes. Yu et al. (2020) evaluates the long-term performance of hollow fiber membranes for contaminant removal in a full-scale drinking water treatment plant in China. Issaka et al. (2022) discuss interaction between pharmaceuticals and membrane surfaces in advanced catalytic ozonation, while Adewuyi et al. (2020) review the development related to pharmaceutical removal for nanocomposite membranes. These studies have finally concluded that ultrafiltration works mainly through size exclusion and adsorption, which does not alter any inherent hydrophobic or hydrophilic properties of pharmaceuticals.

3.2 Principal Component Analysis and Factorial Analysis

PCA analysis allowed the extraction of five components accounting for 89.41% of the cumulative variance. The first two principal components accounted for most of the information (*i.e.*, total explained variance of 53.08%). Table 1 presents the rotated component matrix that regroups all physicochemical properties into the five extracted varifactors. They can be described as follows:

- F1: accounts for 30.87% of the variance and is loaded by MW, MV, polarizability, refractivity, boiling point, flash point; it is representative for the largest pharmaceutical compounds.
- F2: accounts for 22.21% of the variance and is loaded by melting point, surface tension, index of refraction, density.
- F3: accounts for 19.37% of the variance and is loaded by biodegradation half-life, soil absorption, LogKoa, LogD, and Koc; it is representative of the more persistent and potentially accumulating in soil and in living organism fatty tissues (bioaccumulation).
- F4: accounts for 10.49% of the total variance and is inversely loaded by pKa, and solubility and directly loaded by $\log K_{ow}$; it is representative of the most hydrophobic compounds.

Table 1 Principal Component/Factor Analysis: the factor loadings higher than 0.6 of the 20 physicochemical properties are shown for the five rotated varifactors: MV: molar volume; MW: molecular weight; K_{OC}: organic carbon partition coefficient; K_{ow}: octanol–water partition coefficient; Koa: octanol–air partition coefficient; LogD: octanol–water distribution coefficient; pKa: acid dissociation constant. The explained and cumulative percent variances are also shown for all the five varifactors

Rotated Component matrix					
	F1	F2	F3	F4	F5
MW (g/mol)	0.988				
$logK_{ow}$				0.837	
Melting point		0.903			
Boiling point	0.870				
Water solubility				-0.847	
Flash point	0.880				
Surface tension		0.933			
Index of refraction		0.903			
Molar refractivity	0.986				
Polarizability (cm^3)	0.986				
Density (g/cm^3)		0.907			
MV (cm^3)	0.968				
Henrys law (atm m^3/mol)					0.978
LogKoa			0.638		
Biodeg. half-life (days)			0.944		
Soil adsorp. coeff (L/kg)			0.942		
LogD_pH7.4			0.654		
K_{OC}_pH7.4			0.897		
pKa				-0.702	
% of variance	30.87	22.17	19.37	10.49	6.45
Cumulative %	30.87	53.08	72.64	82.95	89.41

- F5: accounts for 6.45% of the total variance and is loaded by Henry's law constant; it is representative of the most volatile compounds.

HCA applied to the five factors indicated the presence of 8 natural clusters. As shown in Fig. 4, Cluster 1 and 2 are the two most populated clusters (*e.g.*, including more than 30 measurements corresponding to 5 to 4 compounds), and have average characteristics, being one almost the opposite of the other. Cluster 1 in fact contains larger and less hydrophobic compounds with respect to Cluster 2.

Clusters 4, 5, 6, 7, and 8 show factor scores above average, however only Clusters 4, 6, and 7 are strong outliers including extremes respectively for F1, F3, and F5 and are made of measurements of single compounds (*e.g.*, respectively (CLA, DZP and EST). Cluster 3 has 4 out of 5 factors below average values, precisely the parameters loading the fourth varifactor (*i.e.*, pKa, $logK_{ow}$, and solubility). The cluster can be characterized as hydrophilic and groups only two compounds (CYC and SAL). Cluster 5 is made by high density, melting point, and surface tension compounds and includes COF, FUR and OFL. Finally, Cluster 8 is characterized by factor scores below average except for the fourth varifactor, loaded by pKa and $logK_{ow}$, with value above average. Cluster 8 is in fact made of GEM and IBU measurements. The eight clusters issued from cluster analysis composition of pharmaceuticals are shown in Figure S1.

3.3 Generalized linear model

A GLM was fitted to compound-specific removals, having influent concentrations as covariate, and treatment (*e.g.*, MBR, CAS, or full WWTP), and physicochemical properties clusters as factors. GLM analysis clearly showed that the physicochemical properties cluster was the most important predictor for the removal (F: 32.4, p-value < 0.001), followed by the influent concentration (F: 20.4, p-value < 0.001). GLM also showed that the type of treatment is not a significant factor of influence for the removal (p-value > 0.05). This is confirmed by the fact that the SLR showed minimal variations for both the WWTP and the MBR. Also, the aerobic/anoxic biomass ratio was 3.1 $gTSS_{AER}/gTSS_{ANOX}$ for the four sampling periods in the MBR and very similar (3.3 $gTSS_{AER}/gTSS_{ANOX}$) in the full-scale CAS.

If GLM was extremely informative in identifying the most relevant predictors of pharmaceuticals' removal, it was not as satisfactory in terms of accuracy. GLM R^2 was in fact 44%, leaving unexplained most of the removal variance. This is probably due to the great variability affecting the data of the studied substances. Nevertheless, this model illustrates the importance of the influent concentration and

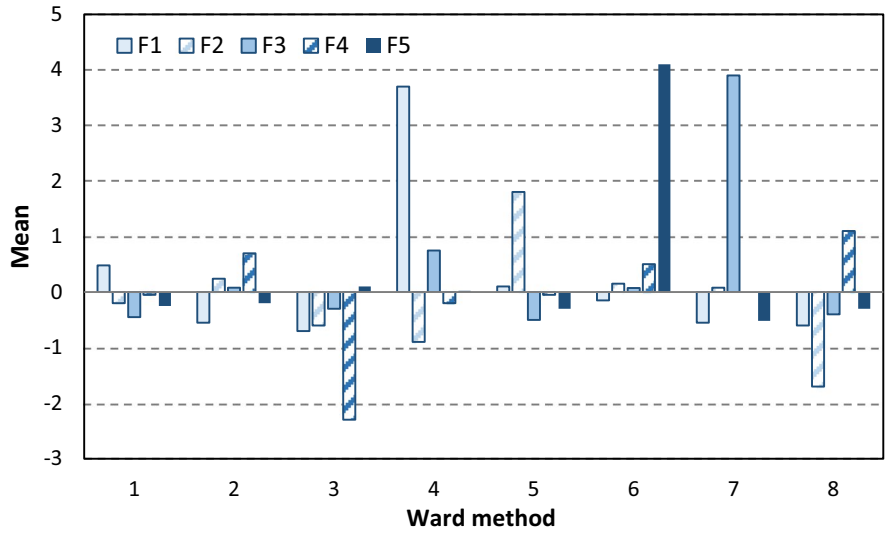

Fig. 4 Factor-score characteristics of the 8 main clusters of pharmaceuticals

physicochemical characteristics as significant influencing parameters on micropollutants removal.

3.4 Canonical Discriminant analysis

Since the GLM was not adequately accurate to predict the removal rates of each compound, the 19 compounds were subdivided into three classes: 1) removal rate lower than 47%, 2) removal rate between 48 and 90% and 3) removal rates above 91%. Canonical Discriminant Analysis (CDA) was used to predict these removal classes. As shown in Table 2, the five varifactors and the influent concentrations were the six predictors used in the CDA with the first Discriminant Function (DF) explaining 79.4% of the variance and the second accounting for the remaining 20.6%. Table 2 also shows that the first discriminant function (DF1) is directly correlated with F4 (*e.g.*, hydrophobicity, $LogK_{ow}$) and inversely correlated with influent concentration. On the other hand, the second discriminant function (DF2) is directly correlated with F1 (*e.g.*, MW, MV and polarizability) and with F2 (*e.g.*, melting point, surface tension, and density) and inversely correlated with F5 (*i.e.*, Henry's law constant), and F3 (*e.g.*, biodegradation halftime and affinity for soil accumulation).

As shown in Table 3, the canonical discriminant model revealed quite accurate classification performances (overall 65.3%) with better classifications for the highest removals (72.9% of correct classifications for removals over 90%) and intermediate removals (63.4% of correct classifications for removals between 48 and 90%), and almost 60% of correct classifications for the removals lower than 47%. The accuracy of the canonical discriminant model was also evaluated through a leave-one-out cross-validation (*i.e.*, each case is classified by the functions derived from all cases other than that case) which confirmed the accuracies previously estimated. Figure S2 shows the DF scores biplot with the removal classes shown in colors. The DF scores biplot clearly shows that the

Table 2 Canonical Discriminant Function correlations with predictors

	DF1	DF2
F1: MW, MV, polarizability, boiling point, flash point, molar refractivity		0.528
F2: Melting point, surface tension, density, index of refraction		0.397
F3: Biodegradability, K_{OC}, Log D, soil adsorption, log Kao		-0.288
F4: $LogK_{ow}$, (-) solubility, (-) pKa	-0.560	
F5: Henry's law		-0.526
Influent concentration	-0.325	

Table 3 Canonical Discriminant Analysis: classification performance for the three classes of pharmaceutical removals

Classification Results [a]						
		RR (Binned)	Predicted Group Membership			Total
			< = 0.47	0.48—0.90	0.91 +	
Original	Count	< = 0.47	77	31	23	131
		0.48—0.90	10	85	39	134
		0.91 +	0	39	105	144
	% Original	< = 0.47	**58.8**	23.7	17.6	100
		0.48—0.90	7.5	**63.4**	29.1	100
		0.91 +	0.0	27.1	**72.9**	100
Cross-validated [b]	Count	< = 0.47	77	31	23	131
		0.48—0.90	10	83	41	134
		0.91 +	0	39	105	144
	%	< = 0.47	**58.8**	23.7	17.6	100
		0.48—0.90	7.5	**61.9**	30.6	100
		0.91 +	0.0	27.1	**72.9**	100

a. 65,3% of original grouped cases correctly classified.

b. In cross validation, each case is classified by the functions derived from all cases other than that case.

highest removal compounds have DF scores lower than the average for both DF1 (*e.g.*, soluble and polar light-weighted compounds) and DF2 (*e.g.*, heavier-weighted hydrophobic, and higher biodegradability compounds).

4 Discussion

This case study, comparing a MBR pilot plant and a full scale WWTP with final filtration, operated in parallel, confirms that for most of the substances the MBR technology did not significantly enhance their removal rates, especially for those which are well removed above 80%, as previously highlighted elsewhere (Sipma et al., 2010). As mentioned in few previous works, MBR may show slightly higher capabilities in removing the substances which are already partially removed in CAS. Good removal was reported for a variety of pharmaceuticals with MBR treatment; nevertheless carbamazepine, diclofenac, and diazepam removal ranged between 24 and 68% (Trinh et al., 2016). With a slightly lower removal efficiency, these results are in good agreement with their reported work. Also, naproxen, ibuprofen, and ketoprofen showed high overall removal efficiency > 90%, due to their hydrophilicity character (Komesli et al., 2015; Trinh et al., 2012).

Contrary to some previous studies (Melvin et al., 2016; Liu et al., 2021), any significant influence of process type was not proven when comparing the efficiency of the MBR pilot plant with that of the full scale WWTP equipped with final filtration. It does not really impact the removals neither of recalcitrant substances, nor of well removed ones, in agreement with the literature (Verlicchi et al., 2012). Indeed, really few substances displayed significantly enhanced removal in one or the other process. Consequently, it seems that MBR, when operated at realistic SRTs (in this work from 15 to 50 days) and fed with the same influent than a municipal WWTP with filtration, do not exhibit a higher potential in removing pharmaceutical substances. This can be highlighted, according to GLM results presented above, by the fact that the type of treatment was not a significant predictor of pollutant's removal. The influent concentration as a process parameter is confirmed to affect transformations pathways (Onesios-Barry et al., 2014). This is in good agreement with the GLM results having the influent concentration considered as the second most important predictor.

The lack of in-depth insights on the influence of physicochemical properties on removal efficiency of pharmaceuticals presents one of the biggest challenges in optimizing their removal under different processes. Multiple research papers are reported discussing the influence of different properties such as MW, solubility, $\log K_{ow}$, K_{OC}, $\log D_{ow}$, pKa, and charge on removal mechanism (Bayati et al., 2021; Ilyas et al., 2021; Luo et al., 2014; Wang et al., 2020).

With this regard, taking into consideration more than one or two properties may probably lead to better understanding. According to previous studies (Wang et al., 2021), four out of 20 properties included in the current study namely (MW, solubility, $logK_{ow}$, Henry's law) were found to be good predictors for micropollutants removal by biotransformation. High molecular weight compounds are difficult to remove, which is the case for cluster 4 compounds (containing only clarithromycin with a removal rate < 70% in MBR and CAS). This falls in line with previous studies reporting a removal efficiency of > 60% for high MW pharmaceuticals (Tadkaew et al., 2011).

Hydrophobicity/hydrophilicity described by $LogK_{ow}$ values contribute significantly to removal (Couto et al., 2019; Ofrydopoulou et al., 2022). Hydrophobic compounds with Log D > 3.2 are generally highly removed, which is the case for cluster 7 (estrone, EST with a removal rate of 98%). This result is in agreement with the literature (Gutiérrez et al., 2022). On the contrary, cluster 3 contains hydrophilic compounds with a removal rate less than 40% (cyclophosphamide and salbutamol). Diazepam, forming its own cluster 6, is characterized by a high Henry's law constant and it is indeed a hydrophilic compound with a poor removal rate of 2% in the MBR. Multiple studies confirmed the minimal elimination of this particular micropollutant (Besha et al., 2017; Cartagena et al., 2013; Joss et al., 2006; Serrano et al., 2011; Wang et al., 2017). It is worth mentioning that the clusters including a variety of compounds, especially cluster 1 and 2, may demand additional monitoring campaigns and further analysis.

As previously mentioned, CDA is a dimensionality reduction technique that is used to transform a set of possibly correlated variables into a smaller number of uncorrelated variables, known as "canonical variates". The purpose of CDA is to find linear combinations of the original variables that can best distinguish between two or more groups of samples based on the class labels. Based on CDA results, the first discriminant function (Wilk's Lamba = 0.45) has a better discriminating power over the second function (Wilk's Lamba = 0.82), which mean that molecular weight, $LogK_{ow}$, pKa, and solubility are good predictors of removal classification. These findings line up

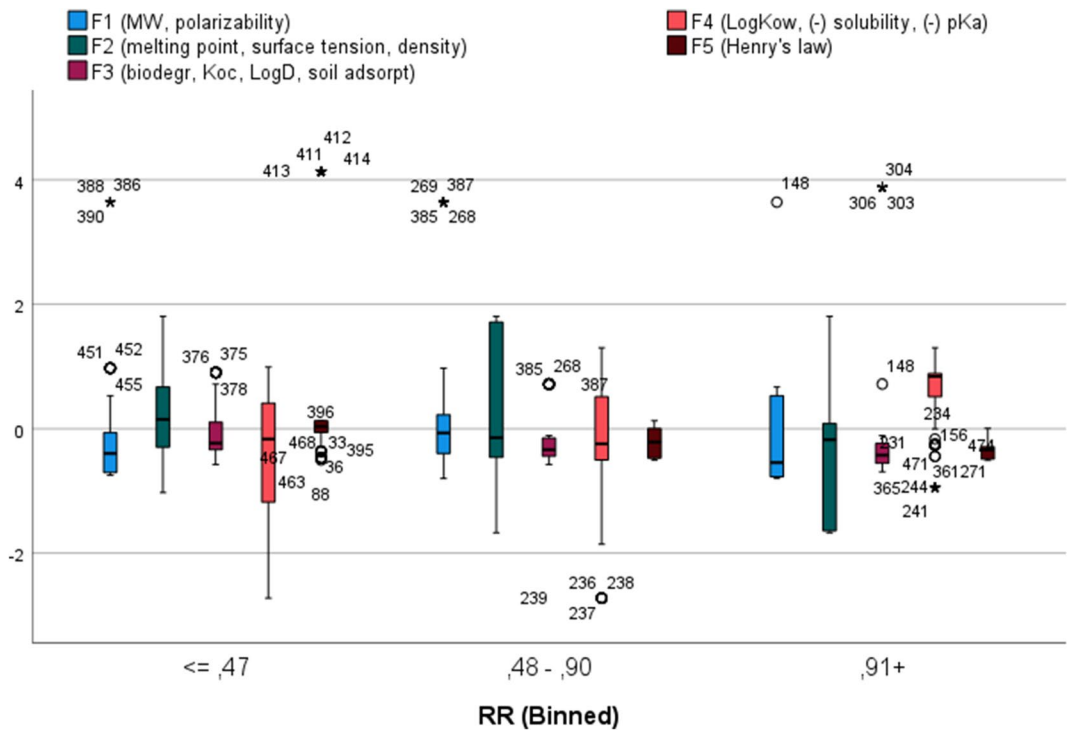

Fig. 5 Varifactors distribution among the three classes of pharmaceutical removal (RR)

with previous studies (Matamoros et al., 2017) that revealed a positive correlation between the removal efficiency of 16 micropollutants in constructed wetlands and their MW and $LogK_{ow}$. As shown in Fig. 5, it is obvious that the higher removal rate class mostly concerns hydrophobic compounds (above average $LogK_{ow}$). This is also the class that has the highest prediction accuracy (> 70%). As for the intermediate removal rate class, it concerns compounds less hydrophobic with high MW and density. Finally, the lower removal class concerns lower MW and hydrophilic compounds.

5 Conclusions

This work is an attempt to address the challenges regarding the hypothesis of the influence of pharmaceuticals' properties on their removal to predict removal efficiency. In general terms, the aforementioned statistical results imply that:

- Removal of pharmaceuticals not significantly different among the three types of treatments
- Influent concentration and physicochemical characteristics (LogKow, log D) strongly predict pharmaceuticals removal.
- Further research incorporating additional parameters like seasonal variation may improve removal efficiency prediction.

Into details, the monitoring of the given WWTP has led to the following observations:

- 19 out of 39 targeted substances were detected in WWTP influent at relevant concentration.
- A high variability in influent concentrations were observed across sampling campaigns and within the same campaign.
- The observed variability can be attributed to consumption patterns, dilution rates, and transport duration in the sewer system, also considering that the WWTP influent is diluted due to a large zone with close water-table and potential infiltrations.

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Data availability The following supporting information was provided as Supplementary Material. Table S1: Micropollutants results in the 4 sampling campaigns. Table S2: Physicochemical properties of micropollutants. Figure S1: Pharmaceutical compounds composition of the eight clusters: counts of specific compound occurrences. Figure S2: Canonical Discriminant function biplot with the three classes of pharmaceutical removal and the group centroid. Other datasets used or analyses during the current study are available from the corresponding author on reasonable request.

Declarations

Competing Interests The authors declare no competing interest.

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